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Periodontitis as risk factor for acute myocardial infarction. A case control study of Spanish adults

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Objective: The present study was designed to determine, in a case-control study of a Spanish population, whether periodontitis is a risk factor for acute myocardial infarction.

Background: Although part of cardiovascular risk could be explained by periodontal disease, available meta-analyses find significant heterogeneity and recommend the need for further observational and intervention studies.

Methods: A case-control study was conducted of 149 Spanish patients aged between 40 and 75 years, with 72 cases (acute myocardial infarction) and 77 controls (trauma patients). Periodontitis was measured as the percentage of sites with clinical attachment loss greater than 3 mm. A multivariate logistic regression model was constructed to estimate the adjusted effect of periodontitis on acute myocardial infarction, after considering the potential confounding effect of a large pool of risk factors.

Results: In a bivariate analysis, males, older patients, smokers, and those with hypertension, diabetes or hypercholesterolemia, showed an increased risk of acute myocardial infarction. The cases, compared to controls, showed worse results for all periodontal variables studied: gingival retraction, pocket depth, and periodontitis. The final multiple logistic model included sex, age, tobacco habit, hypertension, diabetes, hypercholesterolemia, regular exercise, and periodontitis. The association between periodontitis (dichotomized) and acute myocardial infarction was high and significant in both the unadjusted (odds ratio = 4.42, $p < 0.001$) and adjusted analyses (odds ratio = 3.31, $p = 0.005$).

Conclusion: There is evidence of an association between periodontitis and acute myocardial infarction after adjusting for well-known risk factors for acute myocardial infarction.

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Cardiovascular disease is the main cause of morbidity/mortality in developed countries. In Spain, an estimated 63,000 individuals suffered acute myocardial infarction in 2001, with 55.7% dying in the first 28 days (1). The demographic, health, and social impact of this disease will increase over the next few decades, due to the aging of the population, and will pose a major public health challenge (2). Cardiovascular risk factors have been known since the Framingham Heart Study (3). However, epidemiologic and pathologic studies suggest that only half to two-thirds of cardiovascular risk is explained by the classic risk factors (4).

There is growing evidence that poor oral health, especially periodontitis, increases the risk of acute myocardial infarction. Studies of different populations have indicated that atherosclerosis and acute thromboembolic events

may be related to chronic oral infections (5, 6). Thus, periodontitis shares a series of features with cardiovascular diseases, such as a higher incidence in adult males, smokers, diabetics, and individuals with stress and/or a low socioeconomic level. According to the most widely established hypothesis, the relationship between acute myocardial infarction and periodontitis depends on risk factors common to both diseases (7), with tobacco use as the main confounding factor (8).

Other hypotheses point to the direct action of periodontal pathogens that produce endotoxins and the release of proinflammatory mediators by the host monocytes, causing local and systemic destruction of the connective tissue (5) and favoring platelet aggregation and thromboembolic events (9). It has even been proposed that these periodontal pathogens or their lipopolysaccharides are systemically disseminated via the blood flow and directly infect the vascular endothelium, producing an atherosclerotic lesion and subsequent myocardial ischemia (10, 11). Lipopolysaccharides that pass to the blood, alongside inflammation mediators such as tumor necrosis factor or interleukin-1β, can induce secretion in the liver of acute-phase proteins, such as C-reactive protein. These proteins can form deposits in damaged blood vessels, with the consequent activation of phagocytes and release of nitrous oxide, contributing to the formation of atheromas (12).

Two available meta-analyses (13, 14) indicate significant heterogeneity in the association between periodontal disease and acute myocardial infarction, suggesting the need for further studies in different populations. The present study was designed to determine, in a case-control study of a Spanish population, whether periodontitis is a risk factor for acute myocardial infarction.

Material and methods

A case-control study of patients aged from 40 to 75 years was developed in Granada, Southern Spain, in the Virgen de las Nieves and San Cecilio University Hospitals, which serve a population of approximately 500,000 people. The study was approved by the Ethics Committees of both Hospitals, and informed consent was obtained from all patients before their examination.

All 98 patients with acute myocardial infarction admitted to the Departments of Cardiology between June 15 and August 15, 2002 were enrolled as cases in the study. The criterion for inclusion as a case was the presence of a history of acute myocardial infarction verified by characteristic electrocardiogram changes and elevation of serum enzymes (serum glutamic oxaloacetic transaminase, creatinine phosphokinase). Controls were 98 trauma patients (mainly from traffic and work accidents) admitted to the Traumatology Departments of these hospitals (excluding out-patient visits) during the same period; the distribution of their traumatic injuries was as follows: brain ($n = 12$), abdomen ($n = 6$), chest ($n = 9$), extremities ($n = 30$), and multiple ($n = 41$). In the sampling procedure, the controls were randomly selected each week to match the number of cases. Criteria for exclusion from the study were: death before oral examination, prehospital admittance diagnosis of more than one chronic disease (excluding cardiovascular diseases), diagnosis of endocarditis, being completely edentulous, receipt of periodontal treatment less than 1 year before and/or of antibiotic treatment in the 2 days before the examination, and patients with maxillofacial trauma. After

Table 1. Bivariate association between acute myocardial infarction and socio-economic variables

Variable	Controls ($n = 77$)	Cases ($n = 72$)	Crude odds ratio (95% CI)[b]	*p*-value
Hospital, *n* (%)				0.202[c]
San Cecilio	39 (50.6%)	28 (38.9%)	1.00	
Virgen de las Nieves	38 (49.4%)	44 (61.1%)	1.61(0.84–3.09)	
Residence, *n* (%)				0.070[c]
Rural	21 (27.3%)	10 (13.9%)	1.00	
Urban	56 (72.7%)	62 (86.1%)	2.33 (1.01–5.36)	
Sex, *n* (%)				0.030[c]
Female	38 (49.4%)	22 (30.6%)	1.00	
Male	39 (50.6%)	50 (69.4%)	2.21 (1.13–4.33)	
Age (years), mean ± SD[a]	58.5–10.2	62.5–9.9		0.016[d]
Age (years), *n* (%)				0.046[e]
40–49	18 (23.4%)	11 (15.3%)	1.00	
50–59	21 (27.3%)	13 (18.1%)	1.01 (0.36–2.81)	
60–69	28 (36.4%)	26 (36.1%)	1.52 (0.60–3.82)	
70–75	10 (13.0%)	22 (30.6%)	3.60 (1.25–10.37)	
Social level, *n* (%)				0.657[e]
Low	24 (31.2%)	23 (31.9%)	1.00	
Medium–low	41 (53.2%)	34 (47.2%)	0.86 (0.42–1.80)	
High, medium–high, medium	34 (15.6%)	15 (20.8%)	1.30 (0.50–3.37)	
Years of education, *n* (%)				0.853[e]
None	20 (26.0%)	20 (27.8%)	1.00	
1–8	43 (55.8%)	37 (51.4%)	0.86 (0.40–1.84)	
≥ 9	14 (18.2%)	15 (20.8%)	1.07 (0.41–2.79)	
Work status, *n* (%)				0.435[c]
Working	27 (35.1%)	20 (27.8%)	1.00	
Not working	50 (64.9%)	52 (72.2%)	1.40 (0.70–2.82)	
Marital status, *n* (%)				0.701[c]
Not married	18 (23.4%)	14 (19.4%)	1.00	
Married	59 (76.6%)	58 (80.6%)	1.26 (0.57–2.78)	

[a]SD, standard deviation.
[b]CI, confidence interval.
[c]Chi-squared test, with continuity correction.
[d]Student's *t*-test.
[e]Chi-squared test.

exclusions, the final study group comprised 72 cases and 77 controls.

The following variables were gathered from the hospital records of each patient: hospital, place of residence, sex, age, socioeconomic level measured by the validated European Society for Market Research (ESOMAR) questionnaire (15), years of education, marital status, tobacco habit, hypertension, diabetes, hypercholesterolemia, regular practice of physical exercise, body mass index, and family history of cardiovascular disease. The categories of these variables are expressed in the first column of Tables 1 and 2.

The oral examination was carried out by a single calibrated dentist (AC). The calibration was done approximately 4 weeks before the start of the study in the Department of Periodontology of the Dental School (University of Granada). The diagnosis was compared with that of another author (FM) in 13 adult periodontal patients, obtaining intraclass correlation coefficients (for gingival retraction and pocket depth) of above 0.71, considered substantial on the Landis and Koch scale (16). All patients were examined in a hospital bed; the patients with acute myocardial infarction (cases) were examined between 4 and 6 days after their transfer from Intensive Care Unit to the Cardiology ward, and the controls between 2 and 6 days after their hospital admission. Along with the number of present teeth, some periodontal variables were determined using a Michigan 0 periodontal probe and non-magnifying dental mirror number 5. These variables were pocket depth and gingival retraction (their summation = loss of clinical attachment) in the six Ramfjord teeth (or if missing, in the substitutes proposed by Ramfjord), considered to be representative of the whole mouth (17), measuring six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual). The degree of periodontitis was defined, as previously reported (18), by the percentage of sites with loss of attachment > 3 mm as follows: 0% = absent; 0–32% = mild; 33–66% = moderate; and 67–100% = severe.

The design, coding, and debugging of the database and its statistical analysis were carried out using the SPSS-PC/Windows version 11.0.1 software package (SPSS Inc., Chicago, IL, USA). The bivariate associations between the studied variables, acute myocardial infarction and periodontitis (dichotomized as explained below) were analyzed with the appropriate test according to the type of variable (see footnotes in tables), regarding $p \leq 0.05$ as significant, and the odds ratios with 95% confidence intervals were calculated.

Finally, in order to identify the factors associated with acute myocardial infarction, a multivariate logistic regression model was constructed. Continuous variables were categorized to accomplish the logistic model requirements. Very well-known risk factors (sex, age, tobacco habit, hypertension, diabetes, hypercholesterolemia and regular exercise) were forced into the model. Periodontitis, collapsed into two categories (absent or mild vs. moderate or severe) to achieve reasonably narrow confidence intervals, was also forced into the model to represent periodontal disease, excluding the other periodontal variables. Once the main model was constructed, the other variables (the remaining variables in Tables 1 and 2) were tested and included in the model if they produced a change of at least 10% in the estimated _β-coefficient of the periodontitis variable. Variables that showed a Spearman correlation of > 0.75 with other variables were excluded to avoid colinearity effects. This strategy for building the model is

Table 2. Bivariate association between acute myocardial infarction and risk factors of acute myocardial infarction

Variable	Controls ($n = 77$)	Cases ($n = 72$)	Crude odds ratio (95% CI)[b]	*p*-value
Tobacco habit, *n* (%)				0.009[c]
Never smoked	45 (58.4%)	24 (33.3%)	1.00	
Ex-smoker	16 (20.8%)	24 (33.3%)	2.81 (1.26–6.28)	
Current smoker	16 (20.8%)	24 (33.3%)	2.81 (1.26–6.28)	
History of hypertension, *n* (%)				0.018[d]
No	48 (62.3%)	30 (41.7%)	1.00	
Yes	29 (37.7%)	42 (58.3%)	2.32 (1.20–4.47)	
History of diabetes, *n* (%)				0.013[d]
No	64 (83.1%)	46 (63.9%)	1.00	
Yes	13 (16.9%)	26 (36.1%)	2.78 (1.29–5.99)	
History of hypercholesterolemia, *n* (%)				0.024[d]
No	62 (80.5%)	45 (62.5%)	1.00	
Yes	15 (19.5%)	27 (37.5%)	2.48 (1.18–5.19)	
Regular exercise, *n* (%)				0.080[d]
Yes	42 (54.5%)	28 (38.9%)	1.00	
No	35 (45.5%)	44 (61.1%)	1.89 (0.98–3.62)	
Body mass index (kg/m^2), mean ± SD[a]	28.4–4.8	28.6–4.3		0.781[e]
Body mass index, *n* (%)				0.827[c]
< 25	17 (22.1%)	13 (18.1%)	1.00	
25–< 30	35 (45.5%)	34 (47.2%)	1.27 (0.54–3.01)	
≥ 30	25 (32.5%)	25 (34.7%)	1.31 (0.53–3.25)	
Family history: cardiovascular disease, *n* (%)				0.967[d]
No	39 (55.8%)	39 (54.2%)	1.00	
Yes	34 (44.2%)	33 (45.8%)	1.07 (0.56–2.04)	

[a]SD, standard deviation.
[b]CI, confidence interval.
[c]Chi-squared test.
[d]Chi-squared test, with continuity correction.
[e]Student's *t*-test.

not based on statistical significance but rather on correction for confounding effects (19).

Results

Table 1 exhibits the distributions, means, standard deviations, crude odds ratios for acute myocardial infarction, and statistical significances of the socio-economic variables in this study. Males and older patients showed an increased risk of acute myocardial infarction in a bivariate analysis (Table 1). Other risk factors for acute myocardial infarction are presented in Table 2. Tobacco habit, hypertension, diabetes and hypercholesterolemia were statistically associated with being a case.

Out of the total study group of 149 patients, 15 (10%) were free of periodontitis, 66 (44.3%) presented mild periodontitis, 32 (21.4%) moderate periodontitis, and 36 (24.3%) severe periodontitis; these four categories were collapsed into two for the statistical analysis. Table 3 exhibits the association between periodontitis and very well-known risk factors for acute myocardial infarction. Sex, tobacco habit and diabetes were statistically associated with periodontitis.

The number of teeth or explored sites was not significantly different between cases and controls. The cases showed worse results for all periodontal variables studied (gingival retraction, pocket depth, and periodontitis) vs. controls (Table 4).

Table 5 shows the results of the multiple logistic regression analysis. The model only contains the forced variables, because no other variable produced a change of at least 10% in the estimated β-coefficient of periodontitis. The adjusted effect of periodontitis was somewhat lower (odds ratio = 3.31) than the unadjusted effect (odds ratio = 4.42) (Table 4), although it remained large and significant, indicating that some confusion was operating in the crude odds ratio.

Table 3. Association between periodontitis and very well-known risk factors for acute myocardial infarction

Variable	Periodontitis[a] Absent–mild[b] ($n = 81$)	Moderate–severe[c] ($n = 68$)	Crude odds ratio (95% CI)[d]	*P*-value
Sex, *n* (%)				0.021[f]
Female	40 (49.4%)	20 (29.4%)	1.00	
Male	41 (50.6%)	48 (70.6%)	2.34 (1.19–4.62)	
Age (years), mean ± SD[e]	59.1–10.6	61.9–9.6		0.100[g]
Age (years), *n* (%)				0.529[h]
40–49	19 (23.5%)	10 (14.7%)	1.00	
50–59	18 (22.2%)	16 (23.5%)	1.69 (0.61–4.68)	
60–69	29 (35.8%)	25 (36.8%)	1.64 (0.64–4.17)	
70–75	15 (18.5%)	17 (25.0%)	2.15 (0.77–6.05)	
Tobacco habit, *n* (%)				0.019[h]
Never smoked	46 (56.8%)	23 (33.8%)	1.00	
Ex-smoker	18 (22.2%)	22 (32.4%)	2.44 (1.10–5.43)	
Current smoker	17 (21.0%)	23 (33.8%)	2.71 (1.21–6.03)	
History of hypertension, *n* (%)				0.974[f]
No	42 (51.9%)	36 (52.9%)	1.00	
Yes	39 (48.1%)	32 (47.1%)	0.96 (0.50–1.83)	
History of diabetes, *n* (%)				0.012[f]
No	67 (82.7%)	43 (63.2%)	1.00	
Yes	14 (17.3%)	25 (36.8%)	2.78 (1.30–5.94)	
History of Hypercholesterolemia, *n* (%)				0.903[f]
No	58 (71.6%)	49 (72.1%)	1.00	
Yes	23 (28.4%)	19 (27.9%)	0.98 (0.48–2.00)	
Regular exercise, *n* (%)				0.883[f]
Yes	38 (46.9%)	32 (47.1%)	1.00	
No	43 (53.1%)	36 (52.9%)	0.99 (0.52–1.90)	

[a]Defined by the percentage of sites with loss of attachment > 3 mm (see Methods).
[b]Absent (0%, $n = 15$) and mild (1– < 33%, $n = 66$) are collapsed into a single category.
[c]Moderate (33–< 67%, $n = 32$) and severe (67–100%, $n = 36$) are collapsed into a single category.
[d]CI, confidence interval.
[e]SD, standard deviation.
[f]Chi-squared test, with continuity correction.
[g]Student's *t*-test.
[h]Chi-squared test.

Discussion

Before discussing the findings in this study, some aspects of the validity will be addressed. The study only included the acute myocardial infarction patients who survived and were transferred to the Cardiology Department, and this may be a study limitation. Technically they are prevalence cases rather than incidence cases. If the unexamined non-survivors had worse health and greater severity of periodontitis than the survivors, then the possible bias would favor nullity, not considered a major drawback by epidemiologists. On the other hand, if individuals who died before arrival at the cardiac unit had less periodontal disease than those in the study, it would have to be interpreted that the presence of periodontal disease allowed the patient to survive the heart attack. It should be borne in mind that the scientific literature points to the first possibility (5, 9–12).

Regarding the selection of controls, we highlight that they derive from the same population as cases. No matching selection was considered but key confounding variables were collected, and the approach to the construction of the logistic model was based on the control of confounders rather than on statistical significance.

Although a blinded observer method would have been preferable for the clinical examinations, the fact that the

Table 4. Bivariate association between acute myocardial infarction and oral health variables

Variable	Controls ($n = 77$)	Cases ($n = 72$)	Crude odds ratio (95% CI)[a]	p-value
Present teeth, mean ± SD[b]	18.9–7.3	17.0–7.6		0.139[f]
Number of explored sites, mean ± SD	33.3–5.6	31.3–7.7		0.073[f]
Loss of epithelial attachment (mm), _mean ± SD	2.93–1.18	4.03–1.63		< 0.001[f]
Gingival retraction, _mean ± SD	0.66–0.91	1.42–1.29		< 0.001[f]
Pocket depth, mean ± SD	2.27–0.47	2.61–0.56		< 0.001[f]
Periodontitis[c], mean ± SD	25.2–28.0	50.9–34.1		< 0.001[f]
Periodontitis[c], *n* (%)				< 0.001[g]
Absent (0%), mild (1–< 33%)[d]	55 (71.4%)	26 (36.1%)	1.00	
Moderate (33–< 67%), severe (67–100%)[e]	22 (28.6%)	46 (63.9%)	4.42 (2.22– 8.82)	

[a]CI, confidence interval.
[b]SD, standard deviation.
[c]Defined by the percentage of sites with loss of attachment > 3 mm (see Methods).
[d]Absent (13 controls and 2 cases) and mild (42 controls and 24 cases) are collapsed into a single category.
[e]Moderate (12 controls and 20 cases) and severe (10 controls and 26 cases) are collapsed into a single category.
[f]Student's *t*-test.
[g]Chi-squared test, with continuity correction.

Table 5. Logistic regression model for study variables and acute myocardial infarction[a]

Variables	β-coefficient	Adjusted odds ratios (95% CI)[c] Cases vs. controls	Wald F p-value
Sex (male)	0.88	2.41 (0.82–7.14)	0.111
Age (years)			0.035
40–49	0.00	1.00	
50–59	0.13	1.14 (0.30–4.37)	
60–69	0.83	2.30 (0.56–9.37)	
70–75	1.89	6.59 (1.47–29.45)	
Tobacco habit			0.031
Never smoked	0.00	1.00	
Ex-smoker	1.16	3.20 (0.97–10.49)	
Current smoker	1.79	6.00 (1.53–23.50)	
History of hypertension (yes)	1.19	3.28 (1.24–8.67)	0.017
History of diabetes (yes)	0.63	1.87 (0.74–4.77)	0.188
History of Hypercholesterolemia (yes)	1.25	3.50 (1.36–9.06)	0.010
Regular exercise (no)	0.79	2.20 (0.93–5.23)	0.073
Periodontitis[b] (moderate or severe)	1.20	3.31 (1.42–7.71)	0.005
Constant	−4.21		

[a]See Methods for a statistical methodology explanation of the construction of the model.
[b]See Methods and Table 3 for a detailed explanation of this variable.
[c]CI, confidence interval.

acute myocardial infarction and trauma patients were in different departments made this impractical. Nevertheless, the observer had been calibrated. The main study variables were gathered from medical records. Epithelial insertion loss was measured by analyzing a representative sample of teeth (Ramfjord teeth), studying the substitute proposed by Ramfjord if one of these was missing. The number of sites measured did not significantly differ between the groups. Baelum and Papapanou (20) advocated assessment of the whole mouth to estimate the true extent and severity of periodontal disease. However, in our opinion, an extensive examination was contraindicated in the acute myocardial infarction patients because of their general health status. Moreover, an adequate global assessment can be derived from periodontal measurements limited to a number of sites (21), and any possible misclassification of patients derived from using a limited number of teeth would again produce a null-tendency bias, which is not especially problematic. Gingival bleeding is an indicator of gingival inflammation, which can be observed approximately 2 weeks after suspending oral hygiene measures (22). In this study, oral hygiene indexes were not considered because the cases could be expected to show worse scores, due in part to their Intensive Care Unit stay and longer hospital stay. Furthermore, acute myocardial infarction patients usually receive anticoagulant drug treatment, which can increase the gingival bleeding measurement. However, periodontitis should not be affected by the aforementioned bias, due to the longer period required for the destruction of periodontal support. In conclusion, it is highly unlikely that these possible biases could affect our finding of a strong and significant association between periodontitis and being a case.

Our results confirm the association between periodontitis and acute myocardial infarction reported in previous studies of similar (23, 24) or different (18, 25–27) design to the present work. Compared with other studies (26, 28), we found a stronger association between the two diseases. Other authors found no significant relationship between coronary disease and the presence of periodontitis when the latter was analyzed as a single entity (29). In our study, however, we compared moderate–severe degrees of periodontitis with absent–mild periodontitis. Advanced periodontitis probably implies a sufficiently long evolution of the disease for it to become a risk factor for coronary disease. In particular, severe periodontitis is associated with a

greater thickness of the lining and middle muscle layers of the carotid artery, supporting the role played by the pathogenesis of periodontitis in the formation of atheromas and consequent acute myocardial infarction (11). On the other hand, studies of health professionals found no association between periodontal disease and coronary disease except when self-reported loss of teeth due to periodontal disease was considered (30). However, these results may be explained by the special characteristics of health professionals.

Advanced periodontitis is characterized by the production of acute episodes of bacteremia that, alongside other factors, can trigger ischemic events (9–11). Some authors have supported the systemic administration of antibiotics in patients with coronary disease in order to reduce the risk of these bacteria-induced ischemic episodes (31).

To our knowledge, the present case-control study represents the first research on periodontal health and acute myocardial infarction in Spanish over-40-year-olds, and has the largest study sample, alongside that studied by Mattila *et al*. (32), among the case-control studies reported in the international literature (13, 14). We found that the association between periodontal health and acute myocardial infarction persisted after controlling for the classic cardiovascular risk factors. As pointed out by other authors (24), if this association is causal, a better control of periodontal diseases is clearly called for, and if it is non-causal, the demonstration that acute myocardial infarction and periodontal diseases cluster in the same sections of the populations still raises an important public health issue.

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