

VIEWPOINT

Association between Periodontitis and Myocardial Infarction: Systematic Review and Meta-Analysis

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Abstract

The association between periodontitis and myocardial infarction remains unclear in the literature. Few studies have addressed periodontitis exposure as a predisposing factor for the development of myocardial infarction. Therefore, the present systematic review aims to analyze the association between periodontitis and myocardial infarction. This meta-analysis systematically searched MEDLINE, EMBASE, The Cochrane Controlled Trials Register, SCIELO, LILACS, CINAHL, Scopus, Web of Science and grey literature for studies estimating the association between periodontitis and myocardial infarction. Quality of evidence was assessed for all studies. The meta-analysis was conducted using random-effects models. Four of the six studies selected were included in the meta-analysis, including 1,035,703 subjects. The association between periodontitis and myocardial infarction was: RR: 5.99 (95% CI: 1.17-30.68), but with high heterogeneity ($I^2 = 100\%$; $p < 0.01$). The results including only the highest quality articles, was lower: RR: 2.62 (95% CI: 1.47-4.70 3.83), but with lower heterogeneity ($I^2 = 85.5\%$; $p < 0.01$). The present systematic review with meta-analysis showed an association between periodontitis and acute myocardial infarction, but with a high level of heterogeneity.

Keywords

Cardiovascular Diseases/mortality; Periodontitis/complications; Pulpitis, Myocardial Infarction/complications; Atherosclerosis/complications. Lipoproteins/analysis; Inflammation; Meta-Analysis.

Introduction

Cardiovascular diseases (CVDs) are the leading causes of death in the world, with an annual mortality of 17.9 million people.¹ Atherosclerotic disease is the most prevalent CVD, characterized by chronic inflammation mediated by the accumulation of lipoproteins in the arteries, which can cause chronic coronary disease and myocardial infarction (MI).² Several risk factors predispose to this condition, notably the genetic determinism, smoking habit, physical inactivity, high body mass index, hypertension, dyslipidemia and diabetes.³ Poor oral health status, especially periodontal conditions, such as periodontitis, has also been reported as a potential aggravating factor for CVD.⁴

The latest consensus of the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) states that periodontitis is characterized by an "inflammation mediated by the host associated with microorganisms that results in loss of periodontal insertion".⁵ It is a chronic, non-curable disease associated with many strains of bacteria, especially gram-negative ones.⁵ There is evidence that oral pathogenic bacteria can cause bacteremia, increased expression of pro-inflammatory proteins (e.g. IL-1, IL-6, IL-8, TNF and of C-reactive protein), leading to vascular infection and development of CVD.^{6,7}

As with CVD, periodontitis is more prevalent in adults. A Brazilian epidemiological survey⁸ showed that about 19.4% of adults between the ages of 35 and 44 years, and approximately 3.3% of elderly between 65-74 years old have some degree of periodontal disease. The lower prevalence in the elderly is justified

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by the greater number of missing teeth for long exposure to oral diseases. Although there is sufficient evidence to support the relationship between CVD and periodontitis,⁹ the association between periodontitis and MI remains unclear in the literature. Most studies have shown the increase of the prevalence of periodontitis in infarcted patients, suggesting a strong association between this condition and the acute ischemic event¹⁰⁻¹². However, few of these studies have addressed periodontitis as a predisposing factor for the development of MI. Thus, the present systematic review aimed to analyze the association between periodontitis and MI.

Methods

This systematic review and meta-analysis were performed following the PRISMA guidelines, and its protocol was registered in the PROSPERO database (CRD42016052902).

Eligibility criteria

The inclusion criteria for studies were the following: (i) use of periodontitis as exposure factor and MI as outcome; (ii) observational studies (of all types). There was no language restriction. Case studies, review studies, case series, experimental models, response letters, editorials and duplicated publications were excluded. Duplicate studies were those published by the same study group, with the same inclusion date and population characteristics. In case of duplicate studies, the study with the larger sample size was considered for analysis.

Information sources

The following databases were used in the literature search, from inception to October 2018: MEDLINE (via PUBMED), EMBASE, Cochrane The Cochrane Controlled Trials Register (CCTR), Latin American Caribbean Health Sciences Literature (LILACS via BIREME), Cumulative Index to Nursing and Allied Health Literature (via EBSCOhost), Scopus and Web of Science (Thomson Reuters). The MEDLINE search strategy was adapted to the other databases.

Study selection and data extraction

Two authors independently screened the abstracts and titles of the studies retrieved. Full texts of all

potentially relevant articles were then analyzed. In both phases, in case of disagreement between the researchers, a third independent researcher was involved to achieve final consensus. For studies that fulfilled the inclusion criteria, three authors worked in the data extraction process. The agreement between the authors, estimated by the Kappa coefficient, was considered good ($k = 0.735$).

The following data were extracted from the articles selected: identification (authors and year of publication), general characteristics of participants (including age and gender), sample size, time of observation, definition of MI and periodontitis, magnitude of exposure and effect size.

Risk of bias

The association between exposure and outcome was synthesized from a meta-analysis using estimated risk calculations.

Risk of bias was analyzed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.¹³ This tool allows the assessment of the risk of bias and the quality of the study, and classified them as "good", "fair" or "bad". "Good" quality was attributed to studies that adopted at least eight of the established criteria. The biases were assessed by two evaluators and, in case of disagreement, a third evaluator was involved.

Statistical analysis

The association between periodontitis and MI was analyzed using meta-analysis with random-effects models. The heterogeneity among studies was assessed using the Q-Cochran test and I^2 statistics. We planned to explore heterogeneity using race as a factor, but the studies did not provide sufficient data. For longitudinal and clinical trials that assessed phase angle in more than one moment, the baseline values were considered for analysis. The authors of the present review were aware that some of issues suitable for sensitivity analysis were only identified during the review process, when the characteristics of each study were identified. At this phase of our review, we performed a sensitivity analysis to assess the robustness of our analyses by including only good-quality studies with good quality. The meta-analysis was performed using the Meta R package (<https://CRAN.R-project.org/package=#61;meta>).

Results

A total of 3,384 articles were retrieved from the selected databases. Of these, 1,272 duplicate articles were excluded. After reading the titles and abstracts, 2,013 articles were excluded according to the exclusion criteria. Of the 99 articles selected for full reading, 93 were excluded, of which 75 did not utilize periodontitis as exposure and/or MI as outcome, 12 articles were not available, one analyzed periodontitis treatment, three were letters to editor, and two were *in vitro* studies (Figure 1).

Characteristics of the included studies

Of the six articles included in qualitative analysis, the studies of Noguchi et al.,¹⁴ Lee et al.,¹⁵ Hansen et

al.¹⁶ and Holmlund et al.¹⁷ were cohort studies, one retrospective¹⁵ and three prospective studies^{14,16,17} and the studies by Arbes et al.,¹⁰ and Holmlund et al.¹⁸ were cross-sectional studies. The shortest observation period was 5 years¹⁴ and the largest was 34 years.¹⁷ The sample size of the studies ranged from 3,081¹⁴ to 1,025,340 participants,¹⁵ and their ages ranged from 1¹⁵ to 85¹⁷ years, with two studies without maximum age restriction.^{10,16} Except for the study by Noguchi et al.,¹⁴ who included only men in their sample, the other studies did not show gender restriction. No study used ‘previous diseases’ as inclusion criteria. Data extracted from the selected studies are described in Table 1. Data regarding the number of outcomes and estimated risks of the six studies included in the qualitative analysis are available in Table 2.

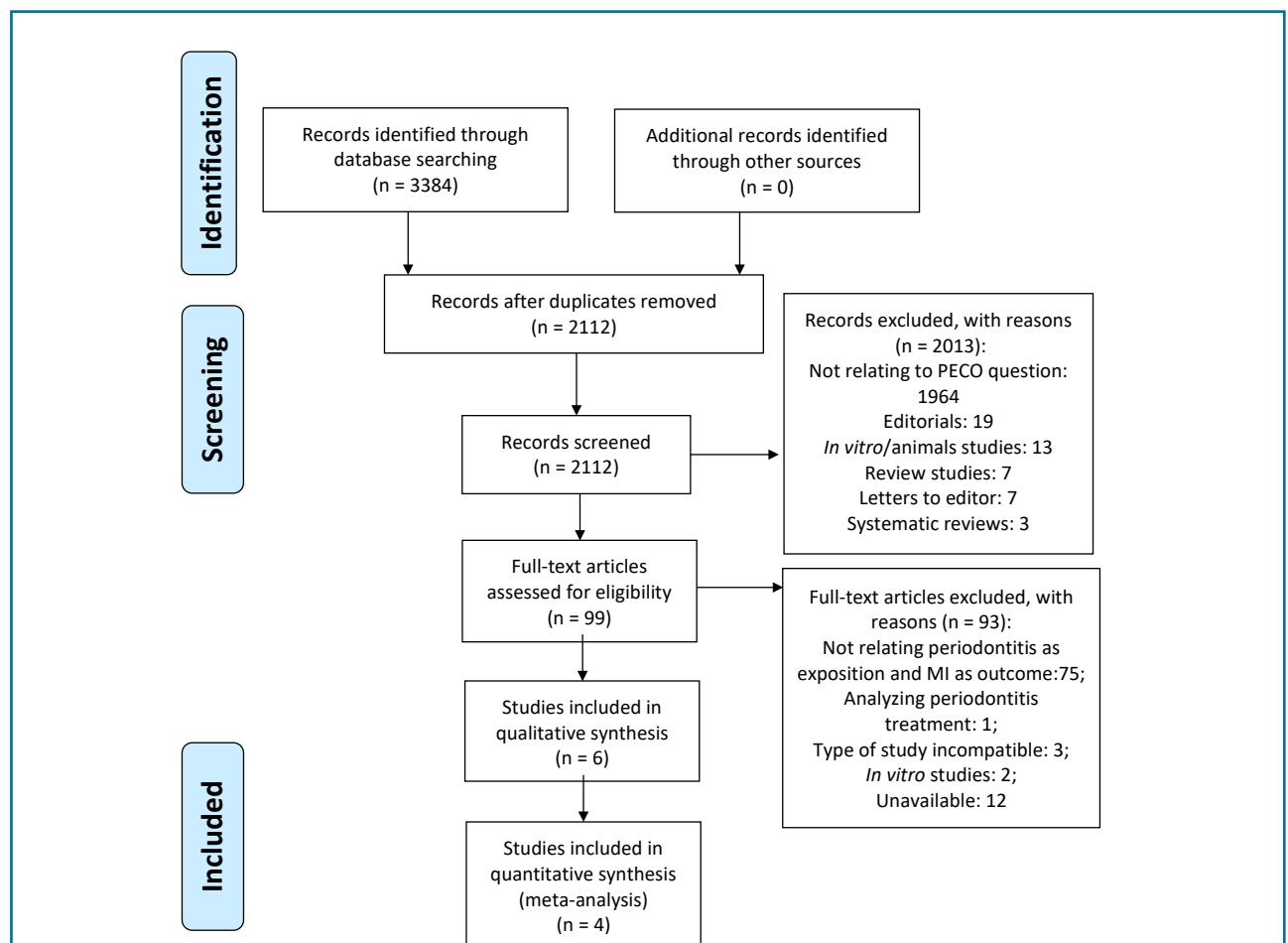


Figure 1 – Flowchart of the study selection process MI: myocardial infarction
 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
 For more information, visit www.prisma-statement.org.

Table 1 – General characteristics of the studies

Author, year	population	n	Age (Years)	Gender	Design and observation time	Definition of mi	Definition of periodontitis
Arbes et al., (1999) ¹⁰	NHANES III* data of United States population sample	5564	≥40	2,757 men 2,807 women	Cross-sectional study	Self-reported heart attack	Clinical attachment loss ≥ 3mm
HOLMLUNet al., (2006) ¹⁷⁻¹⁸	Patients from the Department of Periodontology, Gävle County Hospital	4.254	20 – 70	1,866 men 2,388 women	Cross-sectional study	Self-reported heart attack	Bone loss >2mm
NOGUCHI ET AL., (2014) ¹⁴	Employees of a financial company in Japan	3081	36 – 59	Only men	Prospective cohort between 2004 - 2009	Patients report that they were undergoing myocardial infarction treatment	Self-administered questionnaire produced by the authors.
LEE et al., (2015) ¹⁵	Random sample (2% of total) of South Korean population covered by National Health Insurance	1.025.340	1-79	513,258 men 512,082 women	Retrospective cohort between 2002 a 2013	Records of the 6th ed. Korean Classification of Diseases (KCD-6): Code not specified	Records of the 6th ed. Korean Classification of Diseases (KCD-6): K052 – K056
HANSEN et al., (2016) ¹⁶	Sample of the Danish population from the National Patient Registry	100.694	≥18	57,421 men 43,273 women	Prospective cohort between 1997- 2011	International Classification of Diseases (ICD-10) Records: Codes I21-I22	International Classification of Diseases (ICD-08) Records: Code 523.49 and 523.49 International Classification of Diseases (ICD-10) Records: Code K05.2 - 05.3.
HOLMLUNet al. (2017) ¹⁷⁻¹⁸	Patients from the Department of Periodontology, Gävle County Hospital	8.999	20-85	3,870 men 5,129 women	Prospective cohort between 1979 - 2013	International Classification of Disease Records: 421 (ICD-8 and ICD-9) and I21 (ICD-10)	Probing depth ≥ 4mm

*NHANES III, Third National Health and Nutrition Examination Survey

Meta-analysis

The association of MI in patients with periodontitis was calculated using data retrieved from four studies^{10,14,15,18} including 1,035,703 subjects. The result of this analysis was – RR: 5.99 (95% CI: 1.17-30.68), but

with a high heterogeneity ($I^2 = 100\%$; $p < 0.01$). Result of the analysis including only the highest-quality articles was lower – RR: 2.62 (95% CI: 1.47-4.70 3.83), with a lower heterogeneity also ($I^2 = 85.5\%$; $p < 0.01$) (Figure 2).

Table 2 – Results of risk analysis between periodontitis and AMI found in the studies

Author, year	Severity	Control	Outcome (N. cases/N. controls)	HR, ODDS, RR, OR (IC 95%)	Variable
ARBES S.J, (1999)	>0-33	No periodontitis	88/5.564	ODDS 1,38 (0,75-2,54)	Percent of sites with periodontal attachment loss ≥3; age; sex; race; smoking status; history of diabetes; history of high blood pressure; body mass indices; poverty index; serum cholesterol.
	>33-67		73/5.564	ODDS 2,28 (1,18-4,39)	
	>67-100		55/5.564	ODDS 2,28 (1,18-4,39)	
HOLMLUND A, (2006)	Periodontal bone loss	No periodontal bone loss (<2mm)	Not informed	ODDS 2,69 (1,12-6,46)	Age, gender and smoking.
NOGUCHI S, (2014)	With periodontist or without periodontitis	No periodontitis	9/3081	OR 2,26 (0,84-6,02)	Age; BMI; current smoking; hypertension; diabetes; dyslipidemia; family history of heart disease.
LEE J.H, (2015)	With periodontist or without periodontitis	No periodontal disease	8.179/1.025.340	ODDS 0,98 (0,86-1,12)	Sociodemographic/ economic status and comorbidities.
HANSEN G.M, (2016)	With periodontist or without periodontitis	No periodontitis	Not informed	IRR 1,16 (1,04- 1,30)	Age; sex; smoking; comorbidities; medication and socioeconomic status.
HOLMLUND A, (2017)	Numbers of surfaces with pocket depth > 4mm	No periodontal disease	570/8.999	IRR 1,13 (0,98-1,30)	Age; sex; education level and smoking.

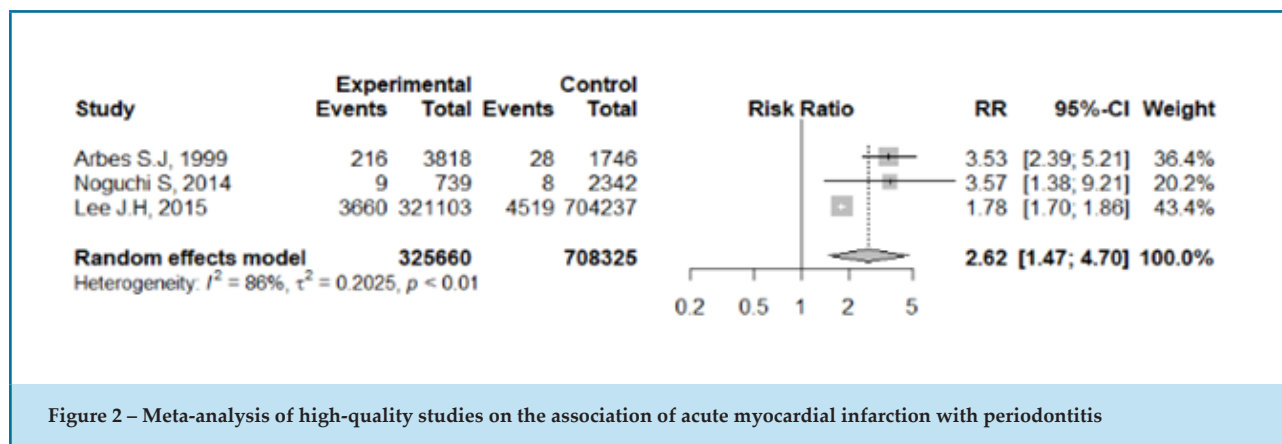


Figure 2 – Meta-analysis of high-quality studies on the association of acute myocardial infarction with periodontitis

Risk of bias

The quality of the included studies was considered reasonable. All of them described adequately the purposes and the population of the study, and evaluated

periodontitis prior to the development of MI. Only in one study (16.67%)¹⁸ the participation rate was less than 50% of the population. No study described the sample calculation in detail, blinded the periodontitis assessment

or performed periodontitis measurement more than once over time. The follow-up time described was considered good in four (66.7%) of the studies.¹⁴⁻¹⁷ In only three^{10,14,18} (50.0%) studies patients were classified according to the degree of periodontitis. Misdiagnosis and/or validation of the diagnosis of acute MI were found in all studies; in contrast, only three^{10,17,18} (50.0%) studies were considered adequate satisfactory in the definition and validation of the diagnosis of periodontitis. Only one study¹⁸ (16.67%) did not perform statistical adjustment for losses to follow-up, and three (50.0%) studies^{10,15,17} reported losses to follow-up of less than 20% of the participants.

Publication bias was not evaluated due to the limited number of studies.

Discussion

The present systematic review with meta-analysis showed an association between periodontitis and MI, but with high heterogeneity.

The results obtained in this study corroborate the hypothesis that chronic inflammation is involved in the pathogenesis of the atherosclerotic process and in triggering acute ischemic events.¹⁹ Previous studies have demonstrated that infectious agents are capable of inducing local and systemic inflammatory mechanisms. In response to pathogens, reactive oxygen and lipoprotein species are released, leading to the recruitment and proliferation of inflammatory cells such as T lymphocytes and macrophages.²⁰ Infection stimulates the release of cytokines (IL-1 beta and TNF-alpha) by the periodontal vascular complex or coronary endothelial cells, promoting platelet aggregation and thrombus formation.^{20,21}

The present study has several limitations. Most of the included studies classified the outcome and exposure according to medical records or self-reports. Only three^{10,17,18} studies used standardized diagnostic methods for periodontitis, and none used

standardized methods to define MI. This variability in the definition criteria of periodontitis and MI may be one of the causes of the great heterogeneity identified in the studies. Another factor is the reduced number of well-structured studies, and the long period between the studies, which compromises the reliability of this meta-analysis. Despite that, the search strategy was broad and included the most relevant evidence available.

The results of this systematic review and meta-analysis suggest an association between periodontitis and an increased risk of MI. The heterogeneity identified between the studies suggests the need for more studies that include the assessment of these factors in a more standardized manner and longer follow-up period to support a causal relationship.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Author contributions

Conception and design of the research: Baptista AH, Bodanese L, Salum FG, Mattiello R. Acquisition of data: Louzeiro GC, Magnus GA. Analysis and interpretation of the data: Louzeiro GC, Magnus GA, Bodanese L, Salum FG, Mattiello R. Statistical analysis: Mattiello R. Writing of the manuscript: Louzeiro GC, Magnus GA. Critical revision of the manuscript for intellectual content: Bodanese L, Baptista AH, Salum FG, Mattiello R.

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*Supplemental Materials

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