Relationship between periodontitis and subclinical risk indicators for chronic non-communicable diseases

Abstract: In view of the epidemiological relevance of periodontal disease and chronic noncommunicable diseases, the study aimed to evaluate the relationship between them through subclinical indicators of systemic risk in a population group with healthy habits, including alcohol and tobacco abstinence. A complete periodontal examination of six sites per tooth was performed in a sample of 420 participants from the Advento study (Sao Paulo), submitted to anthropometric and laboratory evaluation. Periodontitis was defined and classified based on the Community Periodontal Index score 3 (periodontal pocket = 4–5 mm) and score 4 (periodontal pocket ≥ 6 mm). The prevalence of mild/moderate and severe periodontitis was 20% and 8.2%, respectively. Both categories of periodontal disease had significantly higher levels of triglycerides, C-reactive protein, calcium score, and calcium percentile, whereas blood glucose after tolerance test was significantly higher among people with severe periodontitis and HDL-c levels were lower (p < 0.05). Young adults with severe periodontitis had significantly higher prevalence of obesity, pre-diabetes, hypertension, and metabolic syndrome. Besides these conditions, the older adults with severe periodontitis had significantly higher prevalence of dyslipidemia and subclinical atherosclerosis. The group with periodontitis had also a higher coronary heart disease risk based on the PROCAM score (p < 0.05). The results indicated associations of periodontitis with several systemic indicators for chronic noncommunicable diseases, and highlighted the need for multiprofessional measures in the whole care of patients.

Keywords: Periodontitis; Periodontal Diseases; Cardiovascular Diseases; Non-communicable Diseases; Oral Health.

Introduction

Chronic periodontitis is an inflammatory condition that involves a complex relationship between bacteria on the dental surface and in the gingival sulcus combined with the inflammatory response of the host, which results in the irreversible destruction of the supporting tissues of the teeth, leading to tooth loss as the final outcome. The immune response induced by periodontal disease is associated with an increase...
in inflammatory markers that are found in common chronic systemic diseases and can be verified by subclinical conditions.\(^2\)

Physiopathological mechanisms related to local and systemic inflammation have been indicated to explain the strong association between periodontitis and diabetes.\(^3,4\) Scientific evidence on the link between the two conditions support the recent consensus of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology for physicians, oral healthcare professionals, and patients.\(^5\)

An association between periodontitis and hyperlipidemia has also been described and there seems to be an intensification in the periodontal inflammation with the increase of inflammatory cytokines in the plasma and gingival fluid related to a change in the lipid metabolism.\(^6\) An association between overweight/obesity and periodontitis has been shown\(^7\) and this interaction can increase the risk of cardiovascular events.\(^8\) Due to biological mechanisms that remain unclear, severe periodontitis has also been associated with arterial hypertension\(^9\) and there is evidence that metabolic syndrome is associated with an increase in periodontal inflammation and alveolar bone loss.\(^10\)

Systematic reviews have confirmed the evidence of the association between chronic periodontitis and cardiovascular risk,\(^11,12,13\) which was sustained by studies from the American Heart Association.\(^14\) Several physiopathological mechanisms have been implicated in this relationship, the key point of which is systemic inflammation.\(^15,16\)

Given the epidemiological importance of both periodontitis and chronic non-communicable diseases (CNCDs), particularly cardiovascular diseases, and their relationship with living habits, the study of these diseases in population subgroups is important. The aim of the present study was to evaluate the association between clinical periodontal variables and subclinical indicators of systemic disease risk, particularly markers of cardiovascular disease, in a subgroup of the population characterized by healthy habits, including alcohol and tobacco abstinence.

**Methods**

This cross-sectional study was conducted with a convenience sample of 420 participants from the major ADVENTO study — Analysis of Diet and Lifestyle for Cardiovascular Prevention in Seventh-Day Adventists. Participants were 35 to 74 years of age and were members of several Adventist churches in the metropolitan region of Sao Paulo, Brazil, as well as eight other municipalities in the state. All participants had reported their sociodemographic condition and dietary habits and they had been submitted to clinical examination, biological samples' collection, and other complementary tests.

The invitation to participate in an oral assessment was made by telephone and considered volunteers who had been included in the chronogram of examinations in the Advento study in the previous six months and had at least four natural teeth (not including third molars). Individuals that had been submitted to periodontal treatment in the previous six months and those who had used antibiotics in the previous 30 days were excluded from the study. Based on these criteria, among the 586 eligible volunteers, those who consented to participate and appeared for the oral examination were included in this study (n = 420).

This study received approval from the Human Research Ethics Committee of the Menino Jesus Municipal Hospital, Sao Paulo (certificate number: 1.177.873), and all participants signed a statement of informed consent.

**Collection of periodontal clinical data**

The periodontal examinations were performed by four examiners who had undergone training and calibration exercises. The agreement level for reproducibility of periodontal parameters was verified using Kappa test, which ranged from 0.68 to 0.86. A complete periodontal examination (three buccal sites and three lingual sites from all teeth) was performed using a standard millimeter probe (WHO 0.5-mm ballpoint model) and mouth mirror. The following periodontal variables were recorded: probing depth of sulcus/pocket (PD), defined as the distance between the free gingival margin and base of the sulcus/pocket in millimeters; clinical
attachment loss (CAL), defined as the distance between the cementoenamel junction and base of the sulcus/pocket in millimeters; bleeding on probing (BOP), checked approximately 10 seconds after probing; and visible plaque, with no use of any disclosing agent.

**Collection of systemic clinical data**

The following clinical data were extracted from the databank of the Advento study: weight (measured using a digital bioimpedance scale), height (measured using a fixed stadiometer), body mass index (BMI; calculated by the ratio of weight in kilograms and the square of height in meters), waist circumference (measured at the largest abdominal perimeter, following the recommendations of the World Health Organization), arterial pressure (mean of three measurements using a standard sphygmomanometer: Omron HEM 705CPINT, Omron Health Care, Lake Forest, USA); plasma glucose level (hexokinase method - ADVIA Chemistry; Siemens, Deerfield, USA); oral glucose tolerance test (two hours after ingesting 75 g of glucose); glycated hemoglobin (HbA1c; determined using high-performance liquid chromatography); triglycerides, total cholesterol, and HDL-c (determined using enzymatic method), LDL-c (calculated using the Friedewald equation), ultrasensitive C-reactive protein (immunochemical method - Dade Behring, Siemens, USA), calcium score (obtained by angiotomography of coronary arteries), and thickness of the intimal layer of the carotid (determined by ultrasound).

**Study variables**

For the characterization of the sample, sociodemographic variables (sex, age group, race, schooling level, household income) and some behavioral variables like dietary habits and physical activity practice were used.

The periodontal clinical variables evaluated were a) tooth loss (total number of missing teeth, excluding third molars); b) probing depth of sulcus/pocket, quantified as the number of teeth/sites with < 4 mm, 4–5 mm, and ≥ 6 mm; c) clinical attachment loss, quantified as the number of teeth/sites with < 4 mm, 4–5 mm, and ≥ 6 mm; d) bleeding on probing, given by the percentage of teeth with gingival bleeding; e) visible plaque, given by the percentage of teeth with dental biofilm; f) periodontitis, defined and classified on the basis of the Community Periodontal Index score 3 (periodontal pocket = 4–5 mm) and score 4 (periodontal pocket ≥ 6 mm).

The anthropometric characteristics evaluated were BMI (< 18.5 kg/m² = underweight; 18.5–24.9 kg/m² = normal range; 25–29.9 kg/m² = overweight; and ≥ 30 kg/m² = obese) and waist circumference, which was considered increased when larger than 90 cm for men and 80 cm for women.

The clinical and laboratory signs of systemic impairment evaluated were a) fasting blood glucose (pre-diabetes: 100–125 mg/dL; diabetes: > 125 mg/dL); b) glucose tolerance test (reduced tolerance: 140–199 mg/dL; diabetes: 200 mg/dL); HbA1c (indicative of risk: 5.7–6.4%; high: 6.5%); c) dyslipidemia, verified by levels of total cholesterol (200 mg/dL), LDL-c (130 mg/dL), HDL-c (< 40 mg/dL), and triglycerides (> 150 mg/dL); d) ultrasensitive C-reactive protein > 1; e) systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg, indicative of hypertension; f) coronary calcium score (> 100 Agatston), calcium percentile (75%), and/or increase in thickness of carotids (> 0.65), indicative of subclinical atherosclerosis. For metabolic syndrome, the presence of at least three of the following components was considered: increased abdominal circumference (> 94 cm for men and > 80 cm for women), reduction in HDL-c levels (< 40 mg/dL for women and < 50 mg/dL for men), high triglyceride levels (150 mg/dL), blood pressure (≥130 x 85 mmHg) or fasting blood glucose (≥ 100 mg/dL). All reference values were used based on established guidelines.

Cardiovascular risk was also determined based on the Prospective Cardiovascular Münster (PROCAM) score, which is an indicator of risk for acute coronary events that is calculated by the weighted values of age, triglycerides, HDL-c, LDL-c, smoking, systemic blood pressure, diabetes, and a family history of acute myocardial infarction prior to 60 years of age. A score of 0–44 points indicates mild risk (0–9.9%), 45–53 points indicate moderate risk (10–19.9%), and ≥ 54 points indicate high risk (≥ 20%).
Data analysis

Initially, a descriptive analysis of the sample was made according to sociodemographic characteristics and prevalence of periodontitis. The participants were allocated into three groups depending on the absence of periodontitis, presence of mild/moderate, or severe periodontitis, that is periodontal depth < 4 mm, 4–5 mm, and ≥ 6 mm, respectively, according to the proposed case definition. Mean and standard deviation values of the periodontal clinical variables and levels of systemic risk markers were calculated for the total sample as well as for the groups with and without periodontitis. The Mann-Whitney test was used for the comparison of periodontal variables between groups and the Student’s t-test was used for the comparison of mean levels of systemic markers between groups. Prevalence of CNCDs was calculated for each group according to two age groups (34–55 and ≥ 55 years). Pearson’s chi-square test and Fisher’s exact test were used for the comparisons between the prevalence of periodontitis and CNCDs as well as between periodontitis and coronary disease risk. Adjusted residuals were calculated to verify differences between categories. For all analyses the level of significance was set to 5% (p < 0.05).

The statistical power of the tests was estimated on the basis of the prevalence of periodontitis and CNCDs, as well as the mean levels of some risk indicators in both groups. Considering a = 0.05, the power of the test ranged from 82% to 97%.

The analyses were performed using the Statistical Package for the Social Sciences (SPSS) v.22 (IBM®), and OpenEpi (Open Source Epidemiologic Statistics for Public Health, version 3.01).

Results

Among the 420 participants of the study, there was a predominance of females, mean age 53.5 ± 10.5 years, white race, university level education and household income <4 Brazilian monthly minimum wage (Table 1). Regarding living habits, the sample had no smokers or users of alcohol, 58.8% followed a vegetarian diet, and 56.4% practiced physical activity at least three times a week (data not presented in table).

The total prevalence of periodontitis was 28.2% (n = 120), of which 8.2% had severe periodontitis (Table 1). In the comparative analysis of periodontal parameters for the groups with (mild/moderate and severe) and without periodontitis, progressively higher levels were observed for all parameters evaluated (p < 0.001) (Table 2), but low severity/extent of the disease was found, as only 1.2% of the teeth had clinical attachment loss ≥ 6 mm.

In general, the mean levels of risk markers for CNCDs were little affected in comparison to established reference values. In the comparative analysis between the groups with and without periodontitis, however, both categories of periodontal disease had significantly higher levels of triglycerides, C-reactive protein,
calcium score, and calcium percentile, whereas blood glucose after the tolerance test was significantly higher among severe periodontitis, and HDL-c levels were significantly altered (Table 3).
The prevalence of CNCDs was higher among individuals with periodontitis. In the age groups evaluation, significant differences were observed especially for the severe periodontitis level in both age groups. Young adults had significantly higher prevalence of obesity, pre-diabetes, hypertension, and metabolic syndrome. The older group with severe periodontitis had significantly higher prevalence of obesity, dyslipidemia, pre-diabetes, hypertension, subclinical atherosclerosis, and metabolic syndrome, although individuals with mild/moderate periodontitis also had significantly higher levels of dyslipidemia, subclinical atherosclerosis, and metabolic syndrome (Table 4).

The risk of coronary events according to the PROCAM score was also higher among individuals with periodontitis, mainly those with severe condition (Table 5).

**Discussion**

A lower frequency of periodontitis was found in the studied population group in comparison to national surveys and researches conducted in other countries. The periodontal clinical variables evaluated revealed a low severity and extent of periodontitis among the participants, which is probably due to the sociodemographic and behavioral characteristics of the sample. With a higher level of schooling than that of the general population of the state of Sao Paulo, the participants in the present study possibly have greater access to oral care. Moreover, studies report that the practice of healthy habits by Adventists contributes to the low occurrence of CNCDs in this population group, such as abstinence from alcohol and tobacco, the practice of physical activity, and a healthy diet, which are the
main recommended behaviors to reduce the risk of morbidity and mortality due to chronic diseases. Despite the low frequency of periodontitis and CNCDs in the sample, significant differences were found in several markers of systemic risk between the individuals with and without periodontitis.

BMI was significantly higher among the participants with periodontitis. This was in agreement with findings described in systematic reviews,\(^7,29\) which confirmed an association between obesity and periodontitis. Researchers state that obesity may alter the host response to antigens derived from bacterial plaque and cause inflammatory response disorders, thereby exerting an influence on the course of periodontitis.\(^30\) A longitudinal study conducted in Japan involving more than 3500 participants in a five-year follow up reports a 36.8 and 28.3% incidence of periodontitis among obese men and women, respectively.\(^31\) A cohort study involving American men reports a 41–72% increase in the risk ratio for the progression of periodontitis in the group with obesity.\(^32\)

The systemic inflammation produced by chronic periodontitis is also the basis for the association between periodontitis and an increase in plasma levels of LDL-cholesterol and triglycerides as well as reduction in levels of HDL-cholesterol.\(^33\) The significant association with triglycerides and HDL-c was confirmed, but the association with LDL-c was not observed in the present study.

The prevalence of diabetes mellitus in the overall sample was 5.4%, which, together with the low severity of periodontitis, likely explains the non-significant association between these diseases in the population studied, despite the evidence of this association in the literature.\(^3,4\) Although mean fasting glucose and glycated hemoglobin were similar between the individuals with and without periodontitis, the mean glucose level after glucose overload was significantly higher in the group with severe periodontitis (\(p <0.05\)). Considering the reference values for pre-diabetes (\(\geq 100\ \text{mg/dL}\)), this condition was significantly more frequent among the individuals with severe periodontitis.

The mean plasma levels of C-reactive protein were low among the participants in the present study, but significantly higher among those with periodontitis, which indicates the contribution of the disease to the increase in markers of systemic inflammation, as confirmed in a meta-analysis.\(^34\) However, there is evidence that inflammatory markers increase considerably in patients with periodontitis and other systemic diseases, particularly diabetes.\(^2\) A study involving an indigenous population in the United States found that the increase in inflammatory markers was related to the severity of periodontitis.\(^35\)

The occurrence and severity of periodontitis and systemic comorbidities tend to increase with increasing age,\(^3\) which makes this variable a confounding factor in studies of association between the two conditions. In this study, higher prevalence of periodontitis and some of the CNCDs in the \(\geq 55\) years age group was also observed. When prevalence of CNCDs was analyzed by age group, it was higher in individuals with periodontal disease in both age groups, indicating an independent association. However, most of the statistically significant differences were observed only for the severe periodontitis group, which was also found by other investigations.\(^9\)

The higher prevalence of metabolic syndrome among individuals with periodontitis, mainly in older individuals, is in agreement with the conclusions of a systematic review about the relationship between the two conditions.\(^36\) A Japanese study identified a significantly increasing risk of periodontitis with the increase in the number of components of metabolic syndrome, as participants with more than three components had an approximately two-fold higher risk of having periodontitis.\(^37\)

A significant association was found between periodontitis and the mean levels of subclinical variables specific to atheromatous disease, confirming findings reported in several studies.\(^12,13,38\) The biological plausibility for this relationship is based on a direct mechanism (conduction of bacterial components through the bloodstream to endothelial cells) and an indirect mechanism (the systemic inflammatory process).\(^14,15\) It is possible that an effective bacterial plaque control could modify both conditions. Although systematic reviews and meta-analysis studies offer evidence that periodontal treatment decreases systemic markers in the short term,\(^39,40\) its role in the control
of CNCDs requires further investigation, mainly prospective studies.

Based on the PROCAM scores, the majority of participants in the present study had a low risk of coronary disease events. This assessment method considers multiple cardiovascular risk factors, all of which had low frequencies in this population sample. In the presence of periodontitis, however, the number of individuals with moderate to severe risk increased significantly.

The study adds to the existing knowledge on periodontitis in a population sample without some important confounding factors as tobacco and alcohol, and low risk for CNCDs. Even though, the results indicated associations of periodontitis with several systemic indicators. The use of a complete periodontal examination also contributed to the reliability of the periodontal variables evaluated, but the low severity/extent of periodontitis in the sample was a limiting factor for more associations to be observed.

Although this study did not use a probabilistic population sample, the statistical power of the tests for the comparisons between the groups with and without periodontitis were estimated, and values above 80% (with $\alpha = 0.05$) were found for most of the indicators described in the study. Therefore, the sample size was statistically sufficient to confirm the associations found between the studied variables.

The main limitation of the study was its cross-sectional design, which did not allow inferences of cause and effect between the variables. Longitudinal studies are needed to clarify the temporal relationship between periodontitis and chronic systemic diseases.

The associations observed in the present study highlight the need for a whole care of the patient, incorporating measures of prevention and control of periodontitis and CNCDs jointly. This requires a multiprofessional vision from physicians and dentists, together with due support and incentive from the federal, state, and municipality Public Health Departments.

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