Periodontitis Is Associated With Risk of Conventional Stent Restenosis: Pilot Case-Control Study

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Objectives: Percutaneous coronary angioplasty with stent implantation has been established as the main form of treatment of atherosclerosis. However, 16 to 44% of patients may evolve with stent restenosis. Periodontitis is an inflammatory condition associated with bacterial infection, that may lead to periodontal tissue destruction and tooth loss. This study aimed to evaluate the association between stent restenosis and periodontitis.

Materials and Methods: Coronary angiography exams presenting stent imaging with and without restenosis were analyzed. Patients meeting the inclusion and exclusion criteria were selected and allocated in 2 groups: case (restenosis) and control (without restenosis). We evaluated if systemic and periodontal variables were predictors of restenosis (primary outcome) using a multivariable stepwise logistic regression. Additionally, we compared clinical and periodontal conditions between the control and case groups (secondary outcomes) using Chi-square test and ANOVA test.

Results: Data from 49 patients (case n = 15; control n = 34) were analyzed. The results showed that stages III and IV periodontitis and lack of physical activity were significant predictors of stent restenosis (OR 5.82 and 5.98, respectively). Comparisons regarding the diagnosis of periodontal conditions between control and case groups did not present significant differences in the incidence of periodontitis and alveolar bone loss.

Conclusion: Stages III and IV periodontitis increased the incidence of stent restenosis. These findings suggest that advanced stages of periodontal disease might lead to the occurrence of negative outcomes after coronary angioplasty with stent placement.

Keywords: atherosclerosis, cardiovascular disease, stent restenosis, periodontitis, inflammation

INTRODUCTION

Atherosclerosis is a progressive fibroproliferative chronic systemic inflammatory process that affects the intima layer of the middle and large vessels, culminating in the formation of atherosclerotic plaque. Its etiology is multifactorial with dyslipidemia, systemic arterial hypertension, diabetes, smoking, and the genetic hereditary component as the main risk factors for the development of atherosclerosis and coronary artery disease (CAD) (1). These factors increase the permeability of the intima to plasma lipoproteins in the subendothelial space, which when...
oxidized by macrophages become foam cells that are the main component of fatty striae. These immunogenic components stimulate the migration and proliferation of smooth muscle cells from the middle to the intimal layer to produce extracellular matrix that will form part of the fibrous cap of the atherosclerotic plaque (2, 3).

In the last three decades, interventional cardiology has established itself as the main form of myocardial revascularization in the treatment of coronary artery disease. Despite advances in procedural techniques and materials, about 16 to 44% of patients eventually evolve into an event called stent restenosis (4, 5). Restenosis is the onset of new obstruction >50% in the segment previously treated with stent (6) and occurs between the second and sixth month (7, 8) up to the 8 months after implantation of a conventional stent (9). Clinically it may manifest with the return of signs and/or symptoms of myocardial ischemia, associated with angiographic confirmation of new obstruction of the stent. This is the most commonly used concept and is based on vascular physiology studies where from this degree of obstruction we can observe impairment of the coronary flow reserve (10, 11).

Periodontal diseases are inflammatory diseases associated with bacterial infection (12). The initial clinical presentation is gingivitis, which perpetuates the infectious-inflammatory process over the years. In susceptible individuals, gingivitis may be modified by multiple host response genes and, in combination with lifestyle and environmental factors, can culminate in the destructive form of periodontal disease, namely periodontitis (13). Periodontitis is considered a worldwide health problem (14) that over the years has demanded global health policies and programs that can assist in its prevention and treatment (15). It is a highly prevalent disease, with its moderate form affecting 50% and a severe form affecting 5 to 15% of the global adult population (16). Since it was suggested that periodontitis could decrease life expectancy (17), much has been researched on the influence of this disease on quality of life and systemic health of individuals, including cardiovascular disease (18, 19), pregnancy complications (20), neurological diseases (21, 22) and diabetes (23, 24).

Host-microbe interaction in the periodontium can initiate or even aggravate atherosclerotic processes through the activation of innate immunity, bacteremia, and direct involvement of cytokines and inflammatory proteins of oral microbiota (25–27). The association between atherosclerosis and periodontal diseases has already been corroborated in both acute coronary disease and acute myocardial infarction (28, 29), indicating the presence of periodontal diseases as a factor of clinical decompensation of coronary atherosclerosis (30). Despite this, we do not know whether the chronic inflammatory process triggered by periodontal diseases can interfere with the long-term outcome of patients undergoing coronary angioplasty with a consequent episode of restenosis. Whether periodontal diseases, due to their chronic systemic inflammatory state, would be contributing to an increase in restenosis rates of conventional stents is not defined in the literature. Besides that, it is not routine in the clinical practice of interventional cardiologists to consider the oral health status before performing surgical coronary angioplasty. To date, there are no studies evaluating the possible relationship between conventional stent restenosis and periodontal diseases. Therefore, the aim of the present study is to evaluate the association between stent restenosis and periodontitis.

**MATERIALS AND METHODS**

**Experimental Design**

This was an observational, retrospective, case-control, population-based study designed to evaluate the association between conventional stent restenosis and periodontal diseases. This study was approved by the human subjects ethics board of UNESP (CAAE: 60607916.9.0000.0077) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

**Study Population and Inclusion and Exclusion Criteria**

Data from coronary angiography examinations performed at Pio XII Hospital (São José dos Campos, SP, Brazil) from January 4th, 2016 to February 28th, 2018 were analyzed. The study population consisted of patients who underwent coronary angiography at the referred hospital during the established period. Detailed medical records were obtained. Volunteers who fulfilled the inclusion criteria were invited to participate in the study. Inclusion criteria were prior coronary angioplasty with conventional stent implantation; aged ≥40. Exclusion criteria were: edentulism; diabetes mellitus with glycated hemoglobin (HbA1c) levels >7.0%; pharmacological stent implantation; restenosis in stents implanted over the previous 2 years. Informed consent was provided by each volunteer after a thorough explanation of the nature, risks, and benefits of the clinical investigations.

**Allocation**

Patients were allocated into two groups according to the criteria below:

- **Case Group**: Patients who underwent coronary angiography examination of stent with restenosis, whose stent implantation occurred within 2 years.
- **Control Group**: Patients who presented coronary angiography with stent image without restenosis regardless of the implantation period.

**Cardiovascular Evaluation**

For the screening and selection of candidates for both study groups, the reports previously made by interventional cardiologists at the Pio XII Hospital were used. For the definition of angiographic restenosis in coronary angiography reports, the Interventional Cardiology societies criteria were used. These criteria are based on studies of vascular physiology, in which the impairment of coronary flow reserve can be observed considering the degree of obstruction, and consists of the presence of >70% from the lesion in the stent-treated segment (within the stent and within 5 mm beyond the stent) (4). Restenosis was classified using the Guideline Reference...
for Percutaneous Coronary Intervention by the American Heart Association (31, 32). This classification is based on the geographic distribution of intimal hyperplasia in reference to the implanted stent. Peripheral blood was collected to evaluate HbA1c levels and lipid profile. Anthropometric measures including weight and height were recorded. Body mass index (BMI) was calculated as the weight divided by the square of height (kg/m²).
Periodontal Evaluation

All patients were scheduled for a periodontal evaluation at the Department of Periodontology at the Institute of Science and Technology, São Paulo State University–Unesp (São José dos Campos, SP, Brazil). In this session, a thorough periodontal examination was performed by two trained and calibrated periodontists (CFA and NCCS). The examiners participated in a calibration exercise in which PD and CAL of 10 patients were measured twice within a 24-h interval. These measurements were subjected to an intraclass correction test. The agreement for the variables was >90%.

The evaluated parameters were: (1) Probing depth (PD); (2) Clinical attachment level (CAL); (3) Gingival recession (GR); (4) Bleeding on probing (BoP); (5) Supragingival biofilm accumulation (PI) (33). All clinical measures were assessed using a manual probe (University of North Carolina Probe PCPUNC-BR 15, Hu-Friedy).

The presence or absence of periodontal diseases, the diagnosis, and classification of the diseases, the quantification of the extent and severity of the diseases, and the estimated duration of the diseases were determined (34, 35).

Alveolar Bone Loss Analysis

Panoramic radiographs were obtained by a radiologist and evaluated by a trained examiner. The examiner was blind to the status of each group of participants. The severity of alveolar bone loss was measured as a percentage of bone loss in the interproximal sites of each tooth (36). Each site was assigned a score from 1 through 4 according to alveolar bone (1: 0 to 24%; 2: 25 to 49%; 3: 50 to 74%; 4: 75 to 100%). We defined a mean bone loss score ≤2 as mild to moderate periodontal bone loss and score >2 as severe alveolar bone loss.

Statistical Analysis

Data were recorded as mean and standard deviation, median with quartiles or percentage according to the different variables analyzed. Normal distribution was tested by Shapiro-Wilk. For the comparison of quantitative variables, the mean and standard deviation were used. For percentages, Chi-square test ($\chi^2$) was used for qualitative variables. ANOVA test was used to compare groups for mean age and BMI. A multivariable stepwise logistic regression was performed to verify if there is a relationship between restenosis (dependent variable) and independent variables. All data analyses were performed using IBM SPSS, Minitab, and Excel Office. A significance level of 0.05 (5%) was defined for this study, and all confidence intervals throughout the study were constructed with 95% statistical confidence.

RESULTS

A total of 1,685 coronary angiography examinations performed during the period from January 4th, 2016 to February 28th, 2018 were analyzed. At the end of volunteer selection, 61 patients were eligible. Of these, 49 patients accepted to participate in the study and underwent periodontal evaluation (Figure 1). Table 1 presents sociodemographic characteristics of the control group ($n = 34$) and the case group ($n = 15$). There was no statistical difference between most of the variables analyzed, except for previous smoking history (Table 1).

A binary logistic regression was performed to determine if demographic, systemic, and periodontal variables were predictors of restenosis. “Stages III and IV periodontitis” and “No regular physical activity” were significant predictors when restenosis was a dependent outcome variable (OR 5.82 and 5.98, respectively). Other stages of periodontitis, controlled diabetes, obesity, current smoking, age, gender, number of teeth, and severe alveolar bone loss were not statistically significant (Table 2).

We evaluated the groups according to the frequency of different diagnoses and classifications of periodontal diseases. There was a higher percentage of gingivitis and Stages I and II periodontitis when the control group was compared to the case group. On the other hand, Stages III and IV periodontitis presented higher percentages in the case group than...
DISCUSSION

Stages III and IV periodontitis increased the risk of chances for stent restenosis. These results suggest that periodontitis is an important factor to be considered in the clinical cardiological evaluation routine before and after coronary angioplasty interventions.

Growing evidence suggests a link between periodontitis and cardiovascular disease, especially regarding the risk factors shared between these conditions. In this study population, all patients presented atherosclerosis and had already received conventional stent implantation treatment. Thus, the high prevalence of periodontal disease found in our study population is justified, confirming the same results found in a previous study (37). Besides having common risk factors, a mechanism linking the two diseases has been elucidated in a recent longitudinal study. Van Dyke et al. (38) evaluated the F-fluorodeoxyglucose positron emission tomography/computed tomography of 304 individuals, quantifying periodontal and arterial inflammation. The authors showed that periodontitis is associated with arterial inflammation and that periodontitis predicted subsequent major adverse cardiovascular events (38). These findings corroborate the main results of our study, which underscore the hypothesis that periodontitis could influence the occurrence and treatment of CAD.

In addition to periodontitis, we observed that physical activity was associated with a lower restenosis rate. It is well-documented that physical activity helps to control many cardiovascular risk factors (39). In patients with stable CAD, the measurement of C-reactive protein (CRP) may be useful as an independent marker to assess the likelihood of recurrent events, including death, myocardial infarction, or stent restenosis (40), and physical activity in this type of patient is a factor that in itself reduces inflammatory markers such as CRP (41). Thus, the regular practice of physical activity could contribute as a protective factor for restenosis by reducing inflammation.

Risk factors associated with the development of periodontitis comprise local, systemic, and genetic factors, including smoking, diabetes, and possibly obesity (42). Contributions for cardiovascular disease are also multifactorial, which encompass ethnicity, age, family history of CAD, dyslipidemia, hypertension, smoking, obesity, and diabetes. Hence, there are many potentially important confounders for the association between periodontitis and atherosclerotic disease (19). The presence of confounding factors is a relevant limitation aspect of several observational studies (43). In the present study, we assessed if there was an association between risk factors shared by the two diseases and restenosis, but no significant results were observed.

Although diabetes mellitus is considered a risk factor that increases the likelihood of restenosis, patients with controlled diabetes (HbA1c <7.0%) do not present high restenosis rates after conventional stent implantation (44, 45). For this reason, patients with controlled diabetes were included in this study. As expected, controlled diabetes was not associated with an increased risk for restenosis in this study. One of the exclusion criteria was the presence of pharmacological stents, for the use of pharmacological stents alters the physiology of the stent endothelialization phenomenon by inhibiting the cell cycle in different stages, thus delaying the stent phenomenon of cell migration and proliferation (46). Despite the benefits of pharmacological stents observed in large randomized controlled clinical trials, the use of drug-eluting stenting implies longer dual anti-aggregation therapy, thereby increasing the risk of bleeding (47) and decreasing the cost-effectiveness of the procedure (48).

The findings of this study demonstrate that periodontitis is an important predictor of stent restenosis. Nevertheless, this result should be interpreted with caution. The main limitation of this study is the small sample size. Of the 1,685 coronary angiography examinations, 1,402 patients did not present stent imaging, which resulted in 283 possible volunteers for the study. Then, volunteer selection was particularly difficult for the exclusion criterion “edentulism,” which was highly prevalent in the analyzed population. Possibly, most individuals presenting edentulism had lost their teeth due to periodontitis previously to this study. Thus, the number of observed events (restenosis) was modest (15 patients). The main strength of the present study is that periodontal diseases were evaluated as possible predictors for stent restenosis for the first time. This hypothesis was mechanistically plausible and demonstrated to be clinically relevant in this population. Additionally, evaluating the association between periodontal diseases and negative outcomes after cardiological interventions help to increase the awareness of the relevance of periodontal evaluation and treatment in patients with atherosclerosis.

Stages III and IV periodontitis is associated with the incidence of stent restenosis. These findings suggest that advanced stages of periodontal disease might lead to the occurrence of negative outcomes after coronary angioplasty with stent placement.

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**TABLE 3** | Incidence of periodontal diseases for the control and case groups.

| Variables            | Control group | Case group | P-value |
|----------------------|---------------|------------|---------|
|                      | n  | %  | n  | %  |         |
| Gingivitis           | 8  | 23.5 | 2  | 13.3 | 0.414   |
| Stage I periodontitis| 5  | 14.7 | 1  | 6.7  | 0.466   |
| Stage II periodontitis| 10 | 29.5 | 3  | 20.0 | 0.492   |
| Stage III periodontitis| 5  | 14.7 | 5  | 33.3 | 0.111   |
| Stage IV periodontitis| 6  | 17.6 | 4  | 26.7 | 0.470   |

Chi-square test ($\chi^2$) was used to compare the frequency of periodontal diseases between groups ($p < 0.05$).
DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human subjects ethics board–UNESP. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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