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Periodontal Disease and its Connection to Systemic Biomarkers of Cardiovascular Disease in Young American Indian/Alaskan Natives

Nicole Delange, MPH[*], **Suzanne Lindsay, PhD**[*,†], **Hector Lemus, DrPH**[*], **Tracy L. Finlayson, PhD**[‡], **Scott T. Kelley, PhD**[§], and **Roberta A. Gottlieb, MD**[‖]

[*]San Diego State University, Graduate School of Public Health, Division of Epidemiology and Biostatistics, San Diego, CA, USA.

[†]Institute for Public Health, San Diego, CA, USA.

[‡]San Diego State University, Graduate School of Public Health, Division of Health Management and Policy, San Diego, CA, USA

[§]San Diego State University, Department of Biology, San Diego, CA, USA

[‖]Cedars-Sinai Heart Institute and Barbra Streisand Women's Heart Center, Los Angeles, CA, USA

Abstract

Background: Periodontal disease has been shown to be associated with cardiovascular disease (CVD). No known studies evaluate the relationship between periodontal disease status and biomarkers of CVD risk in the American Indian/Alaskan Native (AI/AN) population despite their disproportionately high rates of poor oral health and cardiovascular disease-related outcomes. This study compared levels of interleukin-6 (IL-6) and C-reactive protein (CRP) across increasing severity of periodontal disease status among younger adults between the ages of 21 and 43 years old.

Methods: Plasma levels of IL-6 and CRP were measured in young adult participants (ages 21–43) as part of a study of periodontal disease and CVD risk among an AI/AN population in Southern California (n=59). Periodontal evaluations were performed and disease status was classified into three categories based on highest probing pocket depth (none/mild: <3mm; moderate: 4–5mm; severe: 6+mm). Participants with known systemic disease or active infection were excluded.

Results: Severe periodontitis was significantly associated with increased levels of IL-6 compared to those with none or mild periodontitis, before controlling for other variables (p=0.02), but lacked significance after controlling for sex, BMI, smoking status and high density lipoprotein (p=0.09). Moderate periodontal disease was positively associated with IL-6 levels after controlling for potential confounders (p=0.01). Periodontal status was not associated with CRP, before or after adjusting for covariates.

Conclusion(s): In this otherwise healthy AI/AN adult sample, moderate periodontal disease compared to none or mild periodontal disease was associated with increased levels of IL-6. High levels of CRP found in this young population warrant further research.

Keywords

Periodontal Diseases; C-reactive Protein; Interleukin-6; Indians; North American

Introduction

C-reactive protein (CRP) and Interleukin-6 (IL-6) are pro-inflammatory agents that have received significant attention in the past decade due to increasing evidence of their association with poor cardiovascular disease (CVD) outcomes.[1–3] Particular focus has also been given to the relationship between periodontal disease and inflammatory markers as it relates to increased cardiovascular risk.[4–6] However, there remains little literature on this relationship in younger adult populations and in American Indian/Alaskan Natives (AI/AN). It has been hypothesized that chronic oral infection may lead to the entry of bacteria into the blood stream and that these bacteria activate a host immune response, promoting atheroma formation, maturation, and exacerbation.[6] The purpose of this study is to assess whether worsening periodontal disease status is associated with significantly increased levels of biomarkers of cardiovascular risk in a relatively young AI/AN population.

According to 2009–2012 National Health and Nutrition Examination Survey (NHANES) data, Eke et al. estimated that roughly 46% of adults aged 30 or over in the United States (U.S.) have some form of periodontal disease.[7] While periodontal disease prevalence appears to be decreasing over time, disparities in periodontal health among racial/ethnic minorities compared to whites remain.[8] The Surgeon General's report on oral health found that significant racial disparities in oral health exist and in particular, the AI/AN population had some of the poorest oral health outcomes when compared to other racial and ethnic groups in the U.S.[7,9] A recently 2015 report from the Indian Health Service found that 17% of AI/AN dental patients (age 35+) had severe periodontitis compared to 10% of U.S. adults (age 30+); the AI/AN population also had a disproportionate amount of untreated dental caries and missing teeth.[10] These disparities start at a young age. Levels of tooth decay were four times higher in AI/AN preschool children than white non-Hispanic preschoolers.[11] This may be due to differences in bacterial, environmental, behavioral and sociodemographic risk factors as well as relative geographic isolation of tribal populations that may limit access to dental care.[10,11]

Periodontal disease has been shown in several studies to be associated with CRP, independent of established cardiovascular risk factors.[12–14] CRP is an acute-phase reactant produced primarily in the liver in response to inflammatory cytokines.[15] Evidence from more than a dozen prospective epidemiologic studies demonstrated that CRP was a predictor of future vascular events including myocardial infarction, stroke, peripheral artery disease, and sudden cardiac death.[16] A review of available evidence found that those in the high-risk tertile (CRP >3mg/L) had a two-fold increase in relative risk compared to the low risk group (CRP <1mg/L).[1] A similar increase in CRP-associated CVD risk was found in a study of

older AI/AN individuals and evidence suggests CRP levels in this population tend to be higher, potentially due to higher prevalence of diabetes and obesity.[2] Increased levels of CRP were found to be associated with increased blood pressure, elevated body mass index (BMI), smoking, diabetes mellitus, lower High Density Lipoprotein (HDL) levels and higher triglycerides.[1] Additionally, high-sensitivity C-reactive protein (hs-CRP) levels also increased with increasing age, were higher among women than men, and were variable by race/ethnicity, although evidence for AI/ANs was lacking.[17]

Additionally, a number of studies have investigated the relationship between IL-6 and periodontal disease and found it to be produced in excess in diseased periodontal tissue.[12,16,18,19] IL-6 is a circulating cytokine secreted from different cell types, including macrophages and lymphocytes, and its secretion is stimulated by interleukin-1 (or IL-1) and tumor necrosis factor α (TNF-α).[20] Moreover, IL-6 has been found to be one of the most potent drivers of CRP production, suggesting one possible pathway by which IL-6 contributes to increased CVD risk.[21,22] However, IL-6 has also been shown to have an independent association with CVD after controlling for CRP.[23] Thus, increasing IL-6 levels may play a role in systemic disease outside of its impact on acute phase reactants. Factors affecting levels of circulating IL-6 include hypertension, hyperlipidemia, smoking, diabetes, age, and BMI.[3,23] Periodontal disease shares many of the same risk factors with CRP and IL-6 including age, gender, body mass index, and smoking status, which heightens the difficulty in fully understanding their relationship.[16,19,24–25]

Despite the wealth of literature on the link between CVD biomarkers and periodontal disease status, the association between levels of CRP and IL-6 and periodontal disease in racial/ethnic minority groups, particularly in the AI/AN population, has yet to be extensively studied. As a population at high risk for both periodontal disease and CVD, it is imperative to evaluate potential avenues to effectively reduce the burden of illness among AI/AN individuals. Furthermore, a consensus report of the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) found that more information on biomarkers in younger individuals (<65) was needed.[6] Thus, this study aims to address a gap in the literature exploring the relationship between periodontal disease and CVD biomarkers in a younger adult AI/AN population.

Materials and Methods

Study Design and Setting

The data for this study was collected in 2010 by the San Diego State University (SDSU) Native American Research Center for Health (NARCH), the SDSU Institute for Public Health (IPH), and the SDSU Bioscience Center. Study participants were recruited from an AI/AN population from a Southern California American Indian Health Clinic. Clinic staff and researchers recruited patients and their family members seen at the medical or dental clinic for any reason. Recruitment also occurred throughout the surrounding reservation using flyers and posters. Approval for this study was obtained from the SDSU Institutional Review Board (IRB) and the IRB of the Southern California American Indian Health Clinic. Data was collected from participants after obtaining written informed consent and the study follows a cross-sectional design.

Study Population

AI/AN individuals between the ages of 21 and 40 seeking any type of health care at the study clinic were invited to participate. Due to low enrollment, the study participant age criteria was modified to include individuals up to 43 years of age. Women who were pregnant and individuals with known systemic, chronic conditions such as cancer, diabetes, hypertension, or heart disease, including those that were on medication for such conditions were excluded from the study. Further exclusion criteria included: individuals taking medication for inflammation (except H2 blockers), or blood-thinners; immunosuppressed individuals and those with present or active infection such as human immunodeficiency virus (HIV), hepatitis, or tuberculosis; people who used antibiotics within the previous three months; individuals who were treated for periodontal disease within the last six months; and individuals with fewer than 20 teeth, not including third molars. These factors were excluded because of their impact on inflammation and potential to confound the relationships under investigation in the study. Of 92 individuals who were screened by dental clinic staff, two were ineligible and 30 withdrew from the study resulting in incomplete data. One additional participant was excluded from the analysis due to extremely high CRP levels that may have been attributable to acute infection but could not be confirmed due to lack of subsequent testing. Fifty-nine total participants were available for analysis.

Clinical Examination

Periodontal disease status was assessed using a standardized method by two specially trained registered dental hygienists. Six sites on each tooth were evaluated for pocket depth. Periodontal status was broken into three categories based on periodontal pocket cut points defined by the Community Periodontal Index (CPI) recommended by the World Health Organization (WHO).[26] Classification of periodontal pockets was chosen instead of clinical attachment loss due to the young age of the study population. An age less than 40 years of age captures the window of young adulthood where preventative efforts could have the greatest oral health impact before the presence of irreversible bone loss.[27] It has been reported that among patients 26–32 years of age, changes in pocket depth are greater than changes in clinical attachment loss, for which reason that parameter was chosen.[28] Patients with no periodontal pockets greater than 3mm were collapsed to form a single category of none to mild periodontitis. The presence of periodontal pockets between 4–5mm resulted in a classification of moderate periodontitis, and any pockets 6mm or greater resulted in a classification of severe periodontitis. Periodontal evaluation and assessment of patient vitals, height, and weight were done by a member of the clinic staff to ensure optimal patient care. High blood pressure was defined as systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg.

Interview

Research staff conducted a brief interviewer-administered questionnaire with each participant to ascertain information regarding medical history, demographics, and health behaviors. Smoking was dichotomized into current or former smoker versus never smoker, defined by the Centers for Disease Control and Prevention (CDC) as having ever smoked 100 cigarettes in their lifetime.[29]

Laboratory Analyses

Blood samples were taken by a clinic nurse one week after enrollment to determine serum concentrations of CRP, IL-6, and blood lipid levels. Samples were processed immediately and stored at −70 degrees Celsius until analyzed by a commercial laboratory. Single-molecule counting technology was used for measurement of IL-6.[¶] This approach to molecular counting technology has been described previously and has a lower limit of quantification of 0.08 pg/mL.[30] hs-CRP measurements were performed using a Roche analyzer.[#] Both CRP and IL-6 were analyzed as continuous variables.

Statistical Analysis

Frequencies were reported for all categorical variables. Continuous variables were presented as means and standard deviations for normally distributed data and as median and interquartile range for non-normally distributed data. Bivariate associations of each variable with both outcomes, IL-6 and CRP, were examined using simple linear regression with 95 percent confidence. Pearson correlation coefficients were assessed for any possible colinearity between variables. Multiple linear regression analysis was carried out to assess the relationship between the outcomes, CRP and Interleukin-6, and the primary exposure of interest, periodontal status, defined by the CPI. Both cardiovascular biomarkers, CRP and IL-6, had skewed distributions and were log-transformed to meet the normalized distribution criteria for a linear regression model. A final model was fit using a step-wise addition of variables in order of decreasing bivariate significance, with the exception of the primary exposure, which was examined first and retained throughout subsequent analysis. Variables were retained if they had significance $p < 0.05$ or if there was significant confounding of any level of the primary exposure parameter estimates defined as a change greater than 10%. The final model was tested for overall significance using the F-test and was deemed to be significant if the p-value was less than 0.05. Diagnostics were then run to assess the overall fit of the model. All calculations were done using Statistical Analysis Software version 9.4.[**]

Results

Study Population Characteristics

Baseline characteristics of the subjects are shown in Table 1. On average, study participants were about 30 years of age (mean age: 29.2 ± 5.4) and were overweight, bordering on obese (mean BMI: 29.6 ± 5.7). Additionally, a higher percentage of participants were female (64.4%), non-hypertensive (88.1%), and non-smokers (62.7%). The majority (66.7%) of participants had moderate periodontitis. The median IL-6 level was 1.1 pg/mL and the medial level of CRP was 2.8 mg/L.

[¶]Singulex SMC Erenna Immunoassay, Alameda, CA
[#]Singulex CLIA Lab Roche Analyzer, Alameda, CA
[**]SAS Institute Inc., Cary, North Carolina, USA

The Relationship between CRP and Periodontal Status

There was no significant association found between periodontal status and CRP before controlling for other factors (p = 0.85) (Table 2). A final model was fit with gender, BMI, HDL, and smoking status (Table 3). While the overall model was significant ($p<0.05$), periodontal status remained insignificant after controlling for potential confounders. Female gender, increasing BMI, and decreasing HDL were found to have a significant independent association. The full regression model accounted for 35% of the variance in log-transformed CRP.

The Relationship between IL-6 and Periodontal Status

Table 4 presents the results of bivariate analysis between log-transformed IL-6 and selected patient characteristics. Severe periodontitis was found to have a significant association with increased levels of log-transformed IL-6 compared to those with none or mild periodontitis before controlling for other variables but did not reach statistical significance in the final model ($p=0.09$). Moderate periodontal status maintained significance in the model demonstrating a positive association after controlling for possible confounders (Table 5). As with the CRP model, increasing BMI, and decreasing HDL levels, and female gender were found to be independently associated with increasing log-transformed IL-6 levels at $p<0.05$ (Table 5). The full regression model accounted for 41% of the variance in logarithmically normalized IL-6.

Discussion

There is mounting evidence of an association between periodontal disease and increased risk of future cardiovascular events, but the complexity of the relationship and the large number of shared risk factors has heightened the difficulty in understanding the true underlying and potentially causal mechanisms.[6,16,19] Increased cytokine levels have been hypothesized as one pathway by which this occurs.[31] Overall, this study found that moderate periodontal disease was associated with increased levels of IL-6 compared to mild or no periodontal disease with a trend suggesting increased levels of IL-6 in the severe periodontal group. Consistent with previous studies, this study found a moderate correlation between IL-6 and CRP; however, it failed to demonstrate a significant association between periodontal status and CRP levels.[5,23]

Although no significant association between periodontal status and CRP was found, this study provides useful information about expected CRP levels in a younger adult AI/AN population. An analysis of 8,874 adults as part of the 1999–2002 NHANES study found that median levels of CRP among those aged 20–29 and 30–39 were 1.4 mg/L and 1.9 mg/L respectively.[17] Higher CRP levels found in this study population (median: 2.8 mg/L) are consistent with previous findings that CRP levels are elevated in AI/AN populations.[2] This demonstrates the need for more work to be done in this population.

The findings of this study are in agreement with several other studies assessing this relationship.[32–34] A 2009 study conducted among an otherwise healthy group of middle-aged adults also demonstrated a significant difference in IL-6 levels between controls and

periodontal patients and found it to be significantly correlated with pocket depth, but was unable to detect a noticeable difference in CRP levels.[32] They were, however, able to demonstrate significant decreases in levels of both hs-CRP and IL-6 following treatment providing evidence of a potentially causal relationship rather than the result of residual confounding in otherwise healthy patients. Lopez *et al.* also found no significant difference in the levels of CRP in a case-control study of 150 adolescents, although the relationship was significant between CRP levels and the percentage of sites with bleeding on probing.[33] Finally, a study of periodontal disease in 69 Asian Americans, African Americans, and Hispanic adults of similar age to our study population was unable to find a significant association between periodontal disease and CRP until its study definition was also adjusted to account for the percentage of affected sites.[34]

In contrast, Goyal *et al.* demonstrated, in a similar age study population, evidence to support a difference in CRP levels when comparing non-periodontitis patients with chronic or aggressive periodontal disease.[35] Sun and colleagues also found that IL-6 and CRP levels were higher in relatively young individuals with aggressive periodontitis compared to healthy controls.[36] It should be noted, however, that both Goyal *et al.* and Sun *et al.* used a more severe definition of periodontitis.[35,36] Some studies have found positive associations despite small sample sizes, but in slightly older study populations.[25,37] A study among 94 middle-aged individuals found that those with widespread and severe periodontitis had a higher chance of having high CRP-associated CVD risk as defined by American Heart Association (AHA)/CDC guidelines.[25] Shimada *et al.* also demonstrated significant differences in levels of IL-6 and CRP between patients with chronic periodontitis and healthy controls in a study involving 51 middle-aged adults.[37] Several studies, including a meta-analysis and a consensus report, identified a moderate association.[6,13,14]

While mean IL-6 levels in this study trend in an upward direction across increasing levels of periodontal disease, the small number of study participants in the severe periodontal disease group may contribute to our inability to find a significant association after adjustment for potential confounders. Additionally, the relationship between CRP and periodontitis was shown in three studies to be dependent on the severity of periodontitis with more extensive periodontal disease associated with higher levels of CRP in otherwise healthy adults.[18,24,38] The severity of periodontal disease was significantly less than anticipated in our study population, adding to the challenge of detecting a relationship. Since the definition of periodontal disease was based on patients' highest probing pocket depth, the full extent of periodontal disease, including the number of affected sites, may not be adequately captured by the study definition. It may also explain why the relationship of periodontal disease and CRP is typically found in older populations with more advanced disease, and indicate that IL-6 is a more preferable marker to study in younger groups. However, the lack of consistent case definitions of periodontal disease and different methods of periodontal examination makes comparability across studies difficult.

IL-6, along with interleukin-1β (IL-1β) and TNF-α, modulates the hepatic acute-phase response; IL-6, however, is the only cytokine that stimulates the synthesis of the full spectrum of acute phase proteins, including but not limited to CRP.[39] Consistent with the literature supporting a biological pathway connecting these biomarkers, a moderate

correlation (r=0.61) was also found between logarithmic CRP and IL-6 (Data not shown).[21,22,39] Additionally, both of the final models controlled for the same covariates. While they are pathobiologically linked, a study by Bermudez *et al.* confirmed that circulating levels of IL-6 and CRP may not always track each other, and divergent levels have been seen in apparently healthy women.[23] This study provides evidence of a more direct relationship between IL-6 with periodontal disease, and it is possible that assessment of the relationship between markers of inflammation and periodontal disease using CRP alone may only be capturing a portion of the total impact.[39] A study of apparently healthy men found that those in the highest IL-6 quartile at study entry (>2.28 pg/mL) had a relative risk of myocardial infarction 2.3 times higher than those in the lowest quartile (<1.04 pg/mL) and remained significant after controlling for CRP.[3] IL-6 was also found to be associated with incident coronary heart disease (CHD), stroke, and congestive heart failure (CHF) with relative risks ranging from 1.27 to 1.72 per IL-6 standard deviation after adjustment for potential confounders.[40] While CRP is a more widely studied non-specific marker of inflammation due to its stability, as more reliable and affordable assays become available to study IL-6, its clinical relevance may increase.[41]

Several studies have investigated the relationship between IL-6 and periodontal disease and found that inflammatory cytokines are produced in excess in diseased periodontal tissue.[12,16,18,19] Infection of monocytes with *P. gingivalis*, a periodontal pathogen, has been shown to enhance secretion of IL-6 compared to non-infected controls, suggesting a possible mechanism by which periodontal disease might provoke this inflammatory response.[42] Macrophage foam cells and smooth muscle cells express IL-6 in early atheromatous lesions, further implicating IL-6's involvement in the development of CVD.[43] Evidence also suggests IL-6 stimulates the hypothalamic-pituitary-adrenal axis, indicating its association with a number of other chronic diseases including obesity, hypertension and insulin resistance.[20] Finally, IL-6 has been shown to be associated with fasting blood glucose in patients with aggressive periodontitis, highlighting a potential role for IL-6 in the mechanistic pathway between periodontal disease and diabetes.[36] Therefore, understanding the association of IL-6 with periodontal disease has the potential for large-scale impact on chronic diseases and may not be limited to CVD. It remains unclear how much local infection is required to elicit a change in systemic levels, if indeed this is the causative mechanism.

Understanding the possible complex and multidirectional connections between IL-6, periodontal status, obesity, gender, and cardiovascular disease is particularly important among the AI/AN population because of their high rates of obesity and diabetes.[44,45] It is estimated that roughly 30% of total circulating concentrations of IL-6 originate from adipose tissue.[46] In addition to increases in systemic inflammation hypothesized to be the result of periodontitis, obesity-related inflammation may promote periodontitis.[47] A longitudinal population-based study demonstrated that CVD risk associated with overweight and obesity could be linked to four factors: higher blood pressure, glucose, cholesterol, and IL-6-related pathways.[22] Consistent with this, our study found that increasing BMI was significantly associated with increasing IL-6 and CRP levels. BMI has also been shown have a significant relationship with periodontitis among younger adults (18–34) but not among middle and older age adults.[48] The strong connection between BMI and periodontal status at younger

ages may explain our ability to detect differences in levels of IL-6 but not CRP, a downstream product, with a limited sample size. Finally, the significant association with gender warrants further assessment in future studies as it has implications pregnancy-related oral health changes for women in this young age range.

This study sheds light on important considerations. There are relatively few studies in this age group where more preventative efforts could be taken to improve periodontal status and decrease CRP levels. In particular, the high median CRP level demonstrates the need for further research in the AI/AN population. As a well-studied indicator of increased cardiovascular risk, early detection of such risk could have the potential to decrease adverse cardiovascular events in the future.[1] Caution should be taken in interpreting the results of this study due to the limited sample size and study design. While the findings are interesting, the small, targeted study population limits generalizability of the study's conclusions to other populations. The majority of study participants were in the moderate group and future studies would benefit from a greater distribution of individuals in the healthy and severe periodontal groups. Transportation barriers faced by AI/AN individuals living on the reservation likely contributed to the higher levels of study withdrawal and should be taken into account in future studies of this population. In addition, the cross-sectional study design does not allow for conclusions to be made regarding causality. It should be noted that CRP and IL-6 are only proxies for CVD risk and additional studies are needed to assess whether periodontal treatment decreases the number of adverse CVD-associated events. A prospective, randomized study on the benefits of periodontal therapy in this population would help to further confirm or dispute the health benefits of such treatment on cardiovascular risk.

Conclusion

This study indicates that moderate periodontal disease is associated with increasing levels of IL-6 in this relatively young adult AI/AN population. It also challenges the idea of using CRP as a measure for early detection and periodontal treatment intervention in young adult populations, and emphasizes that further research should be done on IL-6. This remains one of few studies of the AI/AN population, who are at greater risk for negative health outcomes related to cardiovascular disease. In general, the higher levels of CRP appear to be consistent with previous literature, but larger, more representative samples are needed to confirm this finding. Given the moderate association between periodontal disease and CVD biomarkers in the literature, a larger study population is recommended for future research in order to fully understand the relationship between CRP and IL-6 and periodontal disease status in younger AI/AN individuals and younger populations more generally.

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Findings: The study found that moderate periodontal disease compared to mild or no periodontal disease was associated with increased levels of IL-6 whereas no association was found between periodontal status and CRP.

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Table 1.

Characteristics of Study Participants (N=59)

Characteristic	n (%)
Periodontal Status	
Severe	11 (18.6%)
Moderate	40 (67.8%)
None/Mild	8 (13.6%)
Gender	
Male	21 (35.6%)
Female	38 (64.4%)
High Blood Pressure	
Yes	7 (11.9%)
No	52 (88.1%)
Smoking	
Current/Former	22 (37.3%)
Never	37 (62.7%)
	Mean (SD)
Age, yrs	29.2 (5.4)
BMI, kg/m^2	29.6 (5.7)
HDL (mg/dL)	48.4 (13.1)
	Median (IQR)
Triglycerides (mg/dL)	137.0 (96.0)
CRP (mg/L)	2.8 (5.6)
IL-6 (pg/mL)	1.1 (1.7)

SD=Standard Deviation; IQR=Interquartile Range

Table 2.

Bivariate Analysis of Log-Transformed C-Reactive Protein Against Selected Characteristics

Characteristic	β	95% CI	p-value
Periodontal Status			0.85
Severe vs. None/Mild	0.15	−0.39, 0.69	0.57
Moderate vs. None/Mild	0.10	−0.35, 0.55	0.65
Gender (Female vs. Male)	0.22	−0.09, 0.52	0.17
High Blood Pressure (Yes vs. No)	0.38	−0.07, 0.83	0.10
Smoking (Current/Former vs. Never)	0.04	−0.27, 0.35	0.81
Age (yrs)	0.003	−0.02, 0.03	0.83
BMI (kg/m^2)	0.04	0.02, 0.06	0.001†
Triglycerides (mg/dL)	0.0004	−0.001, 0.002	0.62
HDL (mg/dL)	−0.01	−0.02, −0.001	0.03*

CI= Confidence Interval

*p < .05,

†p < .01

Table 3.

Multivariate Analysis Assessing the Relationship Between Log-Transformed CRP and Periodontal Status

Characteristic	β	95% CI	p-value
Periodontal Status			
Severe vs. None/Mild	−0.11	−0.59, 0.37	0.65
Moderate vs. None/Mild	0.15	−0.24, 0.54	0.43
Gender (Female vs. Male)	0.49	0.19, 0.79	0.002*
BMI (kg/m^2)	0.04	0.01, 0.06	0.004*
HDL (mg/dL)	−0.02	−0.03, −0.006	0.004*
Smoking (Current/Former vs. Never)	0.12	−0.15, 0.40	0.38

CI= Confidence Interval

R^2= 0.35; F=0.0004

* $p < .01$

Table 4.

Bivariate Analysis of Log-Transformed Interleukin-6 Against Selected Characteristics

Characteristic	β	95% CI	p-value
Periodontal Status			0.06
Severe vs. None/Mild	0.38	0.07, 0.68	0.02 *
Moderate vs. None/Mild	0.23	−0.02, 0.49	0.07
Gender (Female vs. Male)	0.07	−0.11, 0.26	0.43
High Blood Pressure (Yes vs. No)	0.16	−0.11, 0.43	0.25
Smoking (Current/Former vs. Never)	0.05	−0.13, 0.24	0.57
Age (yrs)	0.004	−0.01, 0.02	0.64
BMI (kg/m^2)	0.03	0.01, 0.04	0.0005 †
Triglycerides (mg/dL)	0.0001	−0.0008, 0.001	0.82
HDL (mg/dL)	−0.009	−0.02, −0.003	0.006 †

CI= Confidence Interval

* $p < .05$,

† $p < .01$

Table 5.

Multivariate Analysis Assessing the Relationship Between Log-Transformed IL-6 and Periodontal Status

Characteristic	β	95% CI	p-value
Periodontal Status			
Severe vs. None/Mild	0.23	−0.03, 0.50	0.09
Moderate vs. None/Mild	0.29	0.07, 0.50	0.01*
Gender (Female vs. Male)	0.25	0.09, 0.42	0.004*
BMI (kg/m^2)	0.02	0.006, 0.03	0.005*
HDL (mg/dL)	−0.01	−0.02, −0.004	0.002*

CI= Confidence Interval

R^2=0.41; F=<0.0001

* p < .01