Oral Health

Patrícia Weidlich^(a) Renata Cimões^(b) Claudio Mendes Pannuti^(c) Rui Vicente Oppermann^(d)

(a) PhD Student; (d) Dean – Department of Periodontology, Federal University of Rio Grande do Sul, Brazil.

(b) PhD, Department of Prosthodontics and Oral Surgery, Federal University of Pernambuco, Brazil.

(4) PhD, Discipline of Periodontics, School of Dentistry, Ibirapuera University, São Paulo, Brazil

Association between periodontal diseases and systemic diseases

Abstract: Current evidence suggests that periodontal disease may be associated with systemic diseases. This paper reviewed the published data about the relationship between periodontal disease and cardiovascular diseases, adverse pregnancy outcomes, diabetes and respiratory diseases, focusing on studies conducted in the Brazilian population. Only a few studies were found in the literature focusing on Brazilians (3 concerning cardiovascular disease, 7 about pregnancy outcomes, 9 about diabetes and one regarding pneumonia). Although the majority of them observed an association between periodontitis and systemic conditions, a causal relationship still needs to be demonstrated. Further studies, particularly interventional well-designed investigations, with larger sample sizes, need to be conducted in Brazilian populations.

Descriptors: Periodontitis; Cardiovascular diseases; Pregnancy complications; Diabetes *mellitus*; Lung diseases.

Corresponding author:

Claudio Mendes Pannuti
Faculdade de Odontologia
Universidade de São Paulo (FOUSP)
Departamento de Periodontia
Av. Prof. Lineu Prestes, 2227
Cid. Universitária
São Paulo - SP - Brazil
CEP: 05508-000
E-mail: pannuti@usp.br

Received for publication on Jun 11, 2008 Accepted for publication on Jun 25, 2008

Disclosures

This article was sponsored by an educational grant from Johnson & Johnson do Brasil Indústria e Comércio para Saúde Ltda.

Introduction

The understanding of the etiology and pathogenesis of periodontal diseases and their chronic, inflammatory and infectious nature¹ necessitates admitting the possibility that these infections may influence events elsewhere in the body. At the same time, recognition of the interaction between oral diseases and some systemic conditions entails that dentists and periodontists should direct their practice and knowledge not only to events strictly related to the oral cavity but also consider systemic conditions and diseases which may change or interfere with established preventive and therapeutic approaches.

The concept that oral diseases could influence distant structures is, to a certain extent, a return to the theory of focal infection. The evidence supporting this theory dates from around 1900 and it was based on the expert opinion and personal clinical experience of a few physicians and dentists. Some reports of questionable scientific merit have also supported the influence of dental sepsis on systemic health.2 The return of this concept since the end of the 80's has been investigated in a quite different scenario. Advances in the methods of scientific investigation were undoubtedly decisive in this context. The development of epidemiological studies and statistical analysis, the enhanced understanding of biological plausibility by means of advances in molecular biology, microbiology, immunology and genetics, the possibility of successfully treating periodontal diseases, caries and endodontic infections and retaining teeth instead of extracting them, all these factors have led dental and medical researchers and clinicians to resume the study of the relationship between oral diseases and systemic conditions with a more scientific approach.

This paper discusses the relationship between periodontal diseases and the most studied systemic conditions: cardiovascular diseases, adverse pregnancy outcomes, diabetes *mellitus* and respiratory diseases. Each section presents the current state of

the field, indicates questions to be answered and presents studies performed in Brazilian populations.

Periodontal diseases and cardiovascular diseases

Cardiovascular diseases (CVD) are a group of diseases that include congestive heart failure, cardiac arrhythmias, coronary artery disease (including atherosclerosis and myocardial infarction), valvular heart disease and stroke. Among these, atherosclerosis, a major component of cardiovascular diseases, is characterized by the deposition of atherosclerotic plaques on the innermost layer of walls of large- and medium-sized arteries. End-stage outcomes associated with atherosclerosis include coronary thrombosis, myocardial infarction and stroke.

CVD and periodontitis are both chronic and multifactorial diseases, and share some of their risk factors: age, male gender, lower socioeconomic status, smoking and psychosocial factors such as stress.³ Recently, periodontal disease (PD) has been investigated as a potential factor contributing to the onset and development of CVD.

Several mechanisms that could explain this association have been investigated. The host response to the presence of periodontal pathogens may trigger the production of inflammatory mediators such as C-reactive protein, TNF-α, PGE₂, IL-1β and IL-6, which can accelerate the progression of pre-existing atherosclerotic plaques⁴ and are related to an increased number of adverse cardiovascular events.⁵ Also, several studies demonstrated the ability of periodontal pathogens to induce platelet aggregation and the formation of atheromas.^{6,7}

A systematic review published in 2003⁸ studied the evidence supporting the association between PD and CVD. Thirty-one human studies were selected. The authors concluded that "periodontal disease may be modestly associated with atherosclerosis, myocardial infarction and cardiovascular events". Other three systematic reviews⁹⁻¹¹ reported a modest but significant association between CVD and periodontal disease.

Another question is whether periodontal treatment can decrease the risk for adverse cardiovascular events. However, so far there is limited evidence regarding this question. Cardiovascular events may take several years to occur, so the possible benefits of periodontal therapy are difficult to observe in interventional studies. Some investigations reported the effects of periodontal treatment on surrogate endpoints, such as C-reactive protein, which is associated with CVD.¹² However, a recent systematic review concluded that, up to now, there is no evidence that periodontal treatment can significantly reduce C-reactive protein levels.¹³

Few studies regarding this association have been conducted in the Brazilian population. One case-control study and two cross-sectional studies were retrieved from the Medline and Scielo databases, using the words "periodontitis", "periodontal", "cardiovascular", "infarction" and "atherosclerosis" (Table 1).

The case control study, conducted in Southern Brazil, found a significant association between periodontitis and acute coronary syndrome. ¹⁶ One cross-sectional study ¹⁴ observed significant association between periodontal disease and severe obstruction of coronary artery. However, the authors did not present multivariate analysis with adjustment for confounders related to periodontitis and CVD. The other cross-sectional study ¹⁵ did not present a multivariate analysis to investigate the association between the two conditions, and reported that periodontal disease was elevated in patients

with Ischemic Coronary Atherosclerosis. Some potential methodological biases should be considered in order to avoid erroneous conclusions about a causal relationship between periodontal disease and adverse cardiovascular events in these populations. The criteria adopted to define periodontal disease exposure in these studies must also be carefully analyzed. More interventional studies, with larger sample sizes, need to be conducted in the Brazilian population.

Adverse pregnancy outcomes and periodontal diseases

This section will focus particularly on the relationship between periodontal diseases and preterm birth and low birth weight, which has been extensively studied in last years all over the world.

The first study to report the influence of poor oral health on the birth of low weight and preterm infants was performed by Offenbacher and colleagues.¹⁷ They obtained obstetric and demographic information from the studied patients' prenatal records and performed full mouth periodontal examinations in 93 mothers who gave birth to preterm or low weight infants and compared them to those of 31 mothers who had term deliveries and normal weight infants. Multivariate analysis showed that the women with more than 60% of sites with clinical attachment loss of 3 mm or more were seven

Table 1 - Studies assessing the relationship between periodontal disease and cardiovascular diseases in Brazilian populations.

Authors	Study design	Population	Periodontal outcome or exposure	Cardiovascular disease outcome	Findings and conclusions
Accarini, de Godoy ¹⁴ (2006)	Cross- Sectional	361 patients from a Hospital in São Paulo (SP)	30% of sites with clinical attachment level and/or periodontal pocket depth ≥ 5 mm	Severe obstruction of coronary artery (at least one obstruction ≥ 50%)	Significant association between periodontal disease and severe obstruction of coronary artery (OR 2.571, CI 1.192-5.547)
Barilli et al. ¹⁵ (2006)	Cross- Sectional	634 patients from a Hospital in Ribeirão Preto (SP)	Presence of periodontal disease according to Community Periodontal Index	Ischemic Coronary Atherosclerosis	Periodontal disease was elevated in patients with Ischemic Coronary Atherosclerosis
Rech <i>et al</i> . ¹⁶ (2007)	Case-control	58 cases (acute coronary syndrome) and 57 matched controls from a hospital in Gravataí (RS)	Presence of periodontal pockets, attachment loss and gingival inflammation	Presence of acute coronary syndrome	Significant association between periodontitis and acute coronary syndrome (OR 5.1 Cl 1.7-14.8)

times more likely to have an adverse pregnancy outcome than periodontally healthy women (OR = 7.5; CI 1.98-28.8).

The etiology of preterm birth is multifactorial, but inflammation is the common pathway that leads to uterine contractions and cervical changes with or without premature rupture of membranes. Inflammation associated to preterm birth can be mainly attributable to intrauterine infection and bacterial vaginosis, and the latter accounts for up to 40% of the cases of spontaneous preterm labor and preterm birth. There is also a causal relationship between bacterial vaginosis and preterm birth¹⁸ and the presence of significantly higher levels of proinflammatory cytokines and prostaglandins in the amniotic fluid. This is a common finding in women with bacterial vaginosis who deliver preterm. 19,20 At the same time, an infection remote to the genital tract can also trigger preterm birth, and this is the case for pregnant women with periodontal disease.

Biological plausibility of the link between both conditions, periodontal disease and preterm birth, does exist and can be summarized in three potential pathways.^{20,21} One of them refers to the hematogenous dissemination of inflammatory products from a periodontal infection, while the second potential pathway involves the fetomaternal immune response to oral pathogens. The third pathway proposed to explain the theoretical causal relationship between periodontal disease and preterm birth involves bacteremia from an oral infection.

Since 1994, several studies have been conducted concerning the relation between periodontal diseases and preterm birth and diverse findings have been reported all over the world. There appears to be an association between both conditions, but whether periodontitis is a confounding factor, a marker or one of the causes of preterm birth remains unclear.²² The reader is referred to additional studies in order to get acquainted with the larger body of literature on this theme.^{23,24}

It is important to point out that, in spite of the high number of studies published, only a few of them are randomized clinical trials, which represents the research design that generates the weightiest evidence when assessing claims of causation. In this context, two clinical trials should be mentioned. The first one was performed by Lopez et al.25 (2002) in Chile with 163 pregnant women who received periodontal treatment during pregnancy and 188 women who received the same treatment after delivery. Preterm/ low birth weight rate was 1.8% for the test group and 10.1% for the control group. The authors demonstrated that the presence of periodontitis was significantly associated with preterm/low birth weight in the population studied (OR 4.7, CI 1.29-17.13). The other randomized clinical trial was performed in the United States²⁶ with 413 pregnant women who received monthly oral health instruction and scaling as needed and 410 pregnant women who were submitted to brief monthly oral exams during pregnancy. Preterm birth occurred in 12% and 12.8% of the patients from the test and control groups, respectively. Periodontal treatment significantly improved all periodontal parameters but it did not improve preterm delivery (OR 0.93, CI 0.63-1.37).

Conflicting findings have been found not only in these two clinical trials but also in the literature published since 1994 in this area. Several criteria, such as the definition of periodontal disease, experimental design, compliance with treatment and the time of periodontal treatment delivered in clinical trials, controlling for confounding variables and outcome definition are pointed out in order to understand the diversity of the results presented. Another issue addressed in this discussion is the fact that different populations may not share the same risk factors to both conditions, periodontal diseases and adverse pregnancy outcomes. It will thus be necessary to conduct studies taking into account socioeconomic, biologic and environmental determinants for each population.

Specifically in the Brazilian population, some studies were performed and are detailed in Table 2. Five case control studies and two cross sectional studies were retrieved from Medline with the words "periodontitis", "preterm birth", "low birth weight" and "Brazil". Two other studies were not included because of inadequate outcome measure²⁷ and partial data reporting.²⁸

One cross sectional study performed in the state of Santa Catarina found no association between

 Table 2 - Studies assessing the relationship between periodontal disease and adverse pregnancy outcomes in Brazilian populations.

Authors	Study design	Population	Periodontal outcome or exposure	Adverse pregnancy outcome	Variables included in the final model	Findings and conclusions
Cruz et al. ²⁹ (2005)	Case-control	102 cases and 200 controls from a public hospital in Feira de Santana (BA)	≥ 4 sites with clinical attachment levels ≥ 4 mm	Low birth weight (< 2,500 g)	No adjustment for classic confounding variables	Significant association between low birth weight and periodontitis for mothers with low educational level (OR 3.98, CI 1.58-10.10)
Lunardelli, Peres³º (2005)	Cross-sectional	449 women from a maternity hospital in Itajaí (SC)	\geq 1 site with probing depth \geq 3.5 mm \geq 4 sites with probing depth \geq 3.5 mm	Preterm birth (< 37 weeks) Low birth weight (< 2,500 g) Preterm and low birth weight	Periodontal disease, schooling, parity, previous low birth weight, body mass index, number of prenatal visits, genitourinary infection, hypertension, dental treatment and oral health guidance	No significant association between periodontal disease and prematurity when maternal health variables were included (OR 2.7, CI 0.7-9.7)
Moliterno <i>et al.</i> ³¹ (2005)	Case-control	76 cases and 75 controls from a public maternity hospital in Rio de Janeiro (RJ)	\geq 4 sites with probing depth \geq 4 mm and clinical attachment level \geq 3 mm	Preterm birth (< 37 weeks) and low birth weight (< 2,500 g)	Periodontitis, genitourinary infection, race, prenatal location, arterial hypertension, vaginal bleeding, alcohol use, smoking, number of prenatal visits, diabetes and educational level	Significant association between low birth weight and periodontitis (OR 3.48, CI 1.17-10.36)
Bassani et al. ³² (2007)	Case-control	304 incident cases and 611 controls from three hospitals in Porto Alegre (RS)	\geq 3 sites with clinical attachment level \geq 3 mm	Low birth weight (< 2,500 g) at > 27 weeks of gestational age	Maternal age, parity, prenatal care, smoking, previous preterm or low birth weight, hypertension, pre eclampsia and weight change during pregnancy	No association between periodontitis and low birth weight (OR 0.93, CI 0.63-1.41)
Siqueira <i>et al.</i> ³³ (2007)	Case-control	263 cases and 1,042 controls from a public hospital in Belo Horizonte (MG)	≥ 4 sites with probing depth ≥ 4 mm and clinical attachment level ≥ 3 mm	Preterm birth (< 37 weeks), low birth weight (< 2,500 g) and intrauterine growth restriction	Educational level, maternal age, prenatal visits, chronic hypertension, primiparity, previous abortion, previous preterm birth and maternal periodontitis	Significant association between preterm birth and periodontitis (OR 1.77, CI 1.12-2.59) Significant association between low birth weight and periodontitis (OR 1.67, CI 1.11-2.51) Significant association between preterm birth and intrauterine growth restriction (OR 2.06, CI 1.00-4.19)
Santos Pereira et al. ³⁴ (2007)	Cross-sectional	68 women with preterm labour and 56 women with term labour from a university hospital in Campinas (SP)	≥ 1 site with clinical attachment level ≥ 1 mm and bleeding on probing	Preterm labour (gestational age < 37 weeks, admitted in the hospital for intravenous tocolysis)	Age, ethnicity, parity, schooling, marital status and number of prenatal visits	Significant association between preterm birth and periodontitis (OR 4.9, Cl 1.9-12.8) Significant association between low birth weight and periodontitis (OR 4.2, Cl 1.3-13.3)
Siqueira et al. 35 (2008)	Case-control	125 cases and 375 matched controls from a public hospital in Belo Horizonte (MG)	≥ 4 sites with probing depth ≥ 4 mm and clinical attachment level ≥ 3 mm	Pre eclampsia Blood pressure > 140/ 90 mm Hg on two occasions after 20 weeks of gestation and ≥ 1+ urine dipstick value	Maternal age, primiparity, chronic hypertension, number of prenatal visits, previous preterm birth and maternal periodontitis	Significant association between pre eclampsia and preterm birth (OR 3.15, Cl 1.04-9.52) Significant association between pre eclampsia and maternal periodontitis (OR 1.52, Cl 1.01-2.29

periodontitis and preterm birth when a high number of variables were included in the analysis.³⁰ Another cross sectional study performed in the state of São Paulo showed that periodontitis may be a risk indicator for women with a diagnosis of preterm labor.³⁴

Four case control studies investigated the relationship between periodontitis and low birth weight. Three of them found a significant association between both conditions^{29,31,33} and the fourth failed to demonstrate an association between periodontitis and the birth of infants with less than 2,500 g.³² It is important to mention that in one of the studies there were no adjustment for classic confounding variables related to periodontitis and low birth weight.²⁹ Studies performed in the city of Belo Horizonte also evaluated the association of periodontitis with preterm birth, intrauterine growth restriction and preeclampsia and the authors showed significant association with all the adverse pregnancy outcomes investigated.^{33,35}

Similarly to the investigations in other populations, studies in the Brazilian population may indicate an association between periodontitis and adverse pregnancy outcomes. However, potential methodological biases should be thoroughly analyzed in order to avoid erroneous and premature conclusions. Moreover, the limited number of randomized clinical trials published up to now in the international literature and the absence of studies with this design in the Brazilian population prevents us from offering a definitive conclusion.

Periodontal disease and diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia and results from either a deficiency in the secretion of insulin and/or reduced insulin action.³⁶ In type 1 diabetes, there is an absolute deficiency of insulin. In type 2 diabetes, there is the involvement of resistance to insulin and an inability of the pancreas to compensate for this resistance. Severe hyperglycemia can cause numerous symptoms, including polyuria, polyphagia, polydipsia, weight loss and blurred vision.³⁷ There is peripheral vascular insufficiency, causing scarring disorders and physiological changes that reduce

the immunological capacity, thereby increasing the susceptibility to infection. A greater glucose and calcium content in the saliva favors an increase in the amount of calculus and irritating factors to oral tissues, leading to periodontal disease, which is the most common dental manifestation in the oral cavity among diabetic patients (75%).³⁸

Chronic periodontal disease and diabetes mellitus are common chronic conditions in adults throughout the world.³⁹ Severe periodontal disease often coexists with diabetes and is considered the sixth most common complication of the disease.⁴⁰ A number of studies have demonstrated that poor blood sugar control may contribute to poor periodontal health41-47 and that such individuals have a 2.8-fold greater chance of developing destructive periodontal disease⁴² as well as a 4.2-fold greater chance of having progressive alveolar bone loss.⁴⁸ The increased risk of developing periodontal disease cannot be explained by age, gender or hygiene.⁴⁹ The interrelationship between periodontal disease and diabetes provides an example of a systemic disease predisposing individuals to oral infection and, once the infection is installed, it exacerbates the systemic disease.39

The interrelationship between diabetes and periodontal disease is established through a number of pathways⁵⁰ and is bidirectional.⁵¹ Diabetes is a risk factor for gingivitis and periodontitis.^{52,53} Blood sugar control is an important variable in the relationship between diabetes and periodontal disease. Individuals who have poor control over glycemia have a greater prevalence and severity of gingival and periodontal inflammation.^{54,56} It has been suggested that hyperglycemia promotes periodontitis and its progression.^{51,57,62}

One of the mechanisms to explain the relationship between diabetes *mellitus* and periodontal disease suggests that the presence of periodontal disease may induce or perpetuate a state of chronic systemic inflammation, as demonstrated by the increase in the C-reactive protein, interleukin-6 (IL-6) and fibrinogen levels found in individuals with periodontitis.⁶³ Periodontal infection may elevate the state of systemic inflammation and exacerbate the resistance to insulin, as the inflammatory pro-

cess induces this resistance. Furthermore, it may induce increased levels of IL-6 and TNF- α , which is similar to obesity inducing or exacerbating the resistance to insulin.⁶⁴

The synergism between diabetes and periodontal disease has been demonstrated in a number of studies. It has been made clear that effective periodontal treatment can improve some complications of diabetes, especially hyperglycemia, and that severe periodontitis is associated to poor blood sugar control. Periodontal treatment improves blood sugar control, especially in individuals with type 2 diabetes, and its association to low glycated hemoglobin levels has been demonstrated.⁶⁰

A number of studies have found that non-surgical periodontal treatment improves the metabolic control of diabetic patients, thereby influencing a reduction in glycated and glycemic hemoglobin levels. ⁶⁵ Patients with diabetes have a good response to periodontal treatment, whether in the short or long term, and this response is similar to that observed

in non-diabetic patients. However, if the diabetes is not well controlled, the recurrence of periodontal disease is more frequent and more difficult to control. The influence of diabetes over periodontal disease is well established, but the effect of periodontitis and its treatment over the control of diabetes remains unclear.⁶⁶

In Brazil, few studies have been carried out assessing the relationship between diabetes and periodontal disease. There are also few studies addressing the benefits of periodontal treatment regarding blood sugar control. Table 3 presents the studies carried out in the Brazilian population. These studies were retrieved from the Medline, Scielo and Lilacs databases, using the words "periodontitis", "Brazil", "Brazilian" and "diabetes".

In 2003, Rodrigues *et al.*⁴⁹ assessed 30 individuals with type 2 diabetes *mellitus* and periodontitis. The authors divided the patients into two groups – one group underwent mechanical periodontal treatment and the other group underwent that treatment

Table 3 - Studies assessing the relationship between periodontal disease and diabetes mellitus in Brazilian populations.

Authors	Population	Diabetes	Findings and conclusions	
Novaes Jr et al. ⁶⁷ (1991)	30 diabetics / 30 controls aged 5 to 18 years	Type 1	Greater mean indices of plaque, gingivitis and alveolar bone loss among diabetics when compared to healthy controls.	
Novaes Jr et 30 diabetics / 30 controls al.44 (1996) aged 30 to 77 years		Type 2	A one-year follow up found no difference in probing depth, but there was a significant difference in insertion loss between diabetics and controls.	
Novaes Jr et al. ⁶⁸ (1997)		Туре 1	Although the patients did not receive periodontal treatment over a 10-year period, there was a slight increase in plaque, gingivitis, probing depth and bone loss.	
Novaes Jr et 30 diabetics / 30 controls al.69 (1997) aged 30 to 77 years		Type 2	Using the BANA test, there was no significant difference between diabetics an controls.	
Rodrigues et al. ⁴⁹ (2003)		Type 2	Patients were divided into 2 groups – one received conventional therapy and the other received therapy + doxycycline. There was a 10% reduction in glycated hemoglobin level, with statistical significance for the group that only received mechanical treatment.	
Martorelli de Lima et al. ⁷⁰ aged 35-55 years (2004)		Туре 1	Patients had pockets with depths ≥ 5 mm treated with conventional therapy and sub-gingival administration of doxycycline gel or conventional therapy + placebo. Better results were obtained in the group that used doxycycline.	
Souza et al. ⁷¹ 44 diabetics / 19 controls (2006)		Type 2	No difference in blood sugar control was found, not even following non- surgical periodontal therapy associated or not to systemic doxycycline.	
Drumond- Santana et al. ⁷² (2007)		Type 1 Type 2	Using the OHIP-14 index, the impact of periodontal disease on the quality of life of diabetic individuals was assessed. It was concluded that diabetics with periodontitis suffered a greater negative impact on quality of life than periodontally healthy diabetics or those with gingivitis.	
O'Connell et 30 diabetics al. ⁷³ (2008)		Type 2	No additional effect from doxycycline associated to conventional mechanical therapy was found.	

associated to the use of amoxicillin and clavulanic acid. Glycated hemoglobin levels, glycemia and clinical periodontal parameters were assessed at baseline and three months following therapy. The authors concluded that non-surgical periodontal therapy improved blood sugar control in both groups and the reduction of glycated hemoglobin was only statistically significant in the group that did not make use of antibiotics.

To assess the effect of the sub-gingival administration of doxycycline as an auxiliary aid in periodontal treatment among patients with type 1 diabetes, Martorelli de Lima *et al.*⁷⁰ (2004) treated 11 individuals, who were required to present two sites with probing depths ≥ 5 mm and bleeding or suppuration upon probing. For one group, the treatment consisted of scaling and root planing therapy associated to the sub-gingival administration of a 10% doxycycline hyclate gel, whereas the other group received scaling and root planing associated to a placebo gel. The authors concluded that the use of doxycycline produced additional favorable effects over the scaling and root planing alone.

Souza *et al.*⁷⁴ (2006) studied the effect of periodontal therapy on glycated hemoglobin levels in 63 non-insulin-dependent diabetic adults, who were divided into four groups: Group 1 – healthy controls; Group 2 – diabetics with no periodontal disease; Group 3 – diabetics with periodontitis submitted to periodontal therapy; and Group 4 – diabetics with periodontitis submitted to periodontal therapy associated to the administration of systemic doxycycline. The authors found no statistically significant difference in blood sugar control following periodontal therapy with or without the use of systemic antibiotics.

In a double-blind, placebo-controlled study assessing the effect of periodontal therapy (scaling and root planing) on glycated hemoglobin levels and biomarkers, O'Connell *et al.*⁷³ (2008) treated 30 patients with type 2 diabetes. One group was treated with doxycycline and mechanical therapy and the other group was treated with mechanical therapy alone. The authors concluded that there was an improvement in blood sugar control, but there was no significant difference between the use and non-use

of doxycycline.

Current evidence is insufficient to determine whether periodontal treatment, whether associated to antibiotic therapy or not, is effective in controlling glycated hemoglobin and blood sugar levels in patients with diabetes.

Periodontal diseases and respiratory diseases

Respiratory diseases is the term for diseases of the respiratory system, including lung, pleural cavity, bronchial tubes, trachea, and upper respiratory tract. They range from a common cold to lifethreatening conditions such as bacterial pneumonia or chronic obstructive pulmonary disease (COPD), which are important causes of death worldwide.

COPD is a pathological and chronic obstruction of airflow through the airways or out of the lungs, and includes chronic bronchitis and emphysema. Its main risk factor is smoking, but air pollution and genetic factors are also strongly implicated.

Pneumonia (both community-acquired and hospital acquired) is an acute infection of the lung and is characterized by cough, breath shortness, sputum production and chest pain. It is caused by the micro-aspiration of oropharyngeal secretions containing bacteria into the lung, and failure of the host to clear the bacteria.

There is increasing evidence that a poor oral health can predispose to respiratory diseases, especially in high-risk patients (nursing home residents, older subjects, intensive care unit patients and hospitalized individuals requiring mechanical ventilation). The oral cavity is contiguous with the trachea and may be a portal for respiratory pathogen colonization. Dental plaque can be colonized by respiratory pathogens,⁷⁵ which may be aspirated from the oropharynx into the upper airway and then reach the lower airway and adhere to bronchial or alveolar epithelium.⁷⁶

A recent systematic review investigated if there was an association between oral health and pneumonia or other respiratory disease.⁷⁷ The authors reviewed 19 studies that met the inclusion criteria and concluded that there is fair evidence of an association of pneumonia with oral health, but there is

poor evidence of a weak association between COPD and oral health. The authors also concluded that improved oral hygiene and professional oral health care reduces the progression or occurrence of respiratory diseases among high-risk elderly adults. A recent prospective study⁷⁸ conducted with 697 elderly individuals observed that the adjusted mortality due to pneumonia was 3.9 times higher in subjects with periodontal disease.

As discussed above, the oral cavity serves as a reservoir for respiratory pathogens. So, oral hygiene interventions may reduce colonization by these pathogens and, consequently, decrease the risk for pneumonia, especially in high-risk populations. Scannapieco et al.79 (2003) conducted a systematic review about the effectiveness of oral decontamination to prevent pneumonia. A meta-analysis on 5 intervention studies revealed that oral interventions improving oral hygiene through mechanical and/or chemical disinfection reduced the incidence of nosocomial pneumonia by an average of 40%. A recent multicenter trial assessed the efficacy of a 0.2% chlrohexidine gel in the reduction of the rate of pneumonia in 228 non-edentulous patients requiring endotracheal intubation and mechanical ventilation.80 Although the intervention significantly decreased the oropharyngeal colonization by aerobic pathogens, no significant reduction in the incidence of respiratory infections was observed.

There is a lack of information about the association between oral health and respiratory diseases in Brazilian populations. One investigation conducted in Brazil was retrieved using the words "periodontitis", "oral health", "dental", "pneumonia" and "respiratory" in the Medline and Scielo databases. In this cross-sectional study, \$1 30 hospital patients with diagnosis of nosocomial pneumonia were included. Samples from tracheal aspirate, supragingival dental plaque and tongue were analyzed. Seventy percent of the bacteria isolated from the tracheal aspirate were also found in the dental biofilm. The authors concluded that dental biofilm could act as a reservoir for respiratory pathogens.

Conclusion

Most of the reviewed studies focusing on the Brazilian population demonstrated an association between periodontal disease and systemic conditions. However, more studies are needed, particularly interventional investigations, in order to establish a causal relationship between the two conditions.

References

- Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. Periodontol 2000. 1997 Jun;14:216-48.
- 2. O'Reilly PG, Claffey NM. A history of oral sepsis as a cause of disease. Periodontol 2000. 2000 Jun;23:13-8.
- 3. Paquette DW, Brodala N, Nichols TC. Cardiovascular disease, inflammation, and periodontal infection. Periodontol 2000. 2007;44:113-26.
- 4. Tousoulis D, Davies G, Stefanadis C, Toutouzas P, Ambrose JA. Inflammatory and thrombotic mechanisms in coronary atherosclerosis. Heart. 2003 Sep;89(9):993-7.
- Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med. 2004 Dec 16;351(25):2599-610.
- Herzberg MC, Weyer MW. Dental plaque, platelets, and cardiovascular diseases. Ann Periodontol. 1998 Jul;3(1):151-60.

- Lalla E, Lamster IB, Hofmann MA, Bucciarelli L, Jerud AP, Tucker S et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol. 2003 Aug 1;23(8):1405-11.
- Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. Ann Periodontol. 2003 Dec;8(1):38-53.
- 9. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol. 2004 Aug;75(8):1046-53.
- 10. Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis, and cardiovascular disease. Crit Rev Oral Biol Med. 2004;15(6):403-13.
- 11. Vettore MV. Periodontal disease and cardiovascular disease. Evid Based Dent. 2004;5(3):69.
- 12. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A *et al*. C-reactive protein and other circulating

- markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004 Apr 1;350(14):1387-97.
- 13. Ioannidou E, Malekzadeh T, Dongari-Bagtzoglou A. Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. J Periodontol. 2006 Oct;77(10):1635-42.
- 14. Accarini R, de Godoy MF. Periodontal disease as a potential risk factor for acute coronary syndromes. Arq Bras Cardiol. 2006 Nov;87(5):592-6.
- Barilli AL, Passos AD, Marin-Neto JA, Franco LJ. Periodontal disease in patients with ischemic coronary atherosclerosis at a University Hospital. Arq Bras Cardiol. 2006 Dec;87(6):695-700.
- Rech RL, Nurkin N, da Cruz I, Sostizzo F, Baiao C, Perrone JA et al. Association between periodontal disease and acute coronary syndrome. Arq Bras Cardiol. 2007 Feb;88(2):185-90.
- 17. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G *et al.* Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol. 1996 Oct;67(10 Suppl):1103-13.
- Leitich H, Bodner-Adler B, Brunbauer M, Kaider A, Egarter C, Husslein P. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. Am J Obstet Gynecol. 2003 Jul;189(1):139-47.
- Guaschino S, De Seta F, Piccoli M, Maso G, Alberico S. Aetiology of preterm labour: bacterial vaginosis. BJOG. 2006 Dec;113 Suppl 3:46-51.
- 20. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. J Perinat Med. 2007;35(2):93-9.
- Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000 May 18;342(20):1500-7.
- 22. Klebanoff M, Searle K. The role of inflammation in preterm birth focus on periodontitis. BJOG. 2006 Dec;113 Suppl 3:43-5.
- Scannapieco FA, Bush RB, Paju S. Periodontal disease as a risk factor for adverse pregnancy outcomes. A systematic review. Ann Periodontol. 2003 Dec;8(1):70-8.
- 24. Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG. 2006 Feb;113(2):135-43.
- 25. Lopez NJ, Smith PC, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol. 2002 Aug;73(8):911-24.
- 26. Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006 Nov 2;355(18):1885-94.
- 27. Gazolla CM, Ribeiro A, Moyses MR, Oliveira LA, Pereira LJ, Sallum AW. Evaluation of the incidence of preterm low

- birth weight in patients undergoing periodontal therapy. J Periodontol. 2007 May;78(5):842-8.
- 28. Cota LO, Guimaraes AN, Costa JE, Lorentz TC, Costa FO. Association between maternal periodontitis and an increased risk of preeclampsia. J Periodontol. 2006 Dec;77(12):2063-9.
- 29. Cruz SS, Costa Mda C, Gomes Filho IS, Vianna MI, Santos CT. [Maternal periodontal disease as a factor associated with low birth weight] [Article in Portuguese]. Rev Saude Publica. 2005 Oct;39(5):782-7.
- Lunardelli AN, Peres MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. J Clin Periodontol. 2005 Sep;32(9):938-46.
- 31. Moliterno LF, Monteiro B, Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. J Clin Periodontol. 2005 Aug;32(8):886-90.
- 32. Bassani DG, Olinto MT, Kreiger N. Periodontal disease and perinatal outcomes: a case-control study. J Clin Periodontol. 2007 Jan;34(1):31-9.
- 33. Siqueira FM, Cota LO, Costa JE, Haddad JP, Lana AM, Costa FO. Intrauterine growth restriction, low birth weight, and preterm birth: adverse pregnancy outcomes and their association with maternal periodontitis. J Periodontol. 2007 Dec;78(12):2266-76.
- 34. Santos-Pereira SA, Giraldo PC, Saba-Chujfi E, Amaral RL, Morais SS, Fachini AM *et al.* Chronic periodontitis and preterm labour in Brazilian pregnant women: an association to be analysed. J Clin Periodontol. 2007 Mar;34(3):208-13.
- 35. Siqueira FM, Cota LO, Costa JE, Haddad JP, Lana AM, Costa FO. Maternal periodontitis as a potential risk variable for preeclampsia: a case-control study. J Periodontol. 2008 Feb;79(2):207-15.
- Almas K, Al-Lazzam S, Al-Quadairi A. The effect of oral hygiene instructions on diabetic type 2 male patients with periodontal diseases. J Contemp Dent Pract. 2003 Aug 15;4(3):24-35.
- Herman WH. Clinical evidence: glycaemic control in diabetes.
 BMJ 1999 Jul 10;319(7202):104-6.
- 38. Sousa RR, Castro RD, Monteiro CH, Silva SC, Nunes AB. O Paciente Odontológico Portador de Diabetes *Mellitus*: Uma Revisão da Literatura. Pesq Bras Odontoped Clin Integr. 2003;3:71-7.
- 39. Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes *mellitus*. J Clin Periodontol. 2005 Mar;32(3):266-72.
- 40. Loe H. Periodontal disease. The sixth complication of diabetes *mellitus*. Diabetes Care. 1993 Jan;16(1):329-34.
- 41. Cianciola LJ, Park BH, Bruck E, Mosovich L, Genco RJ. Prevalence of periodontal disease in insulin-dependent diabetes *mellitus* (juvenile diabetes). J Am Dent Assoc. 1982 May;104(5):653-60.
- 42. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes *mellitus*. J Periodontol. 1991 Feb;62(2):123-31.

- 43. Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC *et al.* Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontol. 2007 Jan;34(1):46-52.
- 44. Novaes Jr AB, Gutierrez FG, Novaes AB. Periodontal disease progression in type II non-insulin-dependent diabetes *mellitus* patients (NIDDM). Part I Probing pocket depth and clinical attachment. Braz Dent J. 1996;7(2):65-73.
- Safkan-Seppala B, Ainamo J. Periodontal conditions in insulin-dependent diabetes *mellitus*. J Clin Periodontol. 1992 Jan;19(1):24-9.
- 46. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC *et al.* Non-insulin dependent diabetes *mellitus* and alveolar bone loss progression over 2 years. J Periodontol. 1998 Jan;69(1):76-83.
- 47. Unal T, Firatli E, Sivas A, Meric H, Oz H. Fructosamine as a possible monitoring parameter in non-insulin dependent diabetes *mellitus* patients with periodontal disease. J Periodontol. 1993 Mar;64(3):191-4.
- 48. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M. Glycemic control and alveolar bone loss progression in type 2 diabetes. Ann Periodontol. 1998 Jul;3(1):30-9.
- Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes *mellitus*. J Periodontol. 2003 Sep;74(9):1361-7.
- 50. Tan WC, Tay FB, Lim LP. Diabetes as a risk factor for periodontal disease: current status and future considerations. Ann Acad Med Singapore. 2006 Aug; 35(8):571-81.
- 51. Grossi SG, Genco RJ. Periodontal disease and diabetes *mellitus*: a two-way relationship. Ann Periodontol. 1998 Jul;3(1):51-61.
- 52. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol. 1996 Nov;1(1):1-36.
- 53. Mealey BL. Periodontal implications: medically compromised patients. Ann Periodontol. 1996 Nov;1(1):256-321.
- 54. Tervonen T, Oliver RC. Long-term control of diabetes *mellitus* and periodontitis. J Clin Periodontol. 1993 Jul;20(6):431-5.
- 55. Ervasti T, Knuuttila M, Pohjamo L, Haukipuro K. Relation between control of diabetes and gingival bleeding. J Periodontol. 1985 Mar;56(3):154-7.
- Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. Diabetes and periodontal disease: a case-control study. J Periodontol. 2005 Mar;76(3):418-25.
- 57. Taylor GW. The effects of periodontal treatment on diabetes. J Am Dent Assoc. 2003 Oct;134 Spec No:41S-8S.
- 58. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Ann Periodontol. 2001 Dec;6(1):99-112.
- Taylor GW. Periodontal treatment and its effects on glycemic control: a review of the evidence. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Mar;87(3):311-6.

- 60. Iacopino AM. Periodontitis and diabetes interrelationships: role of inflammation. Ann Periodontol. 2001 Dec;6(1):125-37.
- Heitz-Mayfield LJ. Disease progression: identification of highrisk groups and individuals for periodontitis. J Clin Periodontol. 2005;32 Suppl 6:196-209.
- 62. Almas K, Al-Qahtani M, Al-Yami M, Khan N. The relationship between periodontal disease and blood glucose level among type II diabetic patients. J Contemp Dent Pract. 2001 Nov 15;2(4):18-25.
- 63. D'Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D *et al.* Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res. 2004 Feb;83(2):156-60.
- 64. Mealey BL, Ocampo GL. Diabetes *mellitus* and periodontal disease. Periodontol 2000. 2007;44:127-53.
- 65. Faria-Almeida R, Navarro A, Bascones A. Clinical and metabolic changes after conventional treatment of type 2 diabetic patients with chronic periodontitis. J Periodontol. 2006 Apr;77(4):591-8.
- 66. Llambes F, Silvestre FJ, Hernandez-Mijares A, Guiha R, Caffesse R. Effect of non-surgical periodontal treatment with or without doxycycline on the periodontium of type 1 diabetic patients. J Clin Periodontol. 2005 Aug;32(8):915-20.
- 67. Novaes Jr AB, Pereira AL, de Moraes N, Novaes AB. Manifestations of insulin-dependent diabetes *mellitus* in the periodontium of young Brazilian patients. J Periodontol. 1991 Feb;62(2):116-22.
- 68. Novaes Jr AB, Silva MA, Batista Junior EL, dos Anjos BA, Novaes AB, Pereira AL. Manifestations of insulin-dependent diabetes *mellitus* in the periodontium of young Brazilian patients. A 10-year follow-up study. J Periodontol. 1997 Apr;68(4):328-34.
- 69. Novaes Jr AB, Gonzalez Gutierrez F, Grisi MF, Novaes AB. Periodontal disease progression in type II non-insulin-dependent diabetes *mellitus* patients (NIDDM). Part II Microbiological analysis using the BANA test. Braz Dent J. 1997;8(1):27-33.
- 70. Martorelli de Lima AF, Cury CC, Palioto DB, Duro AM, da Silva RC, Wolff LF. Therapy with adjunctive doxycycline local delivery in patients with type 1 diabetes *mellitus* and periodontitis. J Clin Periodontol. 2004 Aug;31(8):648-53.
- 71. Souza C, Saba-Chujfi E, Magalhães J. Efeito do tratamento periodontal na hemoglobina glicada de diabéticos não insulino-dependentes. RGO. 2006;54(2):134-8.
- Drumond-Santana T, Costa FO, Zenobio EG, Soares RV, Santana TD. [Impact of periodontal disease on quality of life for dentate diabetics] [Article in Portuguese]. Cad Saude Publica. 2007 Mar;23(3):637-44.
- 73. O'Connell PA, Taba M, Nomizo A, Foss Freitas MC, Suaid FA, Uyemura SA *et al*. Effects of periodontal therapy on glycemic control and inflammatory markers. J Periodontol. 2008 May;79(5):774-83.

- Souza CH, Saba-Chujfi E, Magalhães JC. Efeito do tratamento periodontal na hemoglobina glicada de diabéticos não insulinodependentes. RGO. 2006;54(2):134-8.
- 75. Didilescu AC, Skaug N, Marica C, Didilescu C. Respiratory pathogens in dental plaque of hospitalized patients with chronic lung diseases. Clin Oral Investig. 2005 Sep;9(3):141-7.
- 76. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999 Jul;70(7):793-802.
- 77. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. J Periodontol. 2006 Sep;77(9):1465-82.
- 78. Awano S, Ansai T, Takata Y, Soh I, Akifusa S, Hamasaki T *et al.* Oral health and mortality risk from pneumonia in the elderly. J Dent Res. 2008 Apr;87(4):334-9.

- 79. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. Ann Periodontol. 2003 Dec;8(1):54-69.
- 80. Fourrier F, Dubois D, Pronnier P, Herbecq P, Leroy O, Desmettre T *et al*. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. Crit Care Med. 2005 Aug;33(8):1728-35.
- 81. Oliveira L, Carneiro P, Fischer R, Tinoco E. A presença de patógenos respiratórios no biofilme bucal de pacientes com pneumonia nosocomial. Rev Bras Ter Intens. 2007;19(4):428-33.