Presence and Significance of Interleukin-1 Polymorphism in Patients Who Present With Acute Coronary Syndrome, Angina, and Chronic Periodontitis: An Epidemiologic Pilot Study

David Goteiner,*†‡ Robert Ashmen,* Neal Lehrman,* Malvin N. Janal,§ and Barnet Eskin‖

Background: The purpose of this study was to determine whether acute coronary syndrome (ACS) and angina patients have a greater prevalence of interleukin (IL)-1 polymorphism at the time of hospital admission than groups without ACS or angina.

Methods: A total of 106 patients hospitalized with ACS or angina were compared to a group of 1,959 individuals tested for susceptibility to periodontitis by profiling the IL-1 gene. Blood collected upon admission was analyzed by polymerase chain reaction amplification and gel electrophoresis to determine IL-1 polymorphism. A questionnaire was completed to assess home care and periodontal symptoms. Hospital and dental records were assessed for inclusion in the study, and dental records were analyzed for radiographic bone loss and dental history.

Results: ACS/angina patients with severe radiographic bone loss demonstrated an increase in IL-1–positive polymorphism ($P = 0.06$). If patients were ≥60 years of age, the prevalence of the positive gene was enriched ($P = 0.009$) with IL-1α+4845T increasing significantly ($P = 0.015$).

Conclusions: For patients ≥60 years of age, there was a statistically significant correlation between ACS/angina and IL-1 polymorphism. Patients with ACS or angina were more likely to evidence a positive IL-1 polymorphism and severe periodontitis. *J Periodontol 2008;79:138-143.*

KEY WORDS

Acute coronary syndrome; angina; interleukin-1; myocardial infarction; periodontitis.

* Department of Periodontics, New Jersey Dental School, University of Medicine and Dentistry of New Jersey, Newark, NJ.
† Department of Diagnostic Sciences, New Jersey Dental School, University of Medicine and Dentistry of New Jersey.
‡ Department of Dentistry, Morristown Memorial Hospital, Morristown, NJ.
§ Department of Psychiatry, New Jersey Medical School, University of Medicine and Dentistry of New Jersey.
‖ Department of Emergency Medicine, Morristown Memorial Hospital.

The development of coronary artery disease (CAD) is attributed to several risk factors, including high serum cholesterol, low serum high-density lipoprotein levels, smoking, increased levels of C-reactive protein (CRP), hypertension, and diabetes.[1,2] However, these risk factors do not explain all cases of CAD. Additional risk factors, such as chronic periodontitis, have been suggested; however, no firm linkage has been established.[1-4]

Some studies[5,6] have suggested that bacterial and viral infections are two potential risk factors that may precipitate myocardial pathology in a certain population. Subclinical infections also may play a role in cardiomyopathy.[7-9] Loesche[1] suggested that an equilibrium is maintained in the contained periodontal infection when the immune response of the healthy individual keeps the lesion subclinical. If the host immune system is compromised and plaque is permitted to mature, a critical mass may be reached, and the resulting pathology may no longer be localized to the mouth.[10]

Gingivitis and periodontitis are infectious inflammatory diseases of the gingiva and underlying supporting structures of

doi: 10.1902/jop.2008.070206

the teeth.[11] *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* (previously *T. forsythensis*), and *Actinobacillus actinomycetemcomitans* often are implicated in the pathogenesis of periodontal disease and unsuccessful therapy.[12] These pathogens can be found in the epithelium and connective tissue and within the cells of the periodontal lesion.[13,14] Recently, these microorganisms have been found incorporated in coronary endothelium and atherosclerotic plaques.[15-23] Kozarov et al.[24] demonstrated that *A. actinomycetemcomitans* and *P. gingivalis* were viable and invasive. Kuramitsu et al.[25] demonstrated the ability of *P. gingivalis* to induce foam cell formation, an initial step in plaque formation, in the presence of low-density lipoprotein (LDL) in macrophage cell culture. Pussinen et al.[26] showed that the extent of affected tissue in periodontitis is associated directly with the ability of isolated LDL to activate macrophages in vitro.

Kornman et al.[27] suggested that once the periodontal lesion has been established, the production of such mediators as interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α) can exacerbate the existing lesion. They concluded that patients who carry the marker for IL-1β might be more susceptible to periodontal disease. In reviewing the literature, Greenstein and Hart[28] concluded that IL-1 testing as a predictor of susceptibility to periodontitis is ambiguous. However, Kornman et al.[29] postulated that another IL-1 genetic pattern (–511 and +2018) may be involved in cardiovascular disease. In experiments in mice lacking the IL-1 receptor agonist gene, Devlin et al.[30] and Nicklin et al.[31] suggested that the expression of IL-1 is likely to have a significant role in signaling artery wall damage by effecting lipoprotein metabolism and foam-lesion development.

Cutler and Iacopino[32] suggested that in advanced periodontitis, levels of 1L-1β and TNF-α can be elevated in the gingival crevicular fluid to such a degree that they can cross the ulcerated epithelium and enter the circulation. Likewise, Kinane and Lowe[33] stated that bacteremias could increase the levels of circulating lipopolysaccharides (LPS), which, in turn, cause subintimal leukocyte infiltration with associated cytokine release and smooth muscle cell proliferation. Geerts et al.[34] recently demonstrated that endotoxemia can be induced by gentle mastication and that the levels are higher in patients with severe periodontal disease. Beck et al.[35] concluded that microbial and LPS exposures may be associated with acute aspects of CAD, such as thrombus formation. In support of this, Herzberg and Meyer's[36] in vitro study demonstrated that dental bacteremias could induce platelet aggregation. Czerniuk et al. [37] evaluated 50 patients admitted with a diagnosis of acute coronary syndrome (ACS). They reported that patients with ACS and advanced periodontitis tended to have higher mean values of IL-1β and TNF-α than patients with less advanced disease.

Valtonen[38] proposed that chronic dental infections, among others, may act synergistically along with classic risk factors, such as a genetic propensity, for a more robust inflammatory response in the development of various atherosclerotic diseases. The production of inflammatory cytokines in IL-1–positive individuals as the result of poor dental health could be associated with an acute coronary event.

The purpose of this investigation was to determine the prevalence of a positive IL-1 polymorphism, a genetic marker for inflammation, in patients who present with angina, unstable angina, or myocardial infarction and to see if there is a relationship between IL-1 polymorphism and the subjects' medical and dental findings with special emphasis on radiographic bone loss.

MATERIALS AND METHODS

The study was reviewed and approved by the Institutional Review Boards at the University of Medicine and Dentistry of New Jersey and Morristown Memorial Hospital.

Patient Selection and Evaluation

The experimental group consisted of 137 dentate patients who entered through the Emergency Department and were admitted and discharged from the cardiac care unit at Morristown Memorial Hospital with a discharge diagnosis of acute myocardial infarction (AMI), unstable angina, or angina (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 410 to 413.9). Because AMI and unstable angina are part of a spectrum essentially differing only in the sequelae of cell death, they often are referred to as ACS. After obtaining patient consent, we examined the patient's medical and dental records, contacted the admitting physician, and evaluated blood samples taken in the Emergency Department upon admission. Only the residual blood taken for creatine phosphokinase (CK) and troponin or basic metabolic profile (BMP) were used in the study. Great effort was made to remove patients with confounding factors. Excluded from the population were patients who had a discharge diagnosis of insulin-dependent diabetes mellitus, multiple diagnoses, chronic antibiotic therapy, pregnancy, obesity, or antibiotic regimes or infection at the time of admission to avoid additional variables that would confound interpretation of the results. No patient was undergoing periodontal therapy at the time of admission. No patient had less than six teeth, and the average had 22.9 ± 7.3 teeth. The control group consisted of

1,959 subjects (excluding the 106 in the experimental group) with an unknown medical history who had an IL-1 profile carried out (commonly known as the periodontal susceptibility test). These blood samples were submitted for the purpose of predicting susceptibility to periodontitis.[27] This group (historical group) had their interleukin profile evaluated by a commercial laboratory (A.K. Taylor, Kimball Genetics, Boulder, Colorado; unpublished data). Background data were obtained from the hospital and the patient's dentist. A supplemental questionnaire was sent to the patient. The radiographs were assessed by three periodontists. No attempt was made to measure interobserver reliability, and conclusions were reached by consensus. The results were interpreted and assigned a score as follows: no disease (0); mild or ≤20% loss of support (1); moderate or >20% to ≤50% loss of support (2); and severe or >50% loss of support (3).[39,40] Subjects (mean age: 61.4 ± 12.3 years; 23% were female) were enrolled in the study from May 2001 through May 2004.

IL-1 Polymorphism

The residual blood (used for CK and BMP) taken at the time of admission to the Emergency Department was centrifuged, and the packed cells were evaluated. Collected DNA was isolated from packed cells of the same samples on filter paper and forwarded to a commercial laboratory¶ for evaluation. Testing for the IL-1α+4845 C/T and IL-1β+3954 C/T (formerly +3953 C/T) polymorphisms was performed by polymerase chain reaction (PCR) amplification of 20 μl DNA. PCR products were digested with Fnu 4HI for IL-1α+4845 and Taq I for IL-1β+3954, and fragments were separated by 10% non-denaturing polyacrylamide gel electrophoresis. The genotype at each locus was scored as 1,1; 1,2; or 2,2. The "2" was assigned to the less common sequence (IL-1α+4845T or IL-1β+3954T). The specific composite genotype consisting of allele 2 on IL-1α and -1β was termed positive. Individuals were determined to be positive or negative and were recorded as such.

Statistical Analysis

Data included discrete measures, summarized as proportions, and continuous measures, summarized as mean ± SD. Differences between groups on discrete measures were evaluated by means of the χ^2 test, and the Fisher exact test was used when needed because of the small sample size. Differences between groups on continuous measures were evaluated by *t* tests (if only two groups) or analysis of variance (if more than two groups), with post hoc tests between groups that controlled for experiment-wise error rate. Associations between continuous measures were evaluated with Pearson correlation coefficients. Statistical significance was taken with an $\alpha \leq 0.05$.

RESULTS

Demographics

A detailed analysis of this group was published previously.[41] In summary, ACS/angina patients reported a longer median time between dental visits and hospital appearance compared to patients who registered at the hospital for elective procedures (6.5 months versus 3.0 months; $P = 0.008$). ACS/angina patients had fewer teeth than those who were discharged with a diagnosis of chest pain (22.9 ± 7.3 versus 26.3 ± 6.0; $P < 0.001$), manifested more untreated dental pathology (50.4% versus 24.2%; $P < 0.01$), and had a higher prevalence of severe periodontitis (38.5% versus 9.1%; $P < 0.05$). The number of teeth was related inversely to the radiographic bone loss where $r = -0.424$ ($P < 0.001$).

ACS/angina patients were more likely to evidence severe periodontits compared to the historical group with an unknown medical history ($P = 0.06$) (Table 1).

IL-1 Polymorphism

Of the 137 patients admitted for ACS or angina, 106 had residual bloods available for IL-1 polymorphism testing. They are included in all of the results (Table 1). The experimental group had a higher prevalence of a positive profile (43.4%), which trended toward statistical significance ($P = 0.06$), compared to the historical group (34.8%) with an unknown health record. If the group consisted only of whites, the results became significant ($P = 0.05$).

When patients ≥60 years of age in the experimental group were analyzed separately, the positive frequency increased compared to the historical group ($P = 0.009$). Comparing patients ≥60 years of age (55.4% in the experimental group and 35.4% in the historical group) using the Z test for independent proportion yielded a *P* value of 0.059. Further analysis revealed that the IL-1α gene + 4845 ($P = 0.015$) was enriched in the test group (Table 2).

DISCUSSION

Renvert et al.[42] concluded that of the five parameters studied, radiographic evidence of bone loss was the best individual parameter for associating periodontal disease with AMI. In our study, 38.5% of subjects had severe periodontitis and another 45.5% had moderate periodontitis. The remainder were diagnosed with mild periodontitis. Every subject in this study had some degree of radiographic bone loss.

Our study included only the dentate population. Although the extent of radiographic bone loss trended toward significance, it was not a significant factor. The extent of the insult, rather than the degree of gingival or mucosal pathology, may be all that is necessary to

¶ Kimball Genetics, Boulder, CO.

Table 1.

IL-1 Polymorphism

Group	IL-1 Negative (% [N])	IL-1 Positive (% [N])
AMI	63.0 (34)	37.0 (20)
Unstable angina	50.0 (19)	50.0 (19)
Angina	50.0 (7)	50.0 (7)
Experimental group		
All races	56.6 (60)	43.4 (46)*
Whites only	55.6 (55)	44.4 (44)†
Historical group	65.2 (1,277)	34.8 (682)*†
Dichotomized by age		
≥60 years (experimental)	44.6 (25)	55.4 (31)‡
≥60 years (historical)	64.6 (128)	35.4 (69)‡
Radiographic bone loss		
Mild	65.4 (17)	34.6 (9)
Moderate	58.1 (25)	41.9 (18)
Severe	51.5 (17)	48.5 (16)*

* $P = 0.06$.
† $P \leq 0.05$.
‡ $P = 0.009$. Z-test for independent proportion = 1.89 ($P = 0.059$).

Table 2.

IL-1α Dichotomized by Age

Age	1,1 (% [N])	1,2 (% [N])	2,2 (% [N])
<60 years	55.6 (30)	33.3 (18)	11.1 (6)
≥60 years	33.9 (19)	60.7 (34)	5.4 (3)

2 = +4845T (the less common allele).
Pearson $\chi 2$ ($P = 0.015$); Fisher exact test ($P \leq 0.0147$).

allow the ingress of microbial products and cytokines. The edentulous population seems to be as susceptible to bacteremias as the dentate population because of ill-fitting prostheses, perhaps they should be included in future studies. Slade et al.[43] reported that CRP levels did not improve with loss of all teeth. They concluded it might be due to mucosal pathology induced by ill-fitting prostheses.

In this study, we found a difference in the prevalence of IL-1 polymorphism between the experimental group and the historical group (43.4% versus 34.8%, respectively). The size of the difference was small and may not be of clinical interest to the individual patient; however, it did trend toward statistical significance ($P = 0.06$), which might suggest an etiologic relationship that would need to be verified by further investigation. If only whites were evaluated, the results became statistically significant ($P \leq 0.05$).[28] The experimental group had a statistically significant result ($P \leq 0.05$) compared to Kornman's population of 1,459 healthy individuals (43.4% versus 32.6%; $P \leq 0.05$) (K.S. Kornman, Interleukin Genetics, Framingham, Massachusetts; unpublished data).

IL-1 is a proinflammatory cytokine that can stimulate the liver to produce acute-phase proteins. Kornman et al.[29] stated that another IL-1 genetic pattern, characterized by different alleles, is not associated with periodontitis but with atherosclerotic plaque formation. Our study indicated that the alleles associated with periodontitis are more prevalent in the subjects with ACS and angina who are ≥60 years of age. Berger et al.[44] and D'Aiuto et al.[45,46] reported that in populations with atherosclerosis, +3954 on IL-1β and +4845 on IL-1α to a lesser degree, correlated with CRP serum levels. They concluded that cytokine genotypes are important determinants of the systemic inflammatory response in subjects with periodontitis. Papapanou et al.[47] also noted a significant increase of both alleles in patients with confirmed periodontitis. This also may explain the conclusion of Janket et al.[48] about age and risk. Age seems to increase the risk associated with periodontitis. In a meta-analysis, Janket et al.[48] noted that in persons ≥65 years of age with periodontitis, the future risk for cardiovascular disease increased from 19% to 44%. They believed this might be an underestimate because of confounding adjustments.

Using extreme caution in interpreting these data, it may be possible to conclude that other overwhelming factors, such as family history for cardiovascular disease or a self-destructive lifestyle, masked the importance of this gene until those subjects had been eliminated from the population by death. Perhaps the less robust gene has a protective effect. We did not assess the role of the IL-1 receptor antagonist gene in this study and its ability to affect transcription.[49]

Endotoxemia caused by periodontitis and modified by a robust inflammatory response may be the proximate cause of an acute coronary event in some individuals. It also may be possible that dental prophylaxis will delay such an event by reducing the bacterial load in the periodontium. Finally, being edentulous may not prevent bacteremias due to the presence of oral microbes. More research to establish the role of periodontitis in acute coronary episodes is indicated.

CONCLUSIONS

These very preliminary findings indicate that the production of inflammatory cytokines in IL-1–positive individuals with radiographic bone loss may be associated with an acute coronary event. For patients ≥60 years of age, there is a statistically significant correlation between ACS/angina and IL-1 polymorphism. Patients with ACS or angina were more likely to evidence a positive IL-1 polymorphism and severe periodontitis.

ACKNOWLEDGMENTS

The authors thank Dr. A.K. Taylor, director at Kimball Genetics, Boulder, Colorado, and all of the personnel in the Department of Emergency Medicine, Cardiac Research, The Core Laboratory of Morristown Memorial Hospital, for their invaluable assistance. The authors also thank Drs. Michael Deasy, chairman, Department of Periodontics, and David Furgang, clinical research associate, Department of Oral Biology, University of Medicine and Dentistry of New Jersey, and Dr. John Banas, chairman emeritus, Department of Cardiovascular Medicine, Morristown Memorial Hospital, for guidance and support.

REFERENCES

1. Loesche WJ. Periodontal disease as a risk factor for heart disease. *Compendium* 1994;15:976-991.
2. Ridker PM, Cusman MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973-979.
3. Khader YS, Albashairah ZSM, Alomari MA. Periodontal disease and the risk of coronary heart and cerebrovascular diseases: A meta-analysis. *J Periodontol* 2004; 75:1046-1053.
4. Hujoel PP, Drangsholt M, Spieferman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *JAMA* 2000;284:1406-1410.
5. Shimada K, Mokuno H, Watanabe Y, Sawano M, Daida H, Yamaguchi H. High prevalence of seropositivity for antibodies to *Chlamydia*-specific lipopolysaccharide in patients with acute coronary syndrome. *J Cardiovasc Risk* 2000;7:209-213.
6. Espinola-Klein C, Rupprecht H, Blankenberg S, et al. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation* 2002;105: 15-21.
7. Mattila KJ, Niemines MS, Yalibnen YY, et al. The association between dental health and myocardial infarction. *BMJ* 1989;298:779-782.
8. Mattila KJ, Valtonen VV, Nieminen M, Huttunen JK. Dental infection and the risk of new coronary events: Prospective study of patients with documented coronary artery disease. *Clin Infect Dis* 1995;20:588-592.
9. Rutger Persson G, Ohlsson O, Pettersson T, Renvert S. Chronic periodontitis, a significant relationship with acute myocardial infarction. *Eur Heart J* 2003;24: 2108-2115.
10. Goteiner D, Sonis S. Cavernous sinus thrombosis and brain abscess initiated and maintained by periodontally involved teeth. *J Oral Med* 1982;37:80-84.
11. Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. *J Periodontol* 1965;36:177-187.
12. Socransky SS, Haffajee AD. Dental biofilms: Difficult therapeutic targets. *Periodontol 2000* 2002;28:12-55.
13. Fives-Taylor P, Meyer D, Mintz K. Characteristics of *Actinobacillus actinomycetemcomitans* invasion of and adhesion to cultured epithelial cells. *Adv Dent Res* 1995; 9:55-62.
14. Frank RM. Bacterial penetration in the apical pocket wall of advanced human periodontitis. *J Periodontal Res* 1980;15:563-573.
15. Deshpande RG, Khan MB, Genco CA. Invasion strategies of the oral pathogen *Porphyromonas gingivalis*: Implications for cardiovascular disease. *Invasion Metastasis* 1998/99;18:57-69.
16. Dorn BR, Donn WA Jr., Progulske-Fox A. *Porphyromonas gingivalis* traffics to autophagosomes in human coronary artery endothelial cells. *Infect Immun* 2001;69:5698-5708.
17. Dorn BR, Dunn WA Jr., Progulske-Fox A. Invasion of human coronary artery cells by periodontal pathogens. *Infect Immun* 1999;67:5792-5798.
18. Freudenberg MA, Galanos C. Bacterial liposaccharides: Structure, metabolism and mechanism of action. *Int Rev Immunol* 1990;6:207-221.
19. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000;71:1554-1560.
20. Deshpande RG, Khan MB, Genco CA. Invasion of aortic and heart endothelial cells by *Porphyromonas gingivalis*. *Infect Immun* 1998;66:5337-5343.
21. Fives-Taylor PM, Meyer DH, Mintz KP, Brissette C. Virulence factors of *Actinobacillus actinomycetemcomitans*. *Periodontol 2000* 1999;20:136-167.
22. Dorn BR, Leung KP, Progulske-Fox A. Invasion of aortic and heart endothelial cells by *Prevotella intermedia*. *Infect Immun* 1998;66:6054-6057.
23. Dorn BR, Burks JN, Seifert KN, Progulske-Fox A. Invasion of endothelial and epithelial cells by strains of *Porphyromonas gingivalis*. *FEMS Microbiol Lett* 2000; 187:139-144.
24. Kozarov EV, Dorn BR, Shelburne CE, Dunn WA, Progulske-Fox A. Human atherosclerotic plaque contains viable invasive. *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Arterioscler Thromb Vasc Biol* 2005;25:17-18.
25. Kuramitsu HK, Kang IC, Qi M. Interaction of *Porphyromonas gingivalis* with host cells: Implications for cardiovascular diseases. *J Periodontol* 2003;74:85-89.
26. Pussinen PJ, Jousilahti P, Alfthan G, Palosui T, Aiskainen S, Salomma V. Antibodies to periodontal pathogens are associated with coronary heart disease. *Arterioscler Thromb Vasc Biol* 2003;23:1250-1254.
27. Kornman KS, Crane A, Wang HY, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 1997;24:72-77.
28. Greenstein G, Hart TC. A critical assessment of interleukin-1 (IL-1) genotyping when used in a genetic susceptibility test for severe chronic periodontitis. *J Periodontol* 2002;73:231-247.
29. Kornman KS, Pankopow J, Offenbacher S, Beck J, di Giovine F, Duff GW. Interleukin-1 genotypes and the association between periodontitis and cardiovascular disease. *J Periodontal Res* 1999;34:353-357.
30. Devlin CM, Kuriakose G, Hirsch E, Tabas I. Genetic alterations of IL-1 receptor antagonist in mice affect plasma cholesterol level and foam cell lesion size. *Proc Natl Acad Sci USA* 2002;99:6280-6285.
31. Nicklin MJH, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin-1 receptor antagonist gene. *J Exp Med* 2000;191:303-311.
32. Cutler CW, Iacopino AM. Pathophysiologic relationships between periodontitis and systemic disease: Recent concepts involving serum lipids. *J Periodontol* 2000;71:1375-1384.
33. Kinane DF, Lowe GDO. How periodontal disease contributes to cardiovascular disease. *Periodontol 2000* 2000;23:121-126.

34. Geerts SO, Nys M, DeMol P, et al. Systemic release of endotoxins induced by gentle mastication: Association with periodontitis severity. *J Periodontol* 2002;73:73-78.
35. Beck JD, Slade G, Offenbacher S. Oral disease, cardiovascular disease and systemic inflammation. *Periodontol 2000* 2000;23:110-120.
36. Herzberg MC, Meyer MW. Effects of oral flora on platelets: Possible consequence in cardiovascular disease. *J Periodontol* 1996;67(10 Suppl.):1138-1142.
37. Czerniuk MR, Górska R, Filipiak JK, Opolski G. Inflammatory response to acute coronary syndrome in patients with coexistent periodontal disease. *J Periodontol* 2004;75:1020-1026.
38. Valtonen VV. Role of infection in atherosclerosis. *Am Heart J* 1999;138:S431-S433.
39. Pitiphat W, Crohin C, Williams P, et al. Use of preexisting radiographs for assessing periodontal disease in epidemiologic studies. *J Public Health Dent* 2004; 64:223-230.
40. Valachovic RW, Douglass CW, Berkey CS, McNeil BJ, Chauncey HH. Examiner reliability in dental radiography. *J Dent Res* 1986;65:432-436.
41. Goteiner D, Ashmen R, Lehrman N, Janal MN, Eskin B. Oral health of patients entering Morristown Memorial Hospital with acute coronary syndrome and angina. *J N J Dent Assoc* 2007;78:33-37.
42. Renvert S, Ohlsson O, Persson S, Lang NP, Persson GR. Analysis of periodontal risk profile in adults with or without a history of myocardial infarction. *J Clin Periodontol* 2004;31:19-24.
43. Slade GD, Gheezi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship between periodontal disease and C-reactive proteins among adults in the Atherosclerosis Risk in Communities study. *Arch Intern Med* 2003;163:1172-1179.
44. Berger P, McConnell JP, Nunn M, et al. C-reactive protein levels are influenced by common IL-1 gene variations. *Cytokine* 2002;17:171-174.
45. D'Aiuto F, Parkar M, Andreon G, et al. Periodontitis and systemic inflammation: Control of the local infection is associated with reduction of serum inflammatory markers. *J Dent Res* 2004;83:156-160.
46. D'Aiuto F, Parker M, Brett PM, Tonetti MS. Gene polymorphisms in proinflammatory cytokines are associated with systemic inflammation in patients with severe periodontal infections. *Cytokine* 2004;28:29-34.
47. Papapanou PN, Neiderud A-M, Sandros J, Dahlén G. Interleukin-1 gene polymorphism and periodontal status. A case control study. *J Clin Periodontol* 2001;28: 389-396.
48. Janket S, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:559-569.
49. Iacoviello L, Di Castelnuovo A, Gattone M, et al. Polymorphisms of the interleukin-1β gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro. *Arterioscler Thromb Vasc Biol* 2005;25:222-227.

Correspondence: Dr. David Goteiner, 2A North Rd., Chester, NJ 07930. Fax: 908/879-8367; e-mail: drgoteiner@yahoo.com.

Submitted April 15, 2007; accepted for publication June 11, 2007.