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Association Between Periodontal Disease and Acute Coronary Syndrome

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Summary

Objective: Analisar a relação entre a DP e SCA e verificar a associação entre a DP e periodontite em pacientes com SCA.

Methods: Foram incluídos 58 pacientes com diagnóstico de SCA e 57 controles, sem história de doença arterial coronariana (DAC). Variáveis: hipertensão arterial, diabete, dislipidemia, obesidade, história de DAC, tabagismo e polimorfismo genético do gene da interleucina-1β.

Results: Fizeram parte do estudo 115 indivíduos. No grupo SCA, 58 pacientes foram avaliados, sendo 32 (55,2%) do sexo masculino e 26 (44,8%) do sexo feminino. No grupo controle, 57 indivíduos, sendo 32 (56,1%) do sexo masculino e 25 (43,9%) do sexo feminino. Verificou-se DP em 26 (44,8%) pacientes com SCA e em 15 (26,6%) pacientes do grupo controle ($\beta2 = 4,43$, $p = 0,04$). Análise pela regressão logística, para a associação entre DP e SCA, demonstrou RC de 1,8 (IC 95%: 1,0-5,0); $p = 0,24$. A associação de periodontite com SCA apresentou RC: 4,5 (IC 95%: 1,3-15,6); $p = 0,019$.

Conclusion: Não observamos associação independente entre a DP e SCA. Houve associação independente entre periodontite e SCA.

Key words: Doença periodontais, periodontite, coronariopatia.

Introduction

Cardiovascular diseases are the leading cause of death in the Western world, although a downward trend in its incidence and mortality has been reported in several countries, including Brazil[1-8]. In our country, approximately 260,000 subjects die of cardiovascular disease per year, the vast majority due to acute coronary events. In subjects 60 years or older, circulatory diseases account for over 40% of deaths and nearly 30% of hospital admissions[9].

Risk factors for atherosclerosis and, thereby, for coronary artery disease (CAD) have been identified in epidemiological studies linking their presence with the incidence of clinically overt disease[10]. Foremost among modifiable risk factors associated with increased incidence of coronary disease are hyperlipidemia, systemic arterial hypertension, smoking, and diabetes mellitus[11]. Age, gender, and family history are among the major non-modifiable risk factors associated with ischemic heart disease[12-16].

Evidence suggests an association between inflammatory markers, such as interleukins, C-reactive protein (CRP)[17], protease-activated receptors (PAR), lipoprotein-associated phospholipase A2 ((Lp-PLA2), and matrix metalloproteinase-9 (MMP-9)[18], among others, and atherogenesis and acute ischemic events. Taking into account the new cardiovascular risk markers, some studies suggest an association between periodontal disease (PD) and coronary artery disease CAD. It has been hypothesized that CAD may be triggered by systemic mechanisms, in addition to local inflammatory factors, and chronic periodontal infection is one of the possibilities to be considered[19-22].

Some authors claim that infection may also play a role in the genesis and development of atherosclerotic processes and their complications, based on detection of serological markers related to some agents such as chlamydia pneumoniae, helicobacter pylori and cytomegalovirus[23,24]. Others, however, suggest that the association between CAD and PD is a mere incidental phenomenon, since it may be related only with other cardiovascular risk factors[25,26].

Taylor BA et al. conducted an interventional study in patients with advanced periodontitis requiring full-mouth tooth extraction. Twelve weeks after full-mouth tooth extraction, there was a significant decline in C-reactive protein, plasminogen activator inhibitor-1 (PAI-1), and platelet and white blood cell counts. This study demonstrated that the elimination of advanced periodontitis by full-mouth tooth extraction reduces inflammatory and thrombotic markers of cardiovascular risk, supporting the hypothesis that treatment of PD may lower cardiovascular risk[27].

We believe that this area warrants further studies that may contribute to a better understanding of the association between PD and acute ischemic events. This was the rationale that motivated this study.

Methods

A contemporary case-control study in which cases were

patients admitted with ACS to the Coronary Care Unit (CCU) of the Hospital São Lucas (HSL) of the Pontifical Catholic University of Rio Grande do Sul (PUCRS) and controls were patients from the city of Gravataí, Rio Grande do Sul, with no history of CAD, identified by clinical evaluation and specific complementary examinations.

The research project was submitted to the scientific committee and later approved by the Research Ethics Committee of the PUCRS, Porto Alegre, Rio Grande do Sul. All patients were enrolled after signing an informed consent.

Fifty-eight patients consecutively admitted to the CCU of the HSL-PUCRS in 2002, who met the ACS diagnostic criteria, with or without persistent ST-segment elevation, were included in the study.

ACS with ST-segment elevation was defined as AMI characterized by: chest pain, radiating or not to the upper extremities, lower jaw, upper back or epigastrium lasting 30 minutes or more, associated or not with sweating, nausea or pallor; presence of ST-segment elevation of 1 mm in two or more contiguous peripheral leads or 2 mm in two or more contiguous precordial leads on electrocardiogram (ECG); and elevation in serum markers of myocardial injury and necrosis (CK, CK-MB) three times their reference value[28].

Non-ST-segment elevation ACS on ECG was defined as a clinical condition similar to that mentioned above but with chest pain lasting less than 30 minutes, with or without elevation of serum enzyme markers of myocardial injury and necrosis (CK, CK-MB, cardiac troponins I and T)[28].

Patients with neoplasias, liver cirrhosis, HIV infection, chronic renal failure, hypo- or hyperparathyroidism, chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and Chron's Disease) were not included in the study.

The control group comprised 57 gender-matched patients with no history of CAD included in the Projeto Gravataí of PUCRS' Geriatric Institute.

Covariables analyzed were age $\geq$ 60; male gender; cigarette smoking, defined as current smoker or former smoker for less than one year; systemic arterial hypertension (SAH), defined as blood pressure $\geq$ 140/90 mm Hg in three consecutive readings five minutes apart or treatment with specific drugs; DM, defined as fasting glucose levels above 126mg/dL or treatment with specific drugs; dyslipidemia, defined as serum total cholesterol > 200 mg/dL or LDL >130 mg/dL, triglycerides > 150 mg/dL or use of specific treatment; obesity, defined as body mass index (BMI) $\geq$ 30 (BMI = weight in kg/height^2 in meters); family history of CAD (biological father or brother with CAD documented before 55 years of age and/or biological mother or sister with CAD documented before 65 years of age).

The presence and severity of periodontal disease was determined by the PD team of PUCRS' School of Dentistry, whose members were blind to the presence or not of ACS. Both bacterial plaque and the patient's hygiene status were etiologically quantified and qualified, as well as severity of gingival inflammation and the presence of plaque retentive factors, which favor plaque formation and buildup around the teeth.

Patients presenting characteristics of gingivitis or periodontitis on clinical periodontal examination were defined as having periodontal disease. Patients with hyperemia, gingival edema, irregular gingival contour and gum bleeding, either spontaneous or on probing during examination, were considered as having gingivitis. Periodontitis, the most severe degree of PD, was characterized by periodontal pocket formation, loss of periodontal attachment and alveolar bone, and gingival inflammation.

Periodontal disease severity was determined based on the number of missing teeth; on probing depth, characterized as the distance in millimeters from the gingival margin to the probeable base of the gingival sulcus, in all teeth; and on the clinical level of attachment, characterized as the distance from the cementoenamel junction (CEJ) to the base of the gingival sulcus, also in all teeth. Instruments used for this evaluation were periodontal scalers and pliers, periodontal probe calibrated in millimeters (10 mm) and mouth mirror, manufactured by Duflex.

Statistical analysis - Sample size was calculated in 114 patients, 57 in each group, for a statistical power of 90%, difference in primary endpoint of 20%, and alpha level $\leq$ 0,05. The chi-square test was used for association between PD and ACS. To check the relationship between PD and periodontitis, as independent variables, and other variables with ACS, a logistic regression analysis was performed, using the forward Wald method. Data were processed and analyzed using Excel and SPSS for Windows version 11.0.

Results

One hundred and fifteen subjects were analyzed in this study. Mean age was 59.3 in the ACS group and 70 in the control group (p <0.001). Thirty-two subjects (55.2%) in the ACS group were men, the same occurring in the control group, where 32 subjects (56.1%) were men.

General characteristics of both groups regarding cardiovascular risk factors are described in Table 1.

Table 1 - General characteristics of ACS and control groups regarding the presence of cardiovascular risk factors.

Prevalence of SAH, dyslipidemia, and family history of CAD was significantly higher in the ACS group. This finding was expected when comparing groups with such characteristics. The diabetes mellitus, smoking and obesity variables were statistically similar between both groups.

Periodontal disease was diagnosed in 26 patients (44.8%) of the ACS group and 15 patients (26.6%) of the control group, which translated into an odds ratio (OR) of 2.3 (95% CI =1-5); p = 0.04, as shown in Table 2.

When different forms of PD were taken into account, the absolute frequency of subjects free of PD in the ACS group was 15 (26.3%) patients and in the control group, 11 (19%) patients. The absolute frequency of toothless subjects in the case group was 21 (36.9%) and in the control group, 27 (47.4%). The absolute frequency of subjects with gingivitis in the ACS group was 7 (12.1%) and in the control group, 10 (17.6%). All these were comparative results, with no statistical significance. When evaluating subjects with periodontitis,

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the most severe form of PD, the absolute frequency was 19 (32.8%) in the case group, whereas in the control group was 5 (8.8%), OR = 5.1 (1.7-14.8); p = 0.003 (Tab. 3).

In the multivariate analysis, PD loses its power of association with ACS, yielding an OR of 1.8 (95% CI 0.7-4.7); p = 0.24. However, the subgroup of subjects with periodontitis showed a statistically significant difference regarding ACS incidence, compared with the group free of this form of PD, with an OR of 4.5 (95% CI =1.3-15.6); p = 0.019, as shown in Table 4.

Discussion

Cardiovascular diseases rank among the leading causes of death in our country and thereby have an important clinical and epidemiological role[1-3]. Several studies have already identified risk factors for the development of atherosclerotic diseases and, consequently, of CAD, such as dyslipidemia, SAH, DM, and cigarette smoking[10,13,29-35]. Evidence suggests that endothelial dysfunction detected by the presence of inflammatory[17,18] and possibly serological markers[24,25],

Variables	ACS n = 57	Control n = 57	OR (95% CI)	p
Demographic data				
Mean age - years	59.3	70		<0.001
Masculine gender – N (%)	32 (55.2)	32 (56.1)		0.53
Risk factors for ACS – N (%)				
SAH	45 (77.6)	34 (59.6)	2.34 (1.04-5.28)	0.037
Diabetes mellitus	10 (17.5)	18 (31.0)	2.11 (0.870-5.90)	0.142
Dyslipidemia	38 (65.5)	25 (43.9)	2.43 (1.15-5.16)	0.032
Family history	24 (41.4)	9 (15.8)	3.77 (1.56-9.10)	0.002
Obesity	14 (24.1)	23 (40.4)	0.47 (0.21-1.05)	0.097
Smoking	22 (37.9)	18 (31.6)	1.32 (0.61-2.86)	0.604

N = sample size; P = significance level obtained by univariate analysis using the chi-square test; OR = odds ratio; 95% CI = 95% confidence interval; ACS = acute coronary syndrome, HAS = systemic arterial hypertension. P value ≤ 0.05 was considered statistically significant.

Table 1 - General characteristics of ACS and control groups regarding the presence of cardiovascular risk factors

Variable	ACS n (%)	Control n(%)	OR	p
Periodontal disease	26 (44.8)	15 (26.6)	2.3 (1.0-5.0)	0.04

N = sample size; P= significance level obtained by univariate analysis using the chi-square test; OR = odds ratio; 95% CI = 95% confidence interval. P value ≤ 0.05 was considered statistically significant.

Table 2 - Presence of PD in patients with ACS compared with the control group

Variable	ACS n (%)	Control n (%)	OR	p
Periodontitis	19 (32.8)	05 (8.8)	5.1 (1.7 – 14.8)	0.003

N = sample size; P = significance level obtained by univariate analysis using the chi-square test; OR = odds ratio; 95% CI = 95% confidence interval. P value ≤ 0.05 was considered statistically significant.

Table 3 - Presence of periodontitis in the ACS group compared with the control group

	Non-adjusted analysis			Adjusted analysis*		
Condition	OR	95% CI	p	OR	95% CI	p
Periodontal disease	2.3	1.0 to 5.0	0.06	1.8	0.7 to 4.7	0.24
Periodontitis	5.1	1.7 to 14.8	0.003	4.5	1.3 to 15.6	0.019

* Odds ratio obtained in a logistic regression model including age (older than 60 vs. younger than 60), DM, cigarette smoking (present vs. absent), and gender; n = 115 (58 cases and 57 controls); 95% CI: 95% confidence interval; P: statistical significance.

Table 4 - Odds ratio for ACS according to the presence of PD or periodontitis

associated with traditional cardiovascular risk factors such as those mentioned above[13-16], may be a common early event, resulting in increased systemic inflammatory response[36,37] and contributing to both the atherosclerotic process and development of acute ischemic events[13-16].

A study carried out by Emingil et al[22] suggests that the presence of PD may induce a systemic inflammatory response, resulting in elevated serum levels of inflammatory markers, such as TNF-α, interleukins, and CRP, that contribute to plaque instabilization and atherosclerotic events[17,18]. However, evidence conclusively linking these phenomena is limited and arguable[25,26].

It must be underscored that both CAD and PD are multifactorial diseases, and it is important that a detailed analysis of the results be made that takes into account the prevalence of other risk factors in the ACS and control groups. Published studies showed that approximately 70% of patients with fatal and non-fatal ACS are smokers[22,38]. In our study, the prevalence of smokers in the ACS group was 37.9%. This finding may be related to our sample size. We believe that, in a larger sample, the presence of this variable would be closer to those reported in the literature. Nevertheless, as this variable is an important risk factor for the development of PD and there was no statistically significant difference regarding its presence in either group, the confounding bias for the analysis was reduced or eliminated.

With respect to the presence of DM, its association with atherosclerotic disease and ACS is well-established[38]. As for its association with PD, Emrich et al[39] found a positive association between periodontal bone loss (periodontitis) and type-2 DM, with an OR of 3.43 (95% CI; 2.28-5.16). Seppälä et al[36] suggest that subjects with uncontrolled type-1 DM have higher periodontal bone loss, as compared with subjects with controlled type-1 DM, suggesting also an association between this type of DM and PD. In our sample, no statistically significant difference was found regarding the presence of DM in either group; therefore, the confounding factor for this variable might have been eliminated.

A statistically significant difference was observed concerning age between both groups, in that mean age of the control group was greater, as well as having a larger number of subjects older than 60. It is known that the age factor also accounts for increased cardiovascular risk, and this finding may have reduced both the significance and magnitude of our results.

Ever since the first studies focused on associating periodontal and cardiovascular diseases were published, we have noticed that few of them sought to evaluate the association between PD and ACS[23,39]. Some of these studies attempted to establish an association only between PD and AMI[33, 35].

Hujoel P et al[25] published a prospective cohort study involving 8032 patients with periodontal and medical evaluation who were followed for about 10 years. These patients were divided into three groups: 1859 with periodontitis, 2421 with gingivitis, and 3752 healthy subjects. The endpoints evaluated were coronary death, hospital admission for ACS, or need for myocardial revascularization during this period. After adjustment for cardiovascular risk factors, no association was found either between gingivitis and CAD, with an OR of 1.05 (95% CI; 0.88-1.26), or between periodontitis and CAD, with an OR of 1.14 (95% CI; 0.96-1.36).

Lopez et al[37] evaluated the association between PD and ACS parameters in patients ranging from 30 to 50 years old. Cases were patients admitted for ACS, and controls were patients admitted for elective surgery. Of 86 patients, only 61 were studied. After logistic regression analysis, the association between PD severity, characterized also by loss of clinical attachment and ACS, yielded an OR of 3.17 (95% CI = 1.31-7.65), and the association between probing depth and ACS yielded an OR of 8.64 (95% CI =1.22-61.20), whereas the number of missing teeth showed no association with ACS. These results identified an association between PD severity and ACS. In our study, the association between PD and ACS, through multivariate analysis, yielded an OR of 1.8 (95% CI, 0.7–4.7; p = 0.24), with no significant difference. This result was consistent with that reported by Hujoel et al[25]. However, a multivariate analysis revealed an independent association between periodontitis, the most severe form of PD, and ACS, evidenced by an OR of 4.5 (95% CI: 1.3-15.6), which is consistent with the results reported by Lopez et al[37]. Of note, our study and that of Lopez are among the few that assessed patients with ACS, comparing them with a control group, regarding the presence or not of PD and periodontitis. Most studies published in the literature analyze the relationship between PD and the presence or not of CAD[20-21.]

Our results emphasize the hypothesis that oral infectious processes may be implicated in inflammatory and thrombotic phenomena, leading to the development of acute coronary events. Such processes may induce cytokine release (IL-1 beta, TNF-α) in the presence of (LPS). It is believed that these substances act systemically, from the periodontal vascular complex, or are released from coronary endothelial cells, promoting platelet aggregation and thrombus formation[21-23]. A recent study demonstrated that the elimination of advanced periodontitis by full-mouth tooth extraction reduces inflammatory and thrombotic markers of cardiovascular risk, corroborating the hypothesis that management of periodontal disease may lower the risk of cardiovascular events[27].

Among the limiting factors of our study, we highlight the impossibility, for technical and financial reasons, of performing inflammatory marker determination and serological measurement of infectious agents, which could have contributed to the analysis of the patients studied.

In the future, randomized studies involving larger number of patients and simultaneous analysis of other risk markers – inflammatory, genetic, and serological - may further our knowledge and contribute to a better understanding of the role of inflammatory and infectious processes in atherothrombotic events, responsible for the development of acute ischemic events.

Based on the results of our study, we can conclude that no independent association was found between PD and ACS. An independent association was found, however, between periodontitis and ACS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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