Clinical research

Chronic periodontitis, a significant relationship with acute myocardial infarction

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Background Chronic periodontitis (CP) has been associated with cardiovascular diseases. The study purposes were to identify the odds of acute myocardial infarction (AMI) and CP defined at different thresholds.

Methods and results We studied 80 subjects with clinically confirmed AMI and 80 matched control subjects with no evidence of cardiovascular disease all receiving a comprehensive periodontal examination. Statistical analysis demonstrated a difference in the proportion of sites with a periodontal probing depth \( \geq 6.0 \) mm (2.7\% for non-AMI and 12.1\% for AMI group, 95\% CI: \(-2.8\) to 0.01, \( P < 0.05 \)) but no difference in the extent of gingival bleeding was found between groups. The odds ratio of having AMI and periodontitis varied between 9.2:1 to 14.1:1 with the greatest odds ratio if bone loss exceeded 4 mm at \( \geq 50 \% \) of the teeth (OR: 14.1:1, 95\% CI: 5.5 to 28.2, \( P < 0.0001 \)). The odds ratio remained significant also when only non-smokers were considered (51 subjects) (OR: 7.0:1, 95\% CI: 2.0 to 24.3, \( P < 0.01 \)).

Conclusions Our findings suggest that patients who at routine dental visits demonstrate evidence of bone loss around several teeth can predictably be identified as being at risk for future AMI. Such subjects should be referred for medical and periodontal examinations and treatments.

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KEYWORDS
Acute myocardial infarction; Periodontitis; Risk

Introduction
Cardiovascular diseases (CVD) are common diseases in adults.\textsuperscript{1, 2} Several risk factors for CVD include elevated low-density lipoprotein (LDL), hypertension, smoking, male gender and low socioeconomic status (SES).\textsuperscript{3, 4} A link between infection and atherosclerotic diseases has been suggested. Several bacteria and viruses have been identified as potential etiological factors in CVD.\textsuperscript{5–8}

Periodontitis and dental procedures can be potential factors in transient bacteremia.\textsuperscript{9, 10} Schwartzman reactions have been reported following full mouth debridement.\textsuperscript{11} Thus, gentle mastication can release bacterial endotoxins into the bloodstream in patients with periodontitis. In addition, oral microorganisms can be spread from an infected root canal into the blood stream during and after endodontic therapy.\textsuperscript{12}

Approximately 35\% of adults between ages 30 and 90 in the United States have significant evidence of chronic periodontitis.\textsuperscript{13} Infections of the periodontium are the primary aetiology to chronic periodontitis (CP). Other factors such as genetics, smoking habits, stress, socioeconomic status, gender, and ethnicity are contributory factors.\textsuperscript{14–17}
Several epidemiological and case-control studies have indicated associations between CVD and CP.18–22 Contradictory conclusions have also been reported in that when controlling for one potential confounding factor (smoking) no significant association between CVD and CP could be identified.24,25 These studies, however, did not adequately control for periodontitis. The association between CVD and CP might be questioned in elderly subjects.26 A Cochrane systematic review on the associations between CVD and CP demonstrated that among a large volume of articles only two study could be included.20,27 A majority of published studies on the relationship between CVD and CP have not used appropriate diagnostic methods in either discipline. In one of the studies accepted, a significant association between CVD and CP was reported for fatal coronary heart disease by Beck et al.20 (odds ratio 1.9). Additional studies are warranted to assess the associations between CVD and periodontitis using adequate criteria and appropriate control of confounding factors.

The purpose of the present studies was to identify the odds of having myocardial infarction and CP, and to identify at what diagnostic periodontal threshold this association may become significant.

Methods

The study protocol was approved by the Ethical Committee at Lund University, Sweden (Institutional Review Board approval no. LU556-00) in compliance with the Helsinki declaration and its amendments. All participating subjects signed IRB (Institutional Review Board) approved informed consent. Consecutive surviving subjects admitted to the Central Hospital, Kristianstad with a diagnosis of acute myocardial infarction (AMI) were studied. The diagnosis was based on chest pain associated with typical electrocardiogram (ECG) changes. The initial ECG was considered diagnostic for myocardial infarction if there was ST segment elevation of 2 mm or more in a chest lead, or ST segment elevation of 1 mm or more in a limb lead. ST depression and/or T-wave inversion changes combined with typical serial pattern of cardiac markers [i.e. creatinine kinase isoenzyme (CKMB) and troponin T (TnT)] according to local laboratory standards, were also considered diagnostic for myocardial infarction. Left bundle branch block (LBB) was considered diagnostic for myocardial infarction if chest pain combined with typical serial pattern of cardiac markers were present.

Analysis of high sensitivity CRP levels

A blood sample of 5 ml was centrifuged at 1400×g for 10 min. A total of 300 µl was analysed in the Beckman Coulter IMMAGE automatic analyser for high sensitivity CRP. The IMMAGE assay uses a polyclonal anti-CRP antibody coated to latex particles and rate nephelometric measurements. The IMMAGE nephelometer makes a 1:36 dilution for values up to 80 mg/l and a 1:216 dilution for higher concentrations.

None of the subjects had received dental or periodontal treatment within the preceding 2 months to the AMI event. Once the subjects were stabilized and released from the hospital they received a thorough periodontal examination within 2 months of release from the hospital.

Control subjects were recruited among friends to the subjects with AMI thereby controlling for potential cardiovascular confounders (i.e. gender, smoking status, socio-economic factors). None of the enrolled control subjects had recently received periodontal treatment. All control subjects also received comprehensive medical examination at the Central Hospital Kristianstad by recognized specialists in Cardiology including an ECG and were cleared from evidence of myocardial infarction. It was not possible to enrol perfect matching control subjects among friends. A cohort of subjects available from a research registry meeting the inclusion criteria for not having heart disease and matched in regard to age, gender, SES (socio-economic status; i.e. marital status, education), and smoking habits were enrolled to compensate for potential confounders. It was not always possible to obtain a perfect match on smoking status. The relationship and impact of confounding factors for periodontitis are poorly understood. The primary focus was to control for known medical contributory factors to AMI. Factors known to be indicators of risk for AMI were studied.28 Serum assays assessing fasting serum levels of blood glucose, cholesterol, high and low density lipoproteins were performed at the laboratory of Clinical Chemistry, Central Hospital of Kristianstad.

A routine periodontal examination was performed including assessments of probing pocket depths at four sites per tooth (distance between the gingival margin to the perceived bottom of the pocket and clinical attachment) using mm-graded periodontal probes. Supra-gingival dental plaque was identified as being either present or absent. The presence or absence of gingival bleeding was assessed approximately 10 s after pocket depths were probed. Alveolar bone levels were assessed from intra-oral radiographs that were digitized and computer processed using a custom made image analysis software program developed at the University of Texas San Antonio USA.29 The proportions of marginal bone levels measured at both sides of teeth with a recorded distance ≥4.0 mm between the cementoenamel junction (CEJ) and the level where the alveolar bone and the root surface merged radiographically were calculated providing subject based data on bone status. The 4.0 mm distance was chosen as the cutoff value based on published data demonstrating that a distance ≥4.0 mm clearly constitutes a pathological condition.

All radiographic measurements were performed by one of the investigators (GRP) who was blinded to group belongings and who was not involved in clinical examinations and had no access to other medical data. It was, however, not possible to keep the clinical examiner unaware of the medical status of the subject.

Statistics

The SPSS statistical PC software package 10.1.3 was used (Chicago IL). Descriptive statistics were performed. Independent samples t-tests, and Mann–Whitney U-tests were used to assess differences for studied variables between the two control groups. Comparisons between biomedical variables between the AMI and non-AMI groups were then performed for parametric data using paired sample t-tests and Wilcoxon signed rank tests for non-parametric data as appropriate. The reproducibility of radiographic analysis of alveolar bone loss was assessed by intra-class correlation statistics. Odds ratios between belonging to the AMI group and having periodontitis defined radiographically at various cut-off levels defined by increasing severity of proportions of tooth sites with bone loss ≥4.0 mm using Cochran’s and Mantel Haenszel statistics stratified by age and gender. ROC curves were produced. Paired samples t-tests were used to assess the relationships of continuous data on marginal alveolar bone loss between subjects in the AMI and non-AMI groups.
groups. Binary logistic regression analysis was performed to further study the relationship between AMI status and the extent of alveolar bone loss.

Results

Descriptives

Data based on analysis of 80 patients with AMI and 80 control subjects from a group consisting of friends of the patients (39 subjects) with AMI or from a research registry of subjects (41 subjects) who had participated in a recent health survey. Descriptive data for the AMI group and the two control groups are presented (Table 1). Statistical analysis (independent samples t-tests or non-parametric Mann–Whitney U-test) failed to demonstrate differences in age, gender, SES (marital status, education), smoking habits and periodontal status between the two control groups and therefore these two control groups were merged. The data demonstrated that the matching on smoking yielded no difference in current smoking habits between the AMI and non-AMI groups when subjects who had never smoked were merged with those who had a past history of smoking. At the time of the dental examination all subjects in the AMI group were prescribed antiplatelet drugs. In the control (non-AMI) group one subject had been prescribed an anticoagulant drug (Warfarin) whereas 10 subjects were taking daily low dose aspirin.

The mean TnT value based on the maximum TnT within the first 18 h in subjects with AMI was 2.54 µg/l and the corresponding mean value for highest CKMB within the first 18 h of monitoring was 104.1 (µg/l). Results from statistical analysis of a series of serum assays routinely used to assess risks for cardiovascular diseases are presented (Table 2). It was noticeable that the levels of high reactive CRP and HDL were the only two variables demonstrating significantly higher levels in the AMI group. Subjects in the AMI group (75.4%) and in the non-AMI group (51.7%) had a high reactive CRP level >2.0 mg/l.

No statistically significant differences between the AMI group and the merged non-AMI control group were found for subject characteristics regarding age, the number of remaining teeth, number of endodontically treated teeth, or teeth with periapical lesions or by gender or smoking (yes, no) status. The mean difference in the proportion of sites with gingival bleeding between the AMI and the non-AMI group was not statistically significant (mean difference: 0.5%, 95% CI: −38.6 to 37.5, P>0.98). Statistical analysis demonstrated a difference in the proportion of sites with a periodontal probing depth 6.0 mm (2.7% for non-AMI and 12.1% for AMI group, 95% CI: −2.8 to 0.01, P<0.05). The proportion of tooth sites with visible dental plaque was also significantly higher among subjects in the AMI group (Mean difference: 12.8%, 95% CI: 1.9 to 23.9, t=2.4, P<0.02).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics. Mean values and standard deviation (SD) for study parameters</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
<td>AMI group (n=80)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.4 years ±8.9</td>
</tr>
<tr>
<td>Gender</td>
<td>Female: 15.3%</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>28.2%</td>
</tr>
<tr>
<td>Quit</td>
<td>48.7%</td>
</tr>
<tr>
<td>Current</td>
<td>23.1%</td>
</tr>
<tr>
<td>Never &amp; previous smokers</td>
<td>76.9%</td>
</tr>
<tr>
<td>Remaining teeth</td>
<td>21.1±7.6</td>
</tr>
<tr>
<td>Periapical lesions</td>
<td>0.8±1.1</td>
</tr>
<tr>
<td>Root canal treated teeth</td>
<td>0.5±0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results from serum assays of C-reactive protein, blood lipids and HbA1c values in subjects with an acute myocardial infarct and control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Subjects with acute myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>21.04</td>
</tr>
<tr>
<td>High density lipoprotein (mg/dl)</td>
<td>1.39</td>
</tr>
<tr>
<td>Low density lipoprotein (mg/dl)</td>
<td>3.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>2.03</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>4.96</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.14</td>
</tr>
</tbody>
</table>
Radiographic analysis reproducibility

Full mouth intra-oral radiographs from five subjects with a history of AMI were digitized and analysed on two occasions 1 week apart while the examiner (GRP) was blinded to data previously recorded. The five sets of radiographs represented 152 sets of observations. The intra-class correlation coefficients for the five sets of measurements and the worst marginal bone level were calculated. The sites demonstrated that the distances of CEJ to bone level varied between 0.94 (95% CI: 0.90 to 0.97) and 0.99 (95% CI: 0.97 to 0.99). The correlation coefficients were significantly correlated ($P<0.001$).

Analysis of risk association between AMI and periodontitis based on radiographic criteria

Periodontitis severity was defined as the proportion of sites with a distance between the CEJ and the bone level $\geq 4.0$ mm that exceeded 10%, 20%, 30%, 40%, 50% and 60% of sites respectively. The mean proportional distributions of subjects (AMI and non-AMI group) for the six different periodontal severity levels are presented (Fig. 1). A significant relationship between increasing severity of periodontitis and AMI was observed in that independent t-tests demonstrated that the greatest statistical differences between AMI and merged control groups were found at the 50% severity cutoff level ($t=−8.5$, mean difference: $−0.52$, SE mean difference: $−0.06$, 95% CI: $−0.65$ to $−0.40$, $P<0.001$) followed by the 40% cutoff level ($t=−8.1$, mean difference: $−0.48$, SE mean difference: $−0.06$, 95% CI: $−0.59$ to $−0.36$, $P<0.001$). Furthermore all other cutoff levels also differed ($P<0.001$).

The odds ratios of having AMI and CP defined at various cut-off levels studied are presented in Table 3. Receiver operator characteristic (ROC) curves for a diagnosis of myocardial infarction and periodontitis at the different cut-off values are presented also suggest that with increasing severity of periodontitis a better distinction between AMI and non-AMI can be made except for the worst periodontal severity (>60%) which was only observed in a few cases yielding low statistical power at this level (Fig. 2). Forward stepwise logistic regression analysis demonstrated that the 50% bone loss discriminator had the best association with AMI status ($\beta=1.44$, SE=0.61, Wald coeff. 5.56, exp $\beta=4.22$, $P<0.02$). The 40% bone loss value was also discriminative ($\beta=1.52$, SE=0.72, Wald coeff. 4.51, exp $\beta=4.58$, $P<0.034$).

Analysis of radiographic information on marginal alveolar bone loss as a continuous variable and AMI status

Analysis of the difference between the proportional distribution of sites with marginal alveolar bone loss $\geq 4.0$ mm between subjects in the AMI and non-AMI groups demonstrated highly significant difference (mean difference 35.7%, 95% CI: 22.4 to 49.0%, $t$-value: 5.5, $P<0.001$, paired samples t-test).

**Fig. 1** Mean proportional bone loss $\geq 4.0$ mm at different periodontal diagnostic cut-off levels based on dental radiographic interpretations in subjects with a diagnosis of acute myocardial infarction or not.
Discussion

The results reported are derived from an ongoing study of a larger study population of subjects with or without a defined diagnosis of AMI. A sub-analysis was performed to confirm statistical power for the larger study. Because this sub-analysis yielded very high odds ratios of an association between AMI and CP it was deemed ethically important to report the findings as soon as possible. We thought that it was important to enrol friends to the subjects with AMI as control subjects because we assumed a high likelihood of similar risk exposure to both diseases studied between the two groups of subjects. In our analysis between the two control groups we found no differences for any study variable and hence we concluded that the substitute control group was consistent with the original control group including friends only. This was further confirmed from the analysis of serum HbA1c levels demonstrated that the enrolment strategy for IDDM status in the control group was appropriate and that a majority of subjects had an adequate blood glucose level.

Smoking is a significant risk factor both in cardiovascular disease and periodontitis. A history of smoking has been reported as an important confounder in studies of the association between CVD and CP and when accounted for the odds of an association between the two conditions is drastically reduced. In the present study the enrolment strategy for control subjects had been to control for smoking. Because it would be almost impossible to completely control for past and current smoking habits a sub-analysis of non-smokers only was also performed. The odds of an association between AMI and CP remained statistically significant and higher than reported for any previous study on CVD and CP. This suggests that periodontitis in the absence of smoking remains as a relevant factor to be considered in subjects at risk for acute myocardial infarction.

Specifically, efforts had been made to enrol control subjects with similar characteristics in regards to ethnicity, gender, and smoking habits for which information about their current, past, or never smoking status, the number of cigarettes/year, and the total number of smoke-years was compared. Serum cholesterol values also including LDL, HDL and triglyceride values were also compared between groups demonstrating no group differences. In fact the control group of friends tended to have higher cholesterol values although not statistically significant (data not reported). Because diabetes mellitus might be considered as another confounding factor, both for periodontitis and cardiovascular disease the distribution and severity of diabetes between groups was studied. Blood glucose values were measured as serum fasting glucose as well as serum HbA1c and demonstrated no statistically significant differences between AMI and control groups. Neither was there a difference in those values between the two control groups included. Although several studies have suggested that diabetic and smoking status are confounding factors for periodontitis further studies are in fact needed to confirm this. The results in this study demonstrating statistically significantly higher values for high sensitivity CRP in the AMI group as compared to the controls highlights the relationship between infection/inflammation, high sensitivity CRP and AMI.

Periodontitis is a slowly progressive inflammatory response to infection without obvious signs of disease to the patient. The effect on the host from this chronic infection is poorly understood. It now appears important to carefully investigate what factors are shared between a systemic disease and condition such as AMI and periodontitis. Our data suggest that smoking alone cannot be such a factor.

It is generally accepted that antibiotic prophylaxis is needed in dental treatment of patients with heart valve disease to prevent endocarditis. Oral

<table>
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<th>Table 3 Odds ratios for acute myocardial infarction and a diagnosis of periodontitis based on four different radiographic cut-off levels for periodontitis severity based on the extent of marginal alveolar bone loss</th>
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<tr>
<td>Cut off levels for alveolar bone height</td>
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<tr>
<td>----------------------------------------</td>
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<tr>
<td>Smoking not accounted for (n=160)</td>
</tr>
<tr>
<td>&gt;10%</td>
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<td>&gt;20%</td>
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<tr>
<td>&gt;30%</td>
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<tr>
<td>&gt;40%</td>
</tr>
<tr>
<td>Including only never smokers (n=51)</td>
</tr>
<tr>
<td>&gt;10%</td>
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<tr>
<td>&gt;20%</td>
</tr>
<tr>
<td>&gt;30%</td>
</tr>
<tr>
<td>&gt;40%</td>
</tr>
<tr>
<td>Including never smokers and quit smokers (n=119)</td>
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<tr>
<td>&gt;10%</td>
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microorganisms such as Porphyromonas gingivalis and Streptococcus sanguis have been identified in atherosclerotic plaque.34,35 Similarly to Chlamydia pneumoniae P. gingivalis has a lipopolysaccharide cell wall capsule that may induce macrophage foam cell formation resulting in accumulation of excess cholesterol, contributing to the development of vascular atheroma.36

Studies related to CVD and CP have been published with most ambiguous results with odds ratios of associations varying between 0.9 and 3.2.19–23,27 The reasons for diverse findings or lack of associations may solely reflect inadequate definition of periodontitis. It may also reflect study design not accounting for proper control subjects. In the present study a significant effort was made to enrol carefully matched control subjects who received specialist examination of both cardiovascular and dental status.

A diagnosis of periodontitis is often made using clinical signs of inflammation (pocket depths and bleeding from the gums). CP is a slowly progressive disease of long duration resulting in alveolar bone loss. Whether patients have periodontal pockets exceeding certain threshold values or not depends on several factors that cannot easily be adjusted for. Marginal alveolar bone loss is the accumulated effects of CP. It is therefore pertinent to use loss of marginal alveolar bone as an indicator of CP in subjects with evidence of gingival inflammation. The present study failed to demonstrate that subjects with AMI had significantly higher proportions of sites with gingival inflammation as subjectively demonstrated by the gingival bleeding index. The mean values for gingival bleeding in the two groups (57.0 in the AMI group versus 56.5% in the control group) demonstrated that subjects in both groups had uncontrolled gingival inflammation in regards to the fact that gingival bleeding should not at any time be visible at more than 10–15% of sites.

The lack of a significant difference in bleeding index is inconsistent with the fact that differences were noticed for plaque scores and for the proportion of sites with periodontal probing depths ≥6.0 mm. It is of interest that

Fig. 2  Receiver characteristic curves (ROC) and statistics for selected diagnostic periodontal cut-off values based on the proportional extent of marginal alveolar bone loss in relation to a diagnosis of acute myocardial infarction (AMI) or not. Appropriate data for both groups were used without consideration to matching.
the AMI group did not demonstrate more bleeding on probing as they were, at the time of the dental examination, on anticoagulant therapy. Currently there are no confirmed studies or consensus on the role of low dose aspirin in regards to gingival bleeding. Neither is there information about bleeding tendency in subjects on anticoagulant therapies at a therapeutic level in subjects with a recent history of AMI. In fact few, if any, periodontal studies have presented data on the role of anticoagulant therapy and gingival bleeding indices routinely used in dentistry. Further studies are needed to assess the role of gingival inflammation and AMI. One hypothesis to be tested is that the extensive tendency of bleeding on probing may suggest that the subjects with a history of AMI may have an exaggerated inflammatory response to infection that may in part also explain the cardiovascular history.

Although unlikely, the clinical data may have been confounded by the fact that the clinical examiner by reviewing medical records might have been biased in terms of measurements of periodontal pockets and gingival inflammation. However for the primary outcome measure (radiographic bone levels) this examiner (GRP) only had access to the radiographs and to no other subject data.

Routine intra-oral radiographs taken by general dentists and specialists to identify loss of bone height are used in dental praxis to identify bone loss around teeth and this is a straightforward procedure. Methods for the assessment of alveolar bone height using either direct measurement with mm graded rulers or more elaborate projection methods including the employment of digital imaging and computer software programs have been commonly used in periodontal research. In the present study the most accurate method was used. However, routine dental radiography and the method used in this study should yield comparable results with the advantage of being able to numerically define bone loss with the computer-supported method.

This study was specifically designed to evaluate the relationship between a clearly defined serious cardiovascular event and periodontitis. The odds ratio of an association between AMI and CP reported in the present material was approximately five times higher or more than reported in many previous studies and of clinical relevance.\textsuperscript{19–24} Furthermore, a dose response relationship between AMI and increasing severity of periodontitis was found. The associations between AMI and CP as reported here are consistent with findings from a retrospective study of mortality from heart disease.\textsuperscript{17}

In most welfare states adults receive regularly dental care. It is less likely that they seek preventive cardiovascular examination. The findings from the present study suggest that with increasing severity of periodontitis there is an elevated risk for CVD. Our findings suggest that dentists and specialists in the treatment of periodontal diseases have the responsibility to identify patients at risk for CVD. Extrapolated from the present findings it appears that subjects with 6–8 teeth showing bone loss are at great risk for AMI. A combination of periodontitis defined from radiographs and a case history providing information regarding the patient's general health suggesting risk for CVD should invoke an expedited referral for a comprehensive cardiovascular examination.\textsuperscript{38}

In conclusion, the present case-control study demonstrated that clinical parameters and especially radiographic criteria for periodontitis provide very strong evidence of an association between periodontitis and risk for AMI.

**Contributors**

G. R. Persson, S. Renvert and O. Ohlsson designed the study. O. Ohlsson and T. Pettersson recruited patients and ensured medical diagnosis. S. Renvert managed the study and ensured dental diagnosis. G. R. Persson and S. Renvert analysed data. All researchers wrote the report.

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**References**