The Role of the Composite Interleukin-1 Genotype in the Association Between Periodontitis and Acute Myocardial Infarction

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Background: Recent data indicate that interleukin (IL)-1 polymorphism may influence the susceptibility to periodontitis and coronary heart diseases. The aim of this study was to evaluate the impact of the composite IL-1 genotype (allele 2 at IL-1A –889 and IL-1B +3954) in the association between acute myocardial infarction (AMI) and periodontitis.

Methods: One hundred four white subjects (54 patients with AMI and 50 healthy controls) were studied; each received a comprehensive periodontal examination, including measurement of periodontal probing depth (PD) and clinical attachment level (CAL). The extent of periodontitis was assessed by the percentage of sites with clinical AL >3 mm. Polymorphisms in the IL-1 gene cluster were assessed using a reverse hybridization assay.

Results: Compared to controls, mean values for PD (4.6 mm versus 3.7 mm; $P < 0.0001$) and CAL (5.4 mm versus 4.5 mm; $P = 0.0001$) were significantly increased among patients with AMI. Significantly more subjects with moderate or severe periodontitis (≥33% of sites with clinical AL >3 mm) were found in the AMI group compared to controls (31.5% versus 8%; $P = 0.0016$). These differences remained statistically significant after adjustment for smoking, age, and gender. No significant differences were observed in the allele frequencies of the gene loci IL-1A –889 and IL-1B +C3954 between patients with AMI and controls. Also, there was no difference in the frequency of the composite IL-1 genotype. IL-1 genotype–positive patients with AMI had slightly increased PD and AL compared to IL-1 genotype–negative patients with AMI.

Conclusions: The results confirmed an association between periodontitis and AMI but failed to detect a modifying impact of the composite IL-1 genotype. Although the IL-1 genotype was only weakly associated with compromised periodontal health, it was not associated with AMI. *J Periodontol 2009;80:1095-1102.*

KEY WORDS

Coronary heart disease; interleukin-1; myocardial infarction; periodontitis.

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Periodontitis has been considered a risk factor for coronary heart disease (CHD).[1-7] However, previous results[8-11] were not consistent with regard to the strength of the proposed association. The pathogenic mechanisms by which periodontal infections might contribute to the manifestation of endothelial dysfunction and, consequently, arteriosclerosis or acute coronary events, have not been revealed completely. Explanations for this association comprise ideas of causality and/or co-incidence. From a causal point of view, dissemination of periodontopathic bacteria, lipopolysaccharides, and pro-inflammatory mediators into the bloodstream might lead to a systemic inflammatory response, thereby promoting atherosclerotic processes.[12-14] From the view of co-incidence, both diseases share common risk factors, such as age, smoking, diabetes mellitus, male gender, and genetic polymorphisms.[15-17] Similar to periodontitis, CHD is assumed to have an infectious etiology,

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suggesting the involvement of bacterial or viral infections in the manifestation of atherosclerosis.[18-20] Polymorphisms of genes coding for pro- and anti-inflammatory mediators might explain interindividual differences in the susceptibility to CHD and periodontitis and, therefore, the association between the diseases. Immune response–regulating host factors have been identified in both diseases.[21,22] However, this issue was not considered in most previous association studies.

Interleukin (IL)-1 plays a predominant role in the inflammatory response in periodontal lesions and atherosclerosis. IL-1α and -1β upregulate prostaglandin E_2 and matrix metalloproteinases and, together with these components, promote the loss of connective tissue and bone in periodontitis lesions.[23] In arterial lesions, IL-1 stimulates the vascular smooth muscle cells by transforming growth factor-beta[24] and the expression of adhesion molecules by endothelial cells, promoting coagulation and thrombosis.[25] IL-1β also induces the synthesis of C-reactive protein[26] and other inflammatory mediators involved in atherosclerotic plaque formation.[27,28]

Associations with polymorphisms in the genes regulating IL-1 were reported for periodontitis as well as coronary artery disease. Although a composite IL-1 genotype, e.g., the presence of the less common allele (allele 2) in the gene clusters IL-1A –889 and IL-1B +3954, has been related to severe periodontitis,[29,30] another polymorphism in the gene loci coding for IL-1 receptor antagonist (IL-1RN) was described for atherosclerosis.[31,32] In a recent study in an ethnically mixed population, Goteiner et al.[33] reported an increased frequency of the composite IL-1 genotype in patients with acute coronary syndrome who had severe periodontal bone loss. It was hypothesized that endotoxemia, together with an increased proinflammatory response, might increase the risk for acute coronary events in IL-1 genotype–positive patients. To verify this association, this pilot study investigated the role of the composite IL-1 genotype in the association of periodontitis with acute myocardial infarction (AMI) in a white (German) population.

MATERIALS AND METHODS

Study Population

A total of 104 subjects, aged 35 to 61 years, were enrolled in a case-control study that was carried out between August 2005 and August 2006 in cooperation between the Department of Internal Medicine I, Central Hospital, Augsburg, Germany, and the Department of Operative Dentistry, Periodontology and Preventive Dentistry, University Hospital, Aachen, Germany. The study protocol was approved by the Bavarian Ethics Committee, and written informed consent was obtained from all subjects before their examination.

The test group consisted of 60 patients with AMI who were admitted to the Department of Internal Medicine I, Central Hospital, Augsburg. Diagnosis of AMI was based on contemporary criteria that were described earlier.[34] Briefly, according to the Guidelines of the European Society of Cardiology and the American College of Cardiology,[35] typical chest pain, positive troponin test, and characteristic electrocardiogram with ST elevation or non-ST elevation were considered indicative for AMI. Criteria for exclusion from the study were the presence of diabetes mellitus, pronounced obesity (body mass index [BMI] >35 kg/m^2), pregnancy, and antibiotic therapy at the time of admission to the hospital and/or within the past 2 months. Patients who presented <14 teeth and those who underwent periodontal treatment within the 6 months preceding the AMI event were also excluded.

Controls consisted of 55 healthy subjects without cardiovascular diseases who were matched for gender and age status. They were enrolled from a private dental practice in the Central Hospital neighborhood and were randomly selected on the basis of patient card numbers, birth date, and gender. All control subjects were referred to a specialist in cardiology who conducted a comprehensive medical examination, including electrocardiogram, to determine that they did not have cardiovascular disease. Exclusion criteria were the same as for patients with AMI. After exclusions, the final study cohorts consisted of 54 cases and 50 controls. All subjects were of white ethnicity and were unrelated to each other. Information about smoking status and BMI was obtained from each study participant.

Oral Examination

One dentist (JC) performed all periodontal examinations, including assessment of periodontal probing depth (PD) and clinical attachment level (CAL). PD was measured as the distance from the gingival margin to the bottom of the pocket at six sites per tooth. CAL (distance between the cemento-enamel junction and the bottom of the pocket) was obtained by adding the PD values to the gingival recession values (distance between the gingival margin and the cemento-enamel junction). All measurements were performed with a millimeter-graded, pressure-sensitive probe†† set to 0.25 N probing force. Prior to the study, intra-examiner reliability was assessed by calculating the Cohen kappa coefficient. The simple kappa value was 0.958 (95% confidence interval [CI]: 0.921 to 0.994), and the weighted kappa value was 0.972 (95% CI: 0.948 to 0.996), which were considered excellent.

The extent of periodontitis was defined, as previously described,[36,37] by the percentage of sites with clinical attachment loss >3 mm: 0% = absent, 1% to

†† Click-Probe, KerrHawe, Bioggio, Switzerland.

32% = mild, 33% to 66% = moderate, and 67% to 100% = severe.

Analysis of IL-1 Genotypes

IL-1 genotyping was performed for all cases and controls, for which a swab sample of cheek mucosa was obtained. The sample was inserted in a transfer tube and stored at –25°C until further laboratory analysis. All samples were processed using a commercial assay.[‡‡] DNA was extracted, and sequences of the IL-1 gene cluster were amplified by polymerase chain reaction using Taq polymerase[§§] and a final $MgCl_2$ concentration of 2.5 mM. Subsequently, polymorphisms at the gene loci IL-1A –889 and IL-1B +3954 were investigated by reverse hybridization of the generated amplicons to specific probes immobilized on membrane strips.[38] All amplification analyses were performed in a masked manner.

Statistical Analyses

Values for continuous variables are given as mean ± SD. The unpaired *t* test was used to assess differences in the obtained values of these variables between two patient groups (AMI versus control group or IL-1 positive versus IL-1 negative). To assess the influence of the potential confounders age, gender, and smoking on these group effects, multifactorial analysis of covariance (ANCOVA) models with interaction were fitted to the obtained values of these variables. These models incorporated the main effects of group, age, gender, and smoking as well as the two-factor interaction terms between groups and each of the three confounders (i.e., group*age, group*gender, and group*smoking). Interactions with a *P* value >0.05 were regarded as statistically insignificant and were deleted from the model. The resulting model was used to evaluate the confounder-adjusted group effect on the measured values.

Data for categorical variables are summarized by relative frequencies (%) and were compared between two groups using the χ^2 test. Multiple logistic regression models with interaction were fitted to these categorical data to examine the influence of the potential confounders (age, gender, and smoking) on these group effects. Main and interaction effects studied in these models were the same as in the corresponding ANCOVA models.

All statistical tests were conducted using a global significance level of $\alpha = 5\%$ in an explorative manner only. Data processing and statistical analyses were performed using software packages.[‖‖¶¶##]

RESULTS

Descriptive Data and Periodontal Examination

There were no relevant differences between cases and controls with regard to age, gender, and BMI. The group of patients with AMI had more smokers than the control group (51.9% versus 22.0%; Table 1). Patients with AMI had slightly fewer teeth than control subjects. For all periodontal parameters assessed, cases showed worse results than controls. Mean PD and CAL values were statistically significantly increased among patients with AMI. Adjustment for age, gender, smoking, and the interaction terms AMI*age, AMI*gender, and AMI*smoking (ANCOVA analysis) did not change the statistical significance. The patients with AMI had significantly fewer subjects with mild periodontitis and significantly more individuals with severe (and moderate–severe) periodontitis compared to the control group, even after adjustment for potential confounders. The proportion of subjects with moderate periodontitis did not show a significant difference between cases and controls. (Table 2).

Table 1.

Descriptive Parameters

Variable	Patients With AMI (n = 54)	Controls (n = 50)
Age (years; mean ± SD)	50.8 ± 6.3	51.7 ± 6.5
Age (years; range)	35 to 60	36 to 61
Females (n [%])	4 (7.4)	3 (6.0)
Smokers (n [%])	28 (51.9)	11 (22.0)
BMI (kg/m^2; mean ± SD)	27.1 ± 3.6	27.2 ± 3.7
BMI >30 kg/m^2 (n [%])	10 (18.5)	11 (22.0)

IL-1 Allele and Genotype Frequencies

The distribution of the allele frequencies in the gene loci IL-1A –889 and IL-1B +3954 in cases and controls are displayed in Table 3. None of these allele frequencies were statistically significantly different between the groups. With regard to the composite IL-1 genotype, i.e., allele 2 at IL-1A –889 and IL-1B +3954, no statistically significant difference in relative allele frequencies between cases and controls was found either. The same results were observed when subgroups with mild or moderate–severe periodontitis were compared (Table 4).

To estimate the distribution of the IL-1 genotype with periodontal disease, the frequency of the genotype in subjects with mild periodontitis was compared to that in subjects with moderate–severe periodontitis. Those with moderate–severe periodontitis showed a slightly

‡‡ GenoType PST, Hain Lifescience, Nehren, Germany.
§§ HotStar Taq polymerase, Qiagen, Hilden, Germany.
‖‖ SAS version 9.1, SAS Institute, Cary, NC.
¶¶ SPSS version 11, SPSS, Chicago, IL.
Microsoft Excel version 11.1.1, Microsoft, Redmond, WA.

Table 2.

Periodontal Parameters in Patients With AMI and Controls

Variable	Patients With AMI (n = 54)	Controls (n = 50)	*P* Value (crude)	*P* Value (adjusted)*
Missing teeth (n; mean ± SD)	4.4 ± 3.5	3.9 ± 3.8	0.4274†	0.8903
PD (mm; mean ± SD)	4.6 ± 0.9	3.7 ± 0.8	<0.0001†	<0.0001
CAL (mm; mean ± SD)	5.4 ± 1.2	4.5 ± 1.1	0.0001†	0.0003
Periodontitis				
Mild (n [%])	13 (24.1)	28 (56.0)	0.0009‡	0.0041
Moderate (n [%])	24 (44.4)	18 (36.0)	0.4918‡	0.5035
Severe (n [%])	17 (31.5)	4 (8.0)	0.0016‡	0.0057
Moderate–severe (n [%])	41 (75.9)	22 (44.0)	0.0009‡	0.0041

* *P* value adjusted for age, gender, and smoking.
† Unpaired *t* test.
‡ χ^2 test.

Table 3.

Allele Frequencies of IL-1 Gene Loci IL-1A and -1B in Patients With AMI and Controls

IL-1 Allele	Patients With AMI (n = 54)	Controls (n = 50)
IL-1A –C889 (allele 1) (n [%])	50 (94.4)	48 (96.0)
IL-1A –889T (allele 2) (n [%])	27 (50.0)	26 (52.0)
IL-1B +C3954 (allele 1) (n [%])	48 (96.3)	48 (96.0)
IL-1B +3954T (allele 2) (n [%])	24 (44.4)	21 (42.0)

For all comparisons: $P > 0.05$ (χ^2 test).

Table 4.

Frequency of the Composite IL-1 Genotype in Patients With AMI and Controls With Regard to the Periodontal Diagnosis

	IL-1–Positive* Individuals (n [%])	
Cohort	AMI	Controls
Entire group (N = 104)	20 (37.0)	18 (36.0)
Mild periodontitis (n = 41)	4 (30.8)	9 (32.1)
Moderate–severe periodontitis (n = 63)	16 (39.0)	9 (40.9)

For all comparisons: $P > 0.05$ (χ^2 test).
* Allele 2 (the less common allele) at IL-1A –889 and IL-1B +3954.

higher frequency of the IL-1 genotype; however, the difference was not statistically significant. The same result was observed when cases with AMI and controls were analyzed separately (Table 5.)

When IL-1 genotype–positive and –negative patients with AMI were analyzed with regard to periodontal parameters, a slight increase in mean PD and CAL was observed among genotype–positive patients. IL-1 genotype–positive patients with AMI comprised a higher proportion of subjects with moderate–severe periodontitis and a lower percentage of subjects with mild periodontitis compared to IL-1–negative AMI patients. However, no statistically significant difference was detected between the genotype–positive and –negative patients with AMI (Table 6).

DISCUSSION

The present study aimed to investigate periodontal parameters and the impact of the composite IL-1 -genotype in patients with AMI compared to healthy controls. Patients with AMI were recruited from the hospital, and control subjects were enrolled from a private practice, which may suggest a kind of selection bias. Nevertheless, the control group derived from the same geographic area as cases and consisted of systemically healthy dentate patients who were comparable to cases in terms of lifestyle and socioeconomic status. Further, controls were not selected on the basis of any dental or periodontal diagnosis. Therefore, this aspect should not have introduced selection bias.

The study groups were well matched for age and gender. However, because patients with AMI were examined before controls (frequency matching for age and gender) and most of them were males, it was difficult to recruit enough male control subjects between 35 and 60 years of age within the study period; they were more frequently involved in their careers, and interest for study participation was lower, particularly for medical examination to exclude CHD. This resulted in a smaller number of controls (n = 50) than cases (n = 54).

Periodontitis is a chronic inflammatory disease with a wide interindividual variation in extent and severity. Previous studies used different clinical criteria for periodontal disease. In our study, periodontal pathology was assessed through PD and CAL. To further

Table 5.

Frequency of the Composite IL-1 Genotype in Patients With Mild and Moderate–Severe Periodontitis With Regard to the Presence of AMI

Cohort	IL-1–Positive* Individuals (n [%])	
	Moderate–Severe Periodontitis	Mild Periodontitis
Entire group (N = 104)	25 (39.7)	13 (31.7)
AMI (n = 54)	16 (39.0)	4 (30.8)
Controls (n = 50)	9 (40.9)	9 (32.1)

For all comparisons: $P > 0.05$ (χ^2 test).
* Allele 2 (the less common allele) at IL-1A –889 and IL-1B +3954.

Table 6.

Periodontal Parameters in Patients With AMI

Variable	Patients With AMI (N = 54)	
	IL-1 Positive (n = 20)	IL-1 Negative (n = 34)
PD (mm; mean ± SD)	4.8 (0.8)	4.5 (0.9)
CAL (mm; mean ± SD)	5.5 (1.1)	5.4 (1.3)
Mild periodontitis (n [%])	4 (20.0)	9 (26.5)
Moderate–severe periodontitis (n [%])	16 (80.0)	25 (73.5)

For all comparisons: $P > 0.05$ (t test or χ^2 test).

consider the extent of periodontitis, we differentiated mild, moderate, and severe forms of periodontitis based on the percentage of sites with clinical attachment loss >3 mm, as suggested by Cueto et al.[36] and Arbes et al.[37] Because all study participants had at least one periodontal site with CAL >3 mm, they fell into one of the three periodontitis categories. To establish a binary term allowing a contrast with regard to periodontitis, moderate and severe periodontitis were combined into one group and compared to mild periodontitis. Hygiene indexes were not included because patients hospitalized after AMI events could be expected to neglect their oral hygiene and, therefore, to have worse indexes. Additionally, the majority of patients with AMI received anticoagulant drugs, which increase gingival bleeding and, thus, adds doubt about the value of using hygiene indexes as diagnostic criteria in our study. Although the assessment of these indexes would have been useful in our study, it is unlikely that periodontitis was affected by this kind of bias because of the long period needed for periodontal attachment loss, which was more reliably assessed by PD and CAL.

The results of our clinical investigation demonstrated a worse periodontal health status in patients with AMI compared to healthy controls. Smoking, age, and gender have been considered common risk factors for periodontitis and AMI; therefore, they must be regarded as effect modifiers of the association between periodontitis and AMI.[39,40] Although matching was done for age and gender, it was not achieved for smoking because the number of smokers was limited among the subjects who were available as controls. Nonetheless, even after adjustment for smoking, gender, age, and their interaction terms, cases had significantly higher PD and CAL values and more subjects with severe periodontitis. Thus, our results suggest that periodontitis might be a risk indicator for CHD and, thereby, confirm the findings of the majority of previous case-control studies[1-7,36,41] on CHD and periodontitis.

In contrast to the periodontal parameters, no statistically significant association was found between AMI and IL-1 alleles or the composite IL-1 genotype. Differentiation between subjects with mild and moderate–severe periodontitis did not change this finding. These results are in contrast to those previously reported.[33] Several factors may account for this discrepancy. First, Goteiner et al.[33] investigated an inhomogeneous group of patients with acute CHDs, including AMI (n = 54), unstable angina (n = 14), and angina (n = 38), compared to subjects with unknown medical history (n = 1,959). When only patients with AMI were considered, no association with the IL-1 genotype was found, which is in accordance with our results. It is possible that IL-1 polymorphism is associated with (stable) angina rather than with AMI, which remains speculative at this time. Another reason for the different trend in our study might be the fact that matching and/or adjusting for smoking, age, and gender was not reported in the study of Goteiner et al.[33] Differences in the distribution of smokers, males/females, or age groups between cases and controls may introduce some bias because age and male gender are potential risk factors for CHD.[42-44] Finally, the association with the IL-1 genotype in the Goteiner et al. study[33] was mainly based on a large number of elderly patients with AMI (>60 years). In our AMI group, the oldest patient was 60 years of age. An association among IL-1, periodontitis, and AMI in elderly people might reflect the association of IL-1 with periodontitis, which is more pronounced with increasing age[29] (i.e., periodontitis-based effects on CHD seem to be more likely in elderly IL-1 genotype–positive subjects). This might explain our observation (data not shown) that older patients with AMI (>55 years; n = 17) had an increased frequency of the IL-1 genotype (58.7% versus

37.5%) compared to older controls (>55 years; n = 16), and younger patients with AMI (<55 years) tended to have a decreased frequency.

To test the influence of IL-1 on periodontitis, subjects with mild and moderate–severe forms of periodontitis were compared with regard to the frequency of the IL-1 genotype. No statistically significant difference was found. Similarly, within the AMI group, no periodontal parameter differed significantly with regard to the IL-1 genotype. Nevertheless, we observed a non-significant trend toward an increased frequency of moderate–severe periodontitis among IL-1 genotype–positive patients with AMI. Because our study did not have sufficient power to assess a significant influence of IL-1 genotype on periodontitis (sample size bias) and considering the data of previous studies[29,30,45] with positive associations between IL-1 genotype and chronic periodontitis, a more pronounced association of the IL-1 genotype with severe periodontitis might have been identified in a larger cohort. In this case, it can be speculated that IL-1 genotype might be an effect modifier, i.e., it could promote the manifestation of periodontitis and confer an increased secretion of proinflammatory mediators which may, secondarily, increase the risk for atherosclerosis and coronary events via the dissemination of cytokines (e.g., IL-1 and tumor necrosis factor-alpha) into peripheral vessels.[12] However, to the best of our knowledge, a direct effect of the IL-1 genotype on cytokine release in the coronary endothelium has not been reported (no common risk factor in terms of co-incidence). It seems possible that the proportion of the expression of IL-1α and -1β and IL-1RN are different with regard to cell- and organ-specific stimuli,[31,46] favoring a predominantly pathogenic role for IL-1 secretion in periodontal tissues but IL-1RN release in coronary endothelium. This could explain the observation that atherosclerosis was associated with IL-1RN alleles[31,32] but not with the composite IL-1 genotype. According to Kornman et al.,[16] two haplotypes with different biologic functions influence the risk for CHDs: one corresponding to the composite IL-1 genotype might be a primary risk factor for periodontitis, and the other one corresponding to allele 2 of IL-1RN could be a risk factor for atherosclerosis. In the present study, analysis of the IL-1RN gene locus was not included. Nevertheless, the observed trend for a slightly higher proportion of IL-1 in patients with moderate–severe periodontitis might be compatible with Kornman et al.'s[16] hypothesis in terms of the composite IL-1 genotype.

CONCLUSIONS

The results support previous findings of an association between periodontitis and CHD. Our study failed to prove an association between the composite IL-1 genotype and AMI. Observations of increased PD and clinical attachment loss in IL-1 genotype–positive patients with AMI did not reach statistical significance and must be regarded as trends.

The data must be interpreted with the necessary caution because of the following limitations. First, because of the small sample size, the statistical power of our results is limited, and findings have to be confirmed in larger cohorts. Second, our study population included only a small percentage of females. Gender differences in cytokine polymorphisms were reported,[47,48] which may also affect the association between AMI and periodontitis; this could restrict our interpretation primarily to males. Further, ethnicity influences genetic polymorphisms.[49,50] Thus, our results are only applicable to white populations. Alleles or haplotypes of other gene loci in the IL-1 gene cluster might be more strongly associated with AMI. Therefore, further studies are needed to verify our results and to extend the investigation on IL-1RN alleles and linkage analyses within the IL-1 gene cluster.

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