

## Periodontal Disease as a Potential Risk Factor for Acute Coronary Syndromes

Renata Accarini and Moacir Fernandes de Godoy

Hospital de Base da Fundação Faculdade Regional de Medicina (FUNFARME), Faculdade de Medicina de São José do Rio Preto (FAMERP), Curso de Pós-Graduação em Ciências da Saúde da FAMERP, São José do Rio Preto, SP, Brazil

**Objective:** To investigate whether there is a relationship between active periodontal disease (PD) and acute coronary syndromes (ACS).

**Methods:** Three hundred and sixty-one patients (57,3% male), ages ranging from 27 to 89 (mean  $\pm$  DP = 60.5  $\pm$  12.2), were admitted to the Intensive Care Unit of a Teaching Hospital with symptoms and complementary examinations consistent with acute coronary syndrome. All the patients had a complete periodontal examination in the ICU setting, and 325 (90.9%) underwent coronary angiography for diagnostic confirmation and/or treatment planning. Periodontal examination included evaluation of all the teeth in the oral cavity and the following parameters: probing depth, clinical attachment level, plaque index, and gingival index.

**Results:** Of the 325 patients, 91 (28%) had coronary arteries free of obstruction or with mild obstructions ( $\leq$  50% diameter stenosis), and the remaining 72% had severe obstructions. Fisher's exact test yielded a p value of 0.0245 with an odds ratio of 2.571 (95% CI 1.192 to 5.547), meaning that the group with ACS and significant obstructive coronary artery disease was 2.5-fold more likely to have active PD.

**Conclusion:** A significant association was found between active periodontal disease and severe obstructive coronary artery in patients with acute coronary syndrome, underscoring the importance of prevention and adequate treatment of periodontal disease, which should be considered as a potential risk factor in the etiology and instability of the atherosclerotic plaque.

**Key words:** Periodontal disease, acute coronary syndrome, obstructive coronary artery disease, coronary atherosclerosis, inflammation, risk factor.

In Western countries, cardiovascular disease (CVD) accounts for the majority of deaths, but the so-called classic risk factors do not explain 30% of them, particularly among young adults. Recently, the possible association between oral health (especially the extent and nature of periodontal disease) and cardiovascular diseases has been the focus of several epidemiological and laboratory studies. Although results suggest a positive association, controversies still remain, especially regarding the causal relationship and pathophysiological mechanisms that would explain this association.

Periodontal disease (PD) is moderate in 44% to 57% of adults, 10% of whom, in developed countries, have advanced periodontitis<sup>1</sup>, most often asymptomatic. Periodontal disease is caused by anaerobic and Gram-negative bacterial colonization, such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*.

A number of cohort studies have identified PD as an important predictor of future cardiovascular events<sup>2-7</sup>. More

recently, other studies focused on demonstrating that genetic factors influence biological processes involved in both diseases, representing a potential mechanism that may link PD to CVD<sup>8-13</sup>.

To establish a causal association, several studies have detected the presence of periodontopathogens in atherosclerotic plaques<sup>14-16</sup>.

Since it has been proved that bacteremias may be asymptomatic and occur on a routine basis, some investigators sought a model for the pathophysiological relationship in which poor periodontal health would affect systemic conditions. In this case, they found positive association between dental plaque and systemic neutrophil inflammatory response<sup>17</sup> and endotoxin release, both responses induced by mastication<sup>18</sup>.

Notably, studies along the same lines have demonstrated that both the presence of PD and its treatment affect cytokine production, especially acute phase proteins<sup>19-29</sup>.

As to the direct effect of these microorganisms present in the oral cavity on cardiac ischemic events, it was reported

Mailing Address: Moacir Fernandes de Godoy •

Rua Garabed Karabashian, 570 - 15070-600 - São José do Rio Preto, SP, Brazil

E-mail: moacirgodoy@cardiol.br

Manuscript received September 17, 2005; revised manuscript received January 30, 2006; accepted May 09, 2006.

that *S sanguis* and *P gingivalis* cause thrombus formation and platelet aggregation, in addition to ST-segment changes on ECG, which is a dose-dependent response, suggesting that they may trigger cardiac ischemic episodes<sup>30-32</sup>.

Considering this, the present study was designed to assess the possible association between active periodontal disease and the degree of obstruction in patients with acute coronary syndrome (ACS).

## Methods

Three hundred and sixty-one patients with acute coronary syndrome, that is, unstable angina or acute myocardial infarction (with or without ST-segment elevation) admitted to the Intensive Care Unit of a Teaching Hospital in the interior of São Paulo were evaluated. This diagnosis was based both on patients clinical condition and complementary examinations (electrocardiogram and enzyme measurement). Patients whose clinical condition precluded adequate oral examination, such as those with coagulopathies and those with history of or greater risk for infective endocarditis, were excluded. All the others agreed to participate in the study and signed an informed consent. The study received Institutional Ethics Committee approval (File No.5124/2001; Opinion No. 083/2001). Patients underwent specific odontological anamnesis and intraoral clinical examination by a single periodontist in the ICU during admission, in order to further clarify the condition suggestive of acute coronary failure.

The following parameters were used for PD classification:

- Clinical probing depth or pocket depth (CPD)<sup>33</sup>.
- Clinical attachment level (CAL)<sup>33</sup>.
- Bleeding index (BI)<sup>34</sup>.
- Plaque index (PI)<sup>35</sup>.

CAL and CPD were assessed using a standard manual probe calibrated in millimeters, in both arches, examining all the teeth on their surfaces: mesial buccal, buccal, distal buccal, mesial lingual, distal lingual, and lingual. Periodontal probing was performed moving the probe through these regions parallel to the long axis of the tooth at its free surfaces. All probing measurements were rounded to the nearest whole millimeter.

Periodontal disease was classified according to the following criteria: at least six teeth for assessment and more than 30% of sites whose CPD and/or CAL exceeded 5 mm or more than 30% of sites with CPD or CAL between 0 and 4 mm, but with  $\geq 50\%$  of bleeding on probing (BOP) at six sites per tooth: mesial buccal, mid-buccal, distal buccal, mesial lingual, mid-lingual, and distal lingual.

Of the patients with ACS, 207 (57.3%) were male. Ages ranged from 27 to 89, with mean  $\pm$  standard deviation and median of age 60.5  $\pm$  12.2 years and age 60, respectively. As for the number of teeth, 194 (53.7%) were edentulous (< 6 teeth) and 167 (46.3%) had between 6 and 28 teeth. A total of 2269 teeth were assessed, corresponding to 13,524 surfaces.

Statistical analysis was performed with Graph Pad Instat

3.00 Software using Fisher's exact test and odds ratio (OR), with 95% confidence interval (95% CI). Alpha error was set at 0.05, and p values  $\leq 0.05$  were considered significant.

## Results

Of the 167 patients who had at least six teeth for assessment, 154 (92.2%) underwent cardiac catheterization with coronary angiography during admission, so that the diagnostic of coronary event or risk stratification could be elucidated. In this group, the association between active periodontal disease and severe obstructive coronary disease was evaluated. Of these 154 patients, 49 failed to meet the diagnostic criteria for periodontal disease as established by the Method, but 105 patients did.

Among the 194 edentulous patients, 171 (88.1%) underwent cardiac catheterization during admission. Obviously, this group did not experience periodontal disease, simply because they had no teeth.

Table 1 shows the distribution of patients in each group.

The significant number of edentulous patients (53.7%) may be justified by the fact the hospital where data were collected receives subjects from several regions in the interior of São Paulo state, and many of them belong to lower socioeconomic classes; hence, they are more likely to have poorer oral conditions.

On the other hand, for this very reason, these edentulous patients would be "protected" against active periodontal disease, and according the hypothesis of the study, were expected to have an intermediate behavior between both groups. Thus, among the 49 patients free of periodontal disease and who underwent cardiac catheterization, 28 (57.1%) had severe obstructive coronary disease. Among the 171 edentulous patients who underwent cardiac catheterization, the rate of severe obstructive coronary disease was 73.7% (126 cases), while among the 105 with active periodontal disease, this rate was 76.2% (80 cases). Taking into account the existence of obstructive coronary disease of any degree, these values were 63.3%, 76.0%, and 80.9%, respectively.

Statistical analysis using Fisher's test yielded a p value of 0.0989 and odds ratio of 0.6311, with a 95% CI ranging from 0.3834 and 1.039 for absence of periodontal disease or edentulism when comparing groups with any degree of coronary disease versus absence of coronary disease (Tab. 2).

Also regarding the presence of active periodontal disease or edentulism, no significant difference was found when groups with coronary disease of any degree versus absence of coronary disease were compared, and Fisher's test showed a p value of 0.3726 with an odds ratio of 1.340 and a 95% CI from 0.735 to 2.444 (Tab. 3).

Statistical analysis using Fisher's exact test indicated a p value of 0.0245 (significant) and an odds ratio of 2.571 with a 95% CI ranging from 1.192 to 5.547 for the presence or absence of periodontal disease, when groups of patients with severe obstructive coronary disease ( $\geq 50\%$ ) versus no coronary artery disease were compared (Tab. 4). According to these data, patients with severe obstructive coronary disease are 2.5 times more likely to have periodontal disease than

## Original Article

those with normal coronaries. The inclusion of the subgroup with mild obstructive coronary disease (less than 50% of luminal stenosis) does not change the results, now with a *p* value of 0.0265 and an odds ratio of 2.468 with a 95% CI ranging from 1.156 to 5.267 for the presence or absence of periodontal disease when comparing groups of patients with any degree of coronary disease versus normal coronaries. The approximate 2.5-fold likelihood (odds) of concurrent active periodontal disease and any degree of coronary disease was maintained, compared with normal coronaries (Tab. 5).

### Discussion

One of the great difficulties in comparing different studies about this subject is the lack of a consistent and consensual classification for periodontal disease. Based on published data, it is difficult to reach a conclusion whether there is or not an association between PD and CVD.

We made a point of evaluating all teeth to prevent any bias in data collection. Additionally, our classification sought to aggregate all periodontal parameters simultaneously, namely, bleeding as clinical evidence of gingival inflammation; plaque index as an indicator of infective burden; probing depth, since periodontal pockets are a reservoir for microorganisms with direct access to the connective tissue and circulatory system; and clinical attachment level, because periodontal recession is the record of past history of PD and its remissions.

In this study, the presence of obstructive coronary artery disease in ACS patients was significantly associated with active periodontal disease. The most promising hypothesis to

explain this association may lie in the analysis of inflammatory markers characteristic or predictive of cardiac ischemic events. Analyzing these studies, in which inflammatory markers decrease when the subject receives periodontal treatment, or even comparing these markers in different groups of subjects with and without PD, one may consider periodontal interventions as adjuvant for preventing cardiac events<sup>19-29</sup>.

Our findings suggest that the ability of periodontopathogenic bacteria to invade periodontal tissues may offer a basis for such association. Another explanation that would validate the interrelationship between PD and CVD are gene polymorphisms, including frequency of different interleukin-1 (IL-1) and interleukin-6 (IL-6) genotypes, both of which are present in both the progression of PD and CVD. Accordingly, the patient would be hyper-responsive to harmful stimuli in the periodontal tissues and vascular endothelium. It is interesting to note that, despite the polymorphism, after periodontal treatment these patients show a significant decrease in serum C-reactive protein levels<sup>36</sup>.

In the present study, inflammatory markers were not measured. Czerniuk et al<sup>37</sup> studied 50 consecutive patients with chronic periodontitis (41 males) admitted to the Coronary Care Unit with clinical diagnosis of ACS who underwent serial laboratory measurements, in some cases up to six months after the acute event. Although no significant differences were detected in serum tumor necrosis factor (TNF $\alpha$ ) or IL-1 in ACS patients with advanced periodontal disease, as compared with those with a less advanced stage of the disease, the first tended to be characterized by higher mean levels of IL-1 in early and later phases of ACS, in addition to higher mean

	No periodontal disease	Periodontal disease	Edentulous
No periodontal disease	18 (5.0%)	20 (5.5%)	41 (11.3%)
At least one coronary obstruction, always < 50%	3 (0.8%)	5 (1.4%)	4 (1.1%)
At least one coronary obstruction, $\geq$ 50%	28 (7.7%)	80 (22.2%)	126 (34.9%)
No catheterization	3 (0.8%)	10 (2.8%)	23 (6.4%)

**Table 1 - Distribution of cases without coronary artery disease, with mild obstructive coronary disease (< 50%), with severe obstructive coronary disease (> 50%), and that did not undergo catheterization relative to the presence or not of periodontal disease or edentulous condition**

	No periodontal disease	Edentulism	Total
Obstructive disease (any degree)	31	130	161
Normal coronaries	18	41	59
Total	49	171	220
<i>p</i> = 0.0989 OR = 0.6311 (95%CI 0.3834 to 1,039)			

**Table 2 - Distribution of cases in groups with obstructive coronary disease of any degree and no coronary disease relative to the absence of current periodontal disease or edentulism**

	Periodontal disease	Edentulism	Total
Obstructive disease (any degree)	85	130	215
Normal coronaries	20	41	61
Total	105	171	276
<i>p</i> = 0.3726 OR = 1.340 (95% CI 0.735 to 2.444)			

**Table 3 - Distribution of cases in groups with obstructive coronary disease of any degree and no coronary disease relative to the presence of current periodontal disease or edentulism**

	Periodontal disease	No periodontal disease	Total
Obstructive disease ( $\geq 50\%$ )	80	28	108
Normal coronaries	20	18	38
Total	100	46	146
$p = 0.0245$ OR = 2.571 (95% CI 1.192 to 5.547)			

**Table 4 - Distribution of cases in groups with severe obstructive coronary disease ( $\geq 50\%$ ) and no coronary disease relative to the presence or not of periodontal disease**

	Periodontal disease	No periodontal disease	Total
Periodontal disease (any degree)	85	31	116
Normal coronaries	20	18	38
Total	105	49	154
$p = 0.0265$ OR = 2.468 (95% CI 1.156 to 5.267)			

**Table 5 - Distribution of cases in groups with obstructive coronary disease of any degree and no coronary disease relative to the presence or not of periodontal disease**

levels of TNF $\alpha$  in later phases. Furthermore, in patients with less advanced periodontal inflammatory response decreased more rapidly compared to groups with more advanced periodontal disease.

The statistically significant association between obstructive coronary disease and active periodontal disease strongly suggests that periodontal disease be considered among the risk factors for the development of obstructive coronary disease. Therefore, considering the inflammatory aspects involved, it would represent a potential risk factor in the etiology and atherosclerotic plaque instability and cause

acute coronary syndrome.

Studies that are prospective, controlled and have a larger number of patients are needed to further elucidate this issue.

### Acknowledgment

The authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for funding this research (Case No. 01/03808-1).

### References

- Brown LJ, Brunelle JA, Kingman A. Periodontal status in the United States, 1988-1991: Prevalence, extent and demographic variation. *J Dent Res* 1996;75:672-83.
- DeStefano F, Anda RF, Kahn HS, Williamson DF, Russel CM. Dental disease and risk of coronary heart disease and mortality. *Br Med J* 1993;306:688-91.
- Matilla KJ, Valtonen VV, Nieminen M, Hattunen JK. Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. *Clin Infect Dis* 1995; 20:588-92.
- Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk* 1999;6:7-11.
- Genco R, Chadda S, Grossi S. Periodontal disease is a predictor of cardiovascular disease in a native American population. *J Dent Res* 1997;76:408.
- Beck J, Garcia R, Heiss G, Vokona PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996;67(Suppl.):1123-37.
- Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease. NHANES I. *Arch Intern Med* 2000;160:2749-55.
- Kornman KS, Pankow J, Offenbacher S, Beck J, Di Giovine F, Duff GW. Interleukin-1 genotypes and the association between periodontitis and cardiovascular disease. *J Periodont Res* 1999;34:353-7.
- Kornman KS, Duff G W. Candidate genes as potential links between periodontal and cardiovascular diseases. *J Periodont* 2001;6:48-57.
- Gibson FC, Hong C, Chou H-H, Yumoto H, Chen J, Lien E, et al. Innate immune recognition of invasive bacteria accelerates atherosclerosis in Apolipoprotein E-deficient mice. *Circulation* 2004;109:2801-06.
- Li L MD, Messas E, Batista EL, Levine RA, Amar S. Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation* 2002;105:861-7.
- Chung HJ, Champagne CME, Southerland JH, et al. Effects of P gingivalis infection on atheroma formation in ApoE ( $\pm$ ) mice. *J Dent Res* 2000; 79 (Spec.Issue): 313-(Abstr.1358).
- Lalla E, Lamster IB, Spessor AL, et al. Oral infection with a periodontal pathogen accelerates atherosclerosis in ApoE null mice. *Circulation* 2000;102(suppl. II):II41-II-42(Abstr.188).
- Stelzel M, Conrads G, Pankuweit S, Maisch B, Vogt S, Moodsdorf R, et al. Detection of Porphyromonas gingivalis DNA in aortic tissue by PCR. *J Periodontol* 2002;73:868-70.
- Okuda K, Ishihara K, Nakagawa T, Hirayama A, Inayama Y. Detection of Treponema denticola in atherosclerotic lesions. *J Clin Microbiol* 2001; 39:1114-17.
- Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000;71:1554-60.
- Kowolik MJ, Dowsett SA, Rodrigues J, De La Rosa M, Eckert G. Systemic neutrophil response resulting from dental plaque accumulation. *J Periodont* 2001;72:146-51.
- Geerts SO, Nys M, de Mol P, Charpentier J, Albert A, Legrand V, et al. Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. *J Periodont* 2002;73:73-8.
- Beck JD, Offenbacher S. Relationship among clinical measures of periodontal disease and their associations with systemic markers. *Ann Periodontol* 2002;7:79-89.

## Original Article

20. Ebersole JL, Capelli D, Mathys EC, Steffen MJ, Singer RE, Montgomery M, et al. Periodontitis in humans and non-human primates: oral-systemic linkage inducing acute phase proteins. *Ann Periodontol* 2002;7:102-11.
21. Matilla K, Versanen M, Valtonen V, Nieminen M, Palosuo T, Rasi V, et al. Effect of treating periodontitis on C-reactive protein levels: a pilot study. *BMC Infect Dis* 2002;2:30.
22. Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship between periodontal disease and C-reactive protein among adults in the atherosclerosis risk in community study. *Arch Intern Med* 2003;163:1172-79.
23. Meurman JH, Janket S, Qvarnström M, Nuutinen P. Dental infections and serum inflammatory markers in patients with and without severe heart disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;96:695-700.
24. D'Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready R, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res* 2004;83(2):156-60.
25. D'Aiuto F, Ready D, Tonetti MS. Periodontal disease and C-reactive protein-associated cardiovascular risk. *J Periodontol Res* 2004;39:236-41.
26. Montebugnoli L, Servidio D, Miaton RA, Prati C, Tricoci P, Melooni C. Poor oral health is associated with coronary heart disease and elevated systemic inflammatory and haemostatic factors. *J Clin Periodontol* 2004;31:25-9.
27. Deliagris EN, Madianos PN, Kadoma W, Marron I, Smith S, Beck JD, et al. Periodontal disease in patients with acute myocardial infarction: Prevalence and contribution to elevated C-reactive proteins levels. *Am Heart J* 2004;147:1005-9.
28. Nakamura T, Nitta H, Ishikawa I. Effect of low dose Actinobacillus actinomycetemcomitans lipopolysaccharide pretreatment on cytokine production by human whole blood. *J Periodontol* 2004;39:129-35.
29. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. *J Dent Res* 2004;83(2):151-5.
30. Meyer MW, Gong K, Herzberg MC. Streptococcus sanguis-induced platelet clotting in rabbits and hemodynamic and cardiopulmonary consequences. *Infect Immun* 1998;66:5906-14.
31. Herzberg MC, Meyer MW. Dental plaque, platelets and cardiovascular diseases. *Ann Periodontol* 1998;3:151-60.
32. Herzberg MC. Coagulation and thrombosis in cardiovascular disease: plausible contributions of infectious agents. *Ann Periodontol* 2001;6:16-9.
33. Papanou NP, Lindhe J. Epidemiologia da Doença Periodontal. In: Lindhe J, Karring T, Lang NP, editores. *Tratado de Periodontia Clínica e Implantologia Oral*. 3ª ed. Rio de Janeiro (RJ): Guanabara-Koogan, 1999.
34. Ainamo J, Bay I. Problems and Proposals for recording gingivitis and plaque. *Int Dental J*. 1975; 25(4):229-35.
35. Löe H. The gingival index, the plaque index and the retention index systems. *J Periodont* 1964;38:610-67.
36. D'Aiuto F, Parkar M, Andreou G, Brett PM, Ready D, Tonetti MS. Periodontitis and atherogenesis: causal association or simple coincidence? *J Clin Periodontol* 2004;31:402-11.
37. Czerniuk MR, Gorska R, Filipiak KJ, Opolski G. Inflammatory response to acute coronary syndrome in patients with coexistent periodontal disease. *J Periodontol* 2004;75(7):1020-6.