Endotoxemia, Immune Response to Periodontal Pathogens, and Systemic Inflammation Associate With Incident Cardiovascular Disease Events

Pirkko J. Pussinen, Karolina Tuomisto, Pekka Jousilahti, Aki S. Havulinna, Jouko Sundvall, Veikko Salomaa

Objective—In periodontitis, overgrowth of Gram-negative bacteria may cause endotoxemia and systemic inflammation leading to cardiovascular diseases (CVD). We investigated in a prospective study the associations of serum endotoxin, antibodies to periodontal pathogens, and inflammation markers with the risk of incident CVD.

Methods and Results—The FINRISK 1992 cohort of 6051 individuals was followed up for 10 years. We examined 185 incident CVD events and a control cohort of 320 individuals using a prospective case–cohort design. High antibody response to periodontal pathogens independently predicted incident CVD events with hazard ratios (HR, quartile 4 versus quartiles 1 to 3, 95% CI) of 1.87 (1.13 to 3.08). The subjects with a high antibody response and high CRP or interleukin (IL)-6 had multivariate-adjusted HRs of 3.01 (1.27 to 7.09) and 3.11 (1.42 to 6.83) compared with low-responders, respectively. The corresponding HRs for high endotoxin concentration were 1.82 (1.22 to 2.73, alone), 3.92 (1.99 to 7.74, with CRP), 3.54 (1.78 to 7.03, with IL-6), and 2.26 (1.13 to 4.52, with tumor necrosis factor (TNF)-α) after adjusting for age and gender. These associations were abolished after adjusting for serum lipids. High endotoxin/HDL ratio, however, had a multivariate-adjusted HR of 1.92 (1.19 to 3.08) for CVD events.

Conclusions—Our results suggest that the exposure to periodontal pathogens or endotoxin induces systemic inflammation leading to increased risk for CVD. (Arterioscler Thromb Vasc Biol. 2007;27:000-000.)

Key Words: infection ■ inflammation ■ lipopolysaccharide (LPS), serology ■ atherosclerosis

Periodontitis is a bacterial infection in the tooth-supporting tissues, which leads to chronic local inflammation, destruction of connective tissue and alveolar bone, and eventually loss of teeth. Mounting evidence1–4 suggests that periodontitis is an independent risk factor for atherosclerosis and cardiovascular diseases (CVD). Data on the role of periodontal pathogens in atherogenesis are, however, more scarce. Several serological studies5–10 and two studies based on detection of bacteria in subgingival plaque samples11–12 support a direct relationship of pathogens etiologically linked to periodontal disease with increased risk for subclinical, prevalent, and future CVD.

Concerning atherosclerosis, the most widely studied periodontal pathogens are Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis, which both are Gram-negative, serologically heterogeneous species. DNA13 of these species, as well as viable pathogens,14 have been found in human atherosclerotic plaque. Bacteria or their parts may have an access to circulation via inflamed periodontal tissue during daily routines. Once in the circulation, bacterial components can induce and promote systemic inflammation and proatherogenic responses.

One potentially important bacterial source of inflammation is endotoxin (LPS), a unique glycolipid situated in the outer wall of Gram-negative bacteria. Endotoxin may trigger or accelerate atherosclerosis by multiple mechanisms, which include activation of inflammatory cells, increase in oxidative stress, and modification of lipoprotein metabolism.15 Subclinical endotoxemia results in a 3-fold risk of incident atherosclerosis and CVD.16–18 In the absence of quantitative methods to determine species-specific LPS concentrations, the sources of endotoxin activity measurable in the circulation may be various. Endotoxin can be found in the plasma of apparently healthy subjects,19 because Gram-negative organisms may colonize the human gastrointestinal, respiratory, and genitourinary tracts. These bacteria produce endotoxin not only during acute infections, but also in common chronic and subclinical conditions, like periodontitis.

Despite of the widely accepted hypothesis that endotoxin is a key player in periodontitis-induced systemic...
inflammation and CVD, its role has not been evaluated in a large prospective study. Therefore, our aim was to assess in a prospective case–cohort study, whether endotoxemia and immune response to periodontal pathogens are associated with incident CVD events among middle-aged men and women, and whether the association is modified by systemic inflammation.

Materials and Methods

Baseline Survey

The FINRISK Study, a population-based chronic disease risk factor survey, was conducted in Finland in 1992. A stratified random sample including 7927 men and women aged 25 to 64 years was chosen from the population register of 4 geographic areas. Because the participation rate was 76%, the final sample size was 6051 subjects (Figure 1). The baseline survey protocol consisted of a venous blood sample, a self-administered questionnaire (socioeconomics, medical history, and health behavior), as well as measurements of blood pressure, height, weight, and waist and hip circumference.

Follow-Up

The study cohort was followed-up for 10 years until the end of 2001 through computerized record linkage using the unique personal identification code assigned to every permanent resident of Finland. The study data were linked to the FINAMI myocardial infarction register, FINSTROKE register, as well as to the National Hospital Discharge Register and the National Causes of Death Register. The study cohort was followed-up for 10 years until the end of 2001.

Figure 1. Flow chart of the study design. Prevalent CVD is excluded from the counts of incident CVD and non-CVD death.

Design

We used the case–cohort design within the framework of the FINRISK-92 cohort (Figure 1). Participants with a history of a CVD event at baseline (= prevalent CVD), with the first CVD event during the follow-up (= incident CVD), and those who died from any cause during the follow-up were considered as cases. A stratified random sample (n=320) from the original cohort served as the control cohort, and it was chosen before any laboratory determinations were made. The number of main study end points was used as the reference to determine the size of the cohort random sample and age was controlled through sampling weights. The selection of participants in the random subcohort was independent of the selection of the cases. The original case–cohort sample included 999 participants, but for 216 of them the amount of stored serum was insufficient for the analyses of the present study. Comparison of the characteristics of the participants with and without an adequate serum sample revealed that the proportion of men was slightly larger in the group with missing serum and, consequently, this group had a slightly higher waist to hip-ratio. No other differences were observed. "Missing serum" did not significantly predict incident CVD events in Cox proportional hazards modeling and was considered a random phenomenon. Therefore, 783 subjects were available for the analyses, among them 185 subjects with an incident CVD event (135 CHD events and 56 ischemic stroke events; Figure 1).

Serum Determinations

Serum IgA- and IgG-class antibodies to periodontal pathogens, *A actinomycetemcomitans* and *P gingivalis*, were determined from frozen sera (~20°C) by multisertype-ELISA, where the antigens comprised strains of formalin-killed whole bacteria representing 6 serotypes of *A actinomycetemcomitans* (a to e and one nonserotype-able strain) and 3 serotypes of *P gingivalis* (a to c). Two dilutions of each serum in duplicate were used and the results (ELISA units, EU) consisting of mean absorbances were calculated as continuous variables. The interassay coefficients for variation as calculated from values of the reference serum applied on each plate were 6.3 and 5.5% for *A actinomycetemcomitans* and 5.1 and 4.7% for *P gingivalis* IgA and IgG, respectively. To decrease the interassay variation, a correction coefficient was calculated from the mean of the reference serum values and the ELISA results of each plate were normalized by this coefficient after the whole material was analyzed. Combined antibody response was computed by summing up the IgG levels to *A actinomycetemcomitans* and *P gingivalis*.20
Serum endotoxin concentrations were determined by kinetic Limulus Amebocyte Lysate (LAL) test kit with a chromogenic substrate (HyCult biotechnology b.v.) on diluted (1:5, vol/vol in endotoxin-free water) samples. Concentrations of CRP, IL-6, and TNF-α, which were measured by solid-phase chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation), were available from our previous work. Serum total and HDL cholesterol concentrations were analyzed in 1992 from fresh samples using routine enzymatic methods (CHOD-PAP, Boehringer) and the cholesterol concentrations were analyzed in 1992 from fresh samples using routine enzymatic methods (CHOD-PAP, Boehringer) and the Olli-C analyzer (Thermo Electron Oy).

Statistics

Means and frequencies at baseline were compared using Wilcoxon rank sum tests and chi-square tests, respectively. The associations of antibodies and the inflammation markers with traditional CVD risk factors and with each other were examined using Spearman rank correlations calculated for the stratified random subcohort. A weighted Cox proportional hazards model, modified to account for the case–cohort sampling design, was used for computing the hazard ratios (HR) and 95% confidence intervals (CI) for the CVD end point. Barlow weighting and variance estimator were used for the analyses. Serum antibody levels to periodontal pathogens and endotoxin concentrations were divided into quartiles using cut points obtained from the random subcohort. The 3 lower quartiles were used as reference categories. The HRs were first adjusted for age and sex, and at the next stage, additionally for serum total cholesterol/HDL cholesterol ratio, systolic blood pressure, waist to hip ratio, BMI, diabetes, smoking status, and years of education classified by tertiles. Smoking was added as a 3-category variable: nonsmoker, former smoker, and current smoker. To test the joint effect of inflammation and immune response, the combined antibody response, and serum endotoxin concentration as well as markers of inflammation (CRP, IL-6, and TNFα) were divided into categories “low” and “high” using the highest quartile limit in the subcohort as the cut point. In the proportional hazards regression models, 4 categories constructed from the immune response and level of inflammation were used: persons with (1) a low antibody response or low LPS and a low level of inflammation (reference category), (2) a high antibody response or high LPS and a low level of inflammation, (3) a low antibody response or LPS and a high level of inflammation, and (4) a high antibody response or high LPS and a high level of inflammation. The statistical analyses were carried out using SAS.

Results

We determined serum antibody levels to periodontal pathogens and serum total endotoxin concentration in a case-cohort study of 784 subjects. The study design is presented in Figure 1. A correlation analysis between the variables determined and selected background variables was performed on the stratified random sample (n=320) from the original cohort, which served as the control group (Table 1). Serum endotoxin concentration had a positive correlation with total cholesterol, diastolic blood pressure, waist to hip ratio, BMI, and antibody levels to P. gingivalis, and a negative correlation with HDL cholesterol. Antibody levels to P. gingivalis correlated positively with diastolic blood pressure, waist to hip ratio, and BMI. TNF-α concentration increased linearly with increasing quartiles of P. gingivalis IgG antibodies after adjustment for age and gender (P for trend 0.03; Figure 2).

During the follow-up time of 10 years, among subjects with no history of CVD at baseline (n=5916), altogether 249 incident CVD events appeared (Figure 1). Of them, 185 were available for the present analyses (Figure 1). The characteristics of these subjects and those who remained free of CVD (n=296) are presented in Table 2. There were no significant differences in any of the determined antibody levels between those who had or did not have a CVD event. The subjects

![Figure 2. CRP, IL-6, and TNF-α concentrations in quartiles of P gingivalis IgG-class antibody levels for the subjects free of CVD at baseline. The concentrations are geometric means adjusted for age and gender. The units on Y-axis are mg/L for CRP and ng/L for IL-6 and TNF-α.](http://atvb.ahajournals.org/faithlink/doi/10.1161/ATVBAHA.117.320790)
TABLE 2. Characteristics of Participants* Who Remained Free of CVD and Those Who Had an Incident CVD Event During the Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>No CVD (n=296)†</th>
<th>CVD (n=185)†</th>
<th>P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54 (8.6)</td>
<td>55 (7.7)</td>
<td>. . .</td>
</tr>
<tr>
<td>Gender, % men</td>
<td>68.6</td>
<td>63.8</td>
<td>. . .</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>6.0 (1.0)</td>
<td>6.2 (1.2)</td>
<td>0.020</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.37 (0.39)</td>
<td>1.24 (0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143 (20)</td>
<td>148 (23)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85 (11)</td>
<td>87 (11)</td>
<td>0.050</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.90 (0.10)</td>
<td>0.92 (0.09)</td>
<td>0.160</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 (4.5)</td>
<td>28.3 (4.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>5.1</td>
<td>9.2</td>
<td>0.080</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>21.3</td>
<td>34.1</td>
<td>0.007</td>
</tr>
<tr>
<td>A actinomycetemcomitans IgG, EU§</td>
<td>2.21 (1.30, 3.89)</td>
<td>2.19 (1.36, 3.62)</td>
<td>0.700</td>
</tr>
<tr>
<td>A actinomycetemcomitans IgG, EU§</td>
<td>4.95 (3.61, 7.46)</td>
<td>4.92 (3.42, 7.78)</td>
<td>0.890</td>
</tr>
<tr>
<td>P gingivalis IgA, EU§</td>
<td>1.66 (0.95, 2.97)</td>
<td>1.75 (0.95, 3.30)</td>
<td>0.410</td>
</tr>
<tr>
<td>P gingivalis IgG, EU§</td>
<td>6.54 (4.60, 9.19)</td>
<td>6.78 (4.81,10.35)</td>
<td>0.420</td>
</tr>
<tr>
<td>Combined antibody response, EU§</td>
<td>11.97 (9.34,15.50)</td>
<td>12.20 (9.44,16.45)</td>
<td>0.380</td>
</tr>
<tr>
<td>Total endotoxin concentration, EU/mL§</td>
<td>122.8 (88.8,176.0)</td>
<td>137.1 (95.4,205.5)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

*Persons with a history of CVD at baseline have been excluded (n=134). †Mean (SD) is presented for continuous measures. ‡Wilcoxon rank sum test or chi-square test. §Geometric mean given (1st and 3rd quartile). A actinomycetemcomitans IgG + P gingivalis IgG.

The hazard ratios (HR, 95% CI, p) for CVD in subjects free of CVD at baseline are presented in Table 3. Compared with the quartiles 1 to 3, in the fourth quartile of CVD at baseline are presented in Table 3. Compared with the quartiles 1 to 3, in the fourth quartile of A actinomycetemcomitans IgG and combined antibody response, the multivariate HRs for CVD event were 1.64 (1.00 to 2.69, P=0.048) and 1.87 (1.13 to 3.08, P=0.015), respectively. High serum endotoxin concentration associated with CVD events when adjusted for age and gender: in the highest quartile versus quartiles 1 to 3 (cut point >176.0 EU/mL) the HR was 1.82 (1.22 to 3.73, P=0.004). In a multivariate model, adjustment for total cholesterol/HDL cholesterol ratio, however, abolished the association. Endotoxin/cholesterol ratio was not associated with CVD events, but high endotoxin/HDL cholesterol ratio had a multivariate HR of 1.92 (1.19 to 3.08, P=0.007) for CVD events. Moreover, this association was linear (P for trend 0.006) with quartile 2 to 4 HRs of 0.86 (0.46 to 1.60), 1.39 (0.76 to 2.55), and 2.11 (1.15 to 3.90), respectively. Neither the combined antibody response nor the endotoxin concentration were associated with non-CVD death (n=129) in subjects free of CVD at baseline with HRs of 1.59 (0.77 to 3.28, P=0.103) and 1.05 (0.60 to 1.83, P=0.440), respectively.

Simultaneous occurrence of high antibody response and high CRP or IL-6 concentration increased the risk of CVD significantly (Table 4). When subjects with low levels were used as the reference, the multivariate-adjusted HRs for CVD were 3.01 (1.27 to 7.09) and 3.11 (1.42 to 6.83), respectively. Simultaneous occurrence of high endotoxin and inflammation marker concentration led to significantly elevated HRs for all 3 cytokines, when adjusted for age with an event, however, had higher serum endotoxin concentrations than those without an event.

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**Discussion**

Our prospective study demonstrated that high IgG-class antibody levels to major periodontal pathogens, *A. actinomycetemcomitans* and *P. gingivalis*, were risk factors for future CVD events in a cohort of middle-aged subjects. In addition, high serum endotoxin concentration was a risk factor for CVD event independently of age and gender, but not independently of total cholesterol and HDL cholesterol concentrations. The elevated risk was seen especially in cases, where the high immune response to periodontal pathogens or endotoxin concentration was accompanied by an inflammatory reaction as indicated by elevated concentrations of CRP, IL-6, or TNF-α. Interestingly, these associations seemed to be specific to CVD events and associations with non-CVD deaths were nonsignificant.

Serum endotoxin concentration correlated positively with IgG-class antibody levels to periodontal pathogens. Elevated IgG-class antibody levels reflect the chronic nature of periodontitis. They remain persistently elevated in periodontal patients and do not necessarily display the current disease status, but merely periodontitis recurrence and/or episodes of systemic exposure to periodontal pathogens. Endotoxin, however, is a short-lived compound cleared from the circulation by lipoproteins. Therefore, our results do not distinguish between subjects with a transient bacterial translocation at baseline and those with long-term endotoxia attributable to chronic infections, like periodontitis. It has been reported though that the degree of endotoxia increases with severity of periodontitis—and area of infected/inflamed periodontal tissue, which can in severe cases represent an area equivalent to a palm of a hand. Compared with periodontally healthy subjects or posttreatment situation, periodontal patients are known to have higher serum endotoxin concentrations. In in vitro experiments, LPS isolated from periodontal pathogens induces macrophage-derived cytokine production and foam cell formation, the magnitude of which may be related to the periodontopathic potential of the strain.

Clearly, all endotoxin measured in the present population does not derive from periodontal pathogens alone, because the assay applied identifies a broad spectrum of endotoxins. These include those for example from *Chlamydia pneumoniae* and *Helicobacter pylori*—also Gram-negative bacteria causing chronic infections and associated with increased risk for CVD. Therefore, it is justified to assume that serum total endotoxin concentration merely mirrors the burden of Gram-negative bacteria than a specific infection. Periodonti-
tis, however, is one of the most common infections also in the Finnish adult population: the prevalence of deepened periodontal pockets is 64%, and severe forms of the disease can be found in 21% of adults.30

In the present study, P. gingivalis IgG-antibody quartiles correlated positively with TNF-α concentration, when age and gender were adjusted for. The weak correlation between the endotoxin quartiles and concentrations of inflammation markers failed to reach statistical significance. Endotoxin contributes both directly and indirectly to the release of immunomodulatory and inflammatory cytokines including TNF-α and IL-6 resulting in the secretion of CRP mainly from the liver, but also from the vascular cells.31 The lack of significant correlation between these parameters is not, however, surprising, because all of them are quite short-term compounds in the circulation. The significance of the correlation between the antibody quartiles and CRP concentrations was abolished after adjusting for age and gender. Patients with clinical periodontitis have had higher serum CRP concentrations compared with periodontally healthy subjects.32 Association between inflammation markers and periodontal pathogens directly or through serology is, however, seldom reported.5,11,33 In the study of Dye et al, high P. gingivalis antibody titers were related to high CRP values,33 whereas in our earlier study high CRP concentrations were associated with high combined antibody response to periodontal pathogens in edentulous subjects only.5 In one of the few studies where subgingival plaque samples have been assessed, periodontal microbiology had a direct relationship with subclinical atherosclerosis, independently of CRP concentrations.11 An explanation behind the lack of association may be that most periodontal pathogens are considered residents of normal oral flora and are frequently found also in periododontally healthy subjects. There are no reports, however, on the serum antibody levels of these healthy carriers, but one may assume that they would be low.

Endotoxin concentration had a strong negative correlation with cholesterol and HDL cholesterol concentration. Therefore the association between endotoxin and CVD is not statistically independent of serum lipids. Although endotoxin associates to all lipoprotein classes for clearance, HDL is considered to be particularly effective in binding and neutralizing it.23,24 The capacity of HDL to bind endotoxin is 10- to 1000-fold higher than the LPS concentrations reported in patients with sepsis, and it is therefore not known whether a moderate change in HDL cholesterol concentration would result in additional protection against endotoxin.23 On the other hand, endotoxin-induced inflammation processes decrease HDL cholesterol levels by increasing serum amyloid A concentrations, affecting the HDL remodelling factors,34 and by downregulating receptors involved in the HDL production.28 Consequently, our result, that high endotoxin in combination with low HDL cholesterol concentration is associated with increased risk for CVD events, fits perfectly well with earlier publications.

Induction of systemic inflammation has been proposed to be the pathogenic mechanism behind the association of infection and atherosclerosis, where bacterial endotoxins and proinflammatory cytokines play an important role.15–17 In the present study, the CVD risk associated with high combined antibody response or endotoxin concentration was particularly clear when it was accompanied by simultaneous inflammatory reaction as indicated by high concentrations of CRP and IL-6. This suggests that both serum antibodies and circulating endotoxins are markers of potentially atherogenic infectious agents, but that the CVD risk is highest among those who respond to them with a systemic inflammation. This may be attributable to genetic reasons and applicable also to other chronic, low-grade infections, such as those caused by herpes, cytomegalovirus, and C. pneumoniae.17,35–37

The strengths of the present study include its prospective population-based design and the long and complete follow-up. Furthermore, we carried out versatile laboratory determinations including 3 markers of inflammation, several antibodies to periodontal pathogens, and endotoxin concentration, which is rarely determined. There are, however, also limitations that need to be mentioned. First, all laboratory determinations could not be performed on 216 participants because of the lack of stored sera. This was, however, a random phenomenon and should not have an effect on the results, except for a small reduction of statistical power. Second, we had no information on the actual dental status of our participants, except the antibody levels. Some of the participants may have been edentulous, which may have contributed to the negative findings on IgA antibodies.

Our results suggest that high IgG-class antibody response to periodontal pathogens and endotoxemia in combination with low HDL cholesterol are associated with increased risk for acute CVD events in a prospective setting. In particular, high antibody response combined with high levels of inflammation markers indicated a high risk of incident CVD events.

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Disclosures
None.

References


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