Periodontal parameters and tooth loss were associated with C-reactive protein and leukocyte counts in adult population aged 50 or older

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ABSTRACT
The association between periodontal disease and cardiovascular disease (CVD) has received considerable attention. This study investigated the correlation between tooth loss (the chief clinical parameter of periodontal disease) and systemic biomarkers of CVD, C-reactive protein (CRP) levels, and leukocyte (WBC) counts, in Koreans aged 50 years or older. A cross-sectional data of 5,322 participants was obtained from the 2008 to 2010 Dong-gu Study. Oral examination, survey questionnaire, physical examination, and biochemical assessments were performed. Oral examinations were completed in all dentate participants, and included the percentage of sites with ≥ 4 mm of probing depth (PD4%), clinical attachment level ≥ 4 mm (CAL4%), and bleeding on probing (BOP%). The number of missing teeth was categorized as 0-7, 8-15, 16-31, and edentulous. The serum CRP levels and WBC counts were assessed. Multivariate linear regression analysis was performed after adjusting for other potential confounders, to evaluate the association between the clinical parameters of periodontal disease, CRP levels and WBC counts. In the fully adjusted model, PD4%, BOP% and the number of missing teeth positively correlated with the CRP levels (p < 0.05), but CAL4% did not. The PD4%, CAL4%, and BOP% (p < 0.05) were concomitant with the WBC counts, but the number of missing teeth was not. The clinical parameters of periodontal disease and tooth loss directly correlated with CRP levels and WBC count in adults aged 50 years and above. This association indicates the potential significance of periodontal inflammatory burden for systemic inflammation.

KEY WORDS: C-reactive protein, Leukocytes, Periodontal disease, Tooth loss

Introduction
Periodontal disease is a bacterially induced chronic inflammatory disease of the supporting tissues of the teeth, connective tissue and bone that are slowly destroyed by the action of the inflammatory process [1]. It had been reported that periodontal disease elevates systemic inflammatory burden; therefore, several systemic diseases including cardiovascular disease (CVD), diabetes and obesity are associated with periodontal disease [2]. In particular, studies have reported the relationship between periodontal disease and CVD based on incidence or mortality [3,4]. Continuing studies [5-8] have revealed that periodontal disease is another important risk factor for cardiovascular diseases. The host-mediated inflammatory response to periodontal pathogens and their components, release of
matrix metalloproteinases, alteration in lipoprotein metabolism and poor dietary habits may contribute to the atherosoma pathogenesis in patients with periodontal disease [4]. Periodontal treatment, along with the primary and secondary prevention of traditional risk factors of CVDs (smoking, hypertension, dyslipidemia, diabetes, obesity and lack of exercise), might reduce morbidity and/or mortality of CVD [4]. Inflammation may be one possible pathway to link periodontal disease with CVD [3].

Because these two diseases share similar inflammatory features [9, 10], inflammatory biomarkers should be considered to investigate the mechanism between them. Paquette et al. [9] suggested that elevated C-reactive protein (CRP) levels may be particularly useful for identifying asymptomatic persons who may be at high risk for future cardiovascular events but who have average cholesterol levels. The CRP is an acute-phase reactant primarily produced by the liver in response to infection or trauma. It appears to be directly involved in augmenting the innate inflammatory response via induction of prothrombotic factors and interference with endothelial nitric oxide synthase [9]. Leukocytes (WBC) are the principal component of the immune system and the inflammatory response. Traditionally, the total number of WBC in peripheral blood has been used as a diagnostic measure to investigate whether a given individual suffers from an infection or inflammatory disease [11]. Studies have reported the relation between periodontal disease and inflammatory markers including CRP level [7-17] and WBC count [18,19]. Additionally, many clinical periodontal parameters were included, such as the number of missing teeth, clinical attachment level (CAL), periodontal probing depth (PD) and bleeding on probing (BOP), to determine the effect on systemic biomarkers, respectively. While limited population-based studies have been reported, there has been no study targeting Koreans. Also, since periodontal disease prevalence increases with age and it is very high among the elderly people, we conducted this research targeting Koreans over fifties. The aim of the present study is to investigate the association between the clinical parameters of periodontal disease, tooth loss, CRP levels and WBC counts among Koreans over the age of fifty.

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**Materials and Methods**

**Participants**

The Dong-gu Study is an ongoing prospective study designed to investigate the prevalence, incidence, and risk factors for chronic disease in urban populations. Details of the study participants and measurements have been published previously [20]. From 2007 to 2010, 34,040 eligible people who were aged ≥ 50 years and who resided in the Dong-gu district of Gwangju metropolitan City in Republic of Korea were invited by telephone to participate. A total of 9,260 participants were enrolled (response rate: 27.2%; 3,713 males and 5,547 females). Periodontal examination was carried out on 5,621 participants among the 7,577 people who participated in the study from 2008 to 2010. One hundred and thirty-six participants were excluded because of missing data on blood glucose, blood lipids, anthropometric measurement, blood pressure measurement, medical history, and life-style data, while 163 participants with WBC counts of less than 2.0 × 10^9 cell/μL or more than 12.0 × 10^9 cell/μL, and/or CRP ≥ 1.0 mg/dL were excluded because of a high probability of acute inflammation and other medical disorders. As a result, 5,322 (2,208 males and 3,114 females) participants remained for final analysis. This study was approved by the institutional review board of Chonnam National University Hospital (IRB No: I-2008-05-056). All participants were provided written consent after receiving a full and clear explanation of the study details.

**Questionnaire survey and physical examinations**

Information on demographic characteristics, lifestyle, medical history, and medication use for hypertension or hyperlipidemia of each subject was assessed with a standardized questionnaire administered by trained staff. Smoking status was classified as non-smokers (smoked <100 cigarettes in their lifetime and currently a non-smoker), former smokers (smoked ≥ 100 cigarettes in their lifetime and currently a non-smoker), and current smokers (smoked ≥ 100 cigarettes in their lifetime and currently a smoker).

Weight was measured to the nearest 0.1 kg while the participants were dressed in light clothing. Height was measured to the nearest 0.1 cm in stocking feet. Body mass index (BMI, kg/m^2) was calculated by dividing the body weight (kg) by the square of the height (m^2). Blood pressure (BP) was measured after at least 5 minutes of rest in the sitting position using a mercury sphygmomanometer. The average of three consecutive readings of systolic BP (SBP) and diastolic BP (DBP) taken at 1-minute intervals was used in the analysis.
Biochemical laboratory assessment

Venous blood samples were collected from participants following an overnight fast. Serum was separated on site and stored at -70°C until required. Total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) concentrations were examined using a model 7600 automatic analyzer (Hitachi, Tokyo, Japan). The CRP level was determined by means of particle-enhanced immunonephelometry using a BN II nephelometer (Dade Behring, Marburg, Germany). The lower detection limit for CRP was 0.2 mg/L. The WBC count was determined using a cell counter (Micro 60, ABX, Montpellier, France).

Periodontal examinations

All participants were examined in a standardized protocol with a mouth mirror and a Williams probe (Hu-friedy, Chicago, IL, USA). Oral examinations were performed by three trained examiners. Full-mouth records were made for the number of teeth present and dental caries, while a periodontal examination was limited to a random half-mouth. The distance from the gingival margin to the base of the pocket (periodontal probing depth, PD) and gingival recession were measured at 6 sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual), and sites of bleeding on probing (BOP) were measured. Clinical attachment level (CAL) was calculated as the sum of gingival recession and probing depth. The percentage of sites with PD ≥ 4 mm (PD4%), with CAL ≥ 4 mm (CAL4%) and with BOP (BOP%) were recorded for each patient. Participants were divided into three groups according to the percentage of sites with PD4%, CAL4% and BOP%. When counting the number of teeth, the third molars were included and only the teeth with complete eruption into the oral cavity were counted. Participants without teeth were classified as edentulous. Digital panoramic radiographs (PlanmecaProOne, PlanmecaOy, Helsinki, Finland) were taken at the following exposure conditions: 66 kV, 9 mA, and 18.0s. The number of missing teeth was categorized into four categories (0-7, 8-15, 16-31, or edentulous).

Statistical analysis

Data are presented as the mean ± standard deviation (SD) or as the percentage for categorical variables. CRP and TG levels were not normally distributed. To approximate normal distributions, CRP and TG values were log-transformed prior to analyses, and geometric means with 95% confidence intervals are presented. χ² test and t-test

Table 1. General characteristics, periodontal disease parameters, and biochemical parameters of the study population according to gender

|                      | Men       | Women     | p-value |
|----------------------|-----------|-----------|---------|
| N                    | 2208      | 3114      |         |
| Age, years           | 66.1 ± 7.9| 64 ± 8    | <0.001  |
| Body mass index, kg/m²| 23.9 ± 2.7| 24.6 ± 2.9| <0.001  |
| Current smoking, n (%)| 528 (23.9)| 49 (1.6)  | <0.001  |
| Education (middle school or less), n (%)| 1002 (45.4)| 2309 (74.1)| <0.001  |
| Systolic blood pressure, mmHg | 125.4 ± 16.6 | 122.8 ± 17.3 | <0.001 |
| Diastolic blood pressure, mmHg | 75.4 ± 10.8 | 73.3 ± 10.2 | <0.001 |
| Medication for hypertension, n (%) | 788 (35.7) | 1121 (36.0) | 0.42 |
| Medication for diabetes mellitus, n (%) | 325 (14.7) | 353 (11.3) | <0.001 |
| Medication for dyslipidemia, n (%) | 133 (6.0) | 308 (9.9) | <0.001 |
| Number of missing teeth, medians (IQR)* | 7 (4-13) | 7 (4-12) | 0.65 |
| CAL4%, medians (IQR) | 25.0 (11.9-41.7) | 14.1 (6.3-26.7) | <0.001 |
| PD4%, medians (IQR) | 4.2 (0.0-13.1) | 2.4 (0-8.3) | <0.001 |
| BOP %, medians (IQR) | 5.1 (0.0-15.6) | 6.0 (0.0-16.7) | 0.077 |
| Triglycerides, mg/dL (IQR)* | 117.0 (82.0-174.0) | 117.0 (85.0-167.0) | 0.697 |
| Total cholesterol, mg/dL | 190.7 ± 36.9 | 208.2 ± 39 | <0.001 |
| HDL cholesterol, mg/dL | 49.4 ± 11.7 | 52.6 ± 11.6 | <0.001 |
| Glucose, mg/dL | 113.1 ± 26.7 | 107.3 ± 23.5 | <0.001 |
| C-reactive protein, mg/dL (IQR)* | 0.60 (0.30-1.30) | 0.50 (0.20-1.10) | <0.001 |
| White cell blood count, × 10⁹/μL | 6.1 ± 1.6 | 5.6 ± 1.5 | <0.001 |

Data presented as the means ± SD, medians (interquartile range)* or n (%) CAL4%: the percentage of sites with clinical attachment loss ≥ 4 mm; PD4%: the percentage of sites with probing depth ≥ 4 mm; BOP%: the percentage of sites which bled after probing; HDL: high density lipoprotein.
were conducted for categorical and continuous variables, respectively.

After adjusting for other potential confounders, multivariate linear regression analysis was performed to evaluate the association between clinical parameters of periodontal disease including CAL4%, PD4%, BOP%, tooth loss, CRP levels, and WBC counts. Age, gender and year of survey were adjusted as confounders in the first model, while BMI, smoking, education, medication for hypertension, diabetes mellitus, dyslipidemia, HDL, TG, TC, glucose, SBP and DBP were further adjusted in the second model. Statistical analysis was performed by using the SPSS version 21.0 (IBM SPSS, Chicago, IL, USA). The value of \( p < 0.05 \) was considered significant.

**Results**

The general characteristics and clinical parameters of periodontal disease in this study are presented in Table 1. Of the 5,322 participants analyzed, 2,208 (41.8%) were males and 3,114 (58.2%) were females. The mean age of males and females was 66.1 ± 7.9 and 64.0 ± 8.0, respectively. The CAL4% and PD4% were greater in males than in females. However, for the number of missing teeth and BOP%, there was no significant difference between genders. Biochemical laboratory parameters are presented in Table 1. For all parameters, except TG, statistically significant differences were found between genders.

The association among clinical parameters of periodontal disease, CRP levels and WBC counts is shown in Table 2 and Table 3, respectively. In the fully adjusted model (model 2), the number of missing teeth was positively associated with CRP levels; in particular, participants in the edentulous group showed significantly higher CRP levels (\( p < 0.05 \)). Apart from CRP levels, there were no relations between the number of missing teeth and WBC counts. The CAL4% was associated with WBC counts (\( p < 0.05 \)), but not with CRP levels. The PD4% was associated with CRP levels and WBC counts (\( p < 0.05 \)). The BOP% was associated with CRP levels and WBC counts (\( p < 0.05 \)).

**Discussion**

The association between periodontal disease and the two inflammatory markers (CRP levels and WBC counts) has been investigated, though the reported results were based on a limited population [16,21]. We conducted this population-based study to investigate Korean populations over the age of fifty. In this study, we found that periodontal probing depth and BOP were associated with sys-

| Table 2. Association between periodontal disease parameters and C-reactive protein level (mg/dL) |
|---------------------------------------------------------------|
|                                                                 |
| C-reactive protein (mg/dL)                                    |
| N | Model 1* | p for trend | Model 2† | p for trend |
|----|----------|-------------|----------|-------------|
| Number of missing teeth | |
| 0-7 | 2847 | 0.63 (0.61-0.66) | 0.59 (0.57-0.61) |
| 8-15 | 1478 | 0.71 (0.67-0.75) | 0.65 (0.62-0.68) |
| 16-31 | 776 | 0.75 (0.70-0.81) | 0.70 (0.65-0.75) |
| Edentulous | 221 | 0.80 (0.69-0.92) | <0.001 | 0.73 (0.64-0.83) | <0.001 |
| CAL4% | |
| Tertile 1 (0.0-10.7) | 1698 | 0.61 (0.58-0.64) | 0.62 (0.6-0.65) |
| Tertile 2 (10.8-26.9) | 1702 | 0.60 (0.57-0.62) | 0.59 (0.57-0.62) |
| Tertile 3 (27.0-100.0) | 1701 | 0.65 (0.62-0.68) | 0.057 | 0.64 (0.62-0.67) | 0.363 |
| PD4% | |
| Tertile 1 (0.0) | 1703 | 0.58 (0.55-0.61) | 0.60 (0.57-0.63) |
| Tertile 2 (0.8-6.4) | 1700 | 0.60 (0.58-0.63) | 0.60 (0.58-0.63) |
| Tertile 3 (6.5-100.0) | 1698 | 0.68 (0.65-0.72) | <0.001 | 0.66 (0.63-0.69) | 0.006 |
| BOP% | |
| Tertile 1 (0.0-1.2) | 1686 | 0.58 (0.55-0.61) | 0.59 (0.57-0.62) |
| Tertile 2 (1.3-11.5) | 1712 | 0.61 (0.58-0.64) | 0.61 (0.59-0.64) |
| Tertile 3 (11.6-100.0) | 1703 | 0.67 (0.64-0.71) | <0.001 | 0.65 (0.62-0.69) | 0.009 |

Values presented as geometric means (95% confidence interval) for C-reactive protein level

*Adjusted by age, sex and year of survey. †Adjusted by age, sex, year of survey, body mass index, smoking, education, medication for hypertension, medication for diabetes mellitus, medication for dyslipidemia, HDL cholesterol, logarithm triglycerides, total cholesterol, glucose, systolic blood pressure and diastolic blood pressure. ‡Statistical significance of interaction term was evaluated in Model 2.

CAL4%: the percentage of sites with clinical attachment loss ≥ 4 mm; PD4%: the percentage of sites with probing depth ≥ 4 mm; BOP%: the percentage of sites which bled after probing.
Periodontal disease and inflammatory makers

For CVD patients, the role of systemic inflammation is well established and evaluation of acute phase inflammatory markers such as CRP levels and WBC counts is a reliable method for examining inflammation [22]. CRP levels are found in trace amounts with levels < 0.3 mg/dl in healthy individuals. In the event that the total number of WBC is beyond the normal reference range (>10 × 10^3 cells/μL), leukocytosis should be considered.

A direct causal relationship between periodontal disease and CVD is not established; however, several studies support biologically plausible mechanisms. First, moderate to severe periodontal disease increases the level of systemic inflammatory disease; and periodontal disease has been associated with increased systemic inflammation as measured by CRP and other biomarkers. Treatment of periodontitis sufficient to reduce clinical signs of the disease also decreases the level of systemic inflammatory mediators [6,23,24]. Second, in untreated periodontitis, gram-negative bacteria may be found in periodontal pockets surrounding each diseased tooth, and also the same species have been found in atheroma [4]. But, due to the multifactorial nature of periodontal disease and CVD, establishing a direct casual relation between the two diseases is difficult. In addition, limitations of small sample size, insufficient number of confounding factors and differences in study design create difficulty in investigating the association. Consequently, the large population-based study was designed to contain many confounding factors to investigate the association more precisely.

An indirect relationship between periodontal disease and CVD shares many risk factors, which are commonly shown in the two diseases. Thus, risk factors (including smoking, diabetes mellitus, obesity, plasma TG, TC and hypertension, medication for diastolic blood pressure) are considered as confounders given their relative importance to this relationship. Additionally, advancing age, male gender and familial histories are commonly found in both diseases and may also serve as confounders [5]. In the present study, model 2 was adjusted for age, gender, year of survey, BMI, smoking, education, medication for hypertension, medication for diabetes mellitus, medication for dyslipidemia, HDL cholesterol, logarithm triglycerides, total cholesterol, glucose, systolic blood and diastolic blood pressure.

Table 3. Association between periodontal disease parameters and white blood cell count (× 10^3 cells/μL).

| White blood cell count (× 10^3/μL) | N | Model 1* | p for trend | Model 2† | p for trend |
|-----------------------------------|---|----------|-------------|----------|------------|
| **Number of missing teeth**       |   |          |             |          |            |
| 0-7                               | 2847 | 5.73 (5.67-5.79) | 5.78 (5.72-5.81) |
| 8-15                              | 1478 | 5.83 (5.75-5.91) | 5.81 (5.73-5.88) |
| 16-31                             | 776  | 5.89 (5.78-6.00) | 5.80 (5.70-5.91) |
| Edentulous                        | 221  | 6.00 (5.79-6.20) | 0.002 | 5.85 (5.66-6.05) | 0.445 |
| **CAL4%**                         |   |          |             |          |            |
| Tertile 1 (0.0-10.7)              | 1698 | 5.71 (5.64-5.79) | 5.75 (5.68-5.82) |
| Tertile 2 (10.8-26.9)             | 1702 | 5.71 (5.64-5.78) | 5.72 (5.66-5.79) |
| Tertile 3 (27.0-100.0)            | 1701 | 5.92 (5.84-5.99) | <0.001 | 5.87 (5.80-5.94) | 0.029 |
| **PD4%**                          |   |          |             |          |            |
| Tertile 1 (0.0)                   | 1703 | 5.65 (5.58-5.73) | 5.71 (5.64-5.78) |
| Tertile 2 (0.8-6.4)               | 1700 | 5.74 (5.67-5.82) | 5.76 (5.69-5.82) |
| Tertile 3 (6.5-100.0)             | 1698 | 5.94 (5.87-6.02) | <0.001 | 5.88 (5.81-5.95) | 0.002 |
| **BOP%**                          |   |          |             |          |            |
| Tertile 1 (0.0-1.2)               | 1686 | 5.68 (5.60-5.76) | 5.72 (5.64-5.79) |
| Tertile 2 (1.3-11.5)              | 1712 | 5.73 (5.66-5.80) | 5.74 (5.67-5.81) |
| Tertile 3 (11.6-100.0)            | 1703 | 5.93 (5.85-6.00) | <0.001 | 5.88 (5.81-5.96) | 0.006 |

Values presented as arithmetic means (95% confidence interval) for white blood cell count (× 10^3 cells/μL). *Adjusted by age, sex and year of survey. †Adjusted by age, sex, year of survey, body mass index, smoking, education, medication for hypertension, medication for diabetes mellitus, medication for dyslipidemia, HDL cholesterol, logarithm triglycerides, total cholesterol, glucose, systolic blood pressure and diastolic blood pressure.

CAL4%: the percentage of sites with clinical attachment loss ≥ 4 mm; PD4%: the percentage of sites with probing depth ≥ 4 mm; BOP%: the percentage of sites which bled after probing.
be absent. Meisel et al. [25] reported that subjects with total tooth loss, although devoid of periodontal inflammation, might exhibit increased levels of systemic inflammatory mediators. They also discussed the possibility that denture-related mucosal lesions in toothless persons harboring bacteria or fungi may elicit a systemic burden [26]. In addition, the association between edentulism and systemic markers could be observed as a sign of a special susceptibility to various diseases including periodontitis and early tooth loss.

Elevated WBC in patients with periodontitis have been reported in some studies [19,27,28]. Kweider et al. [19] were the first to report higher numbers of WBC in periodontitis (8.7 × 10^3 cells/μL in patients in comparison to 6.0 × 10^3 cell/μL in controls). In the present study, total white cell counts were elevated according to severity of periodontal disease except for tooth loss. Additionally, intervention studies have observed a decrease in the WBC counts after periodontal therapy [23].

CRP levels and WBC counts did not show statistical significance with CAL and tooth loss, respectively. There are some possible explanations for these results. As mentioned above, CRP and WBC are acute phase inflammatory markers. The CAL is the sum of PD and gingival recession, and represents past periodontal tissue destruction rather than present disease activity. In analysis of PD, which represents present disease severity, however, there is strong statistical significance with CRP. So it is plausible that CAL is not a suitable variable to investigate the association with periodontal disease and CRP levels. On the other hand, there are two studies that diagnosed periodontal disease with clinical attachment loss [13,28]. These studies reported a positive relation with CAL and CRP levels unlike the result of the present study. This discrepancy can be explained by confounding factors. One study [13] did not contain any confounding factors in the statistical analysis, which can confuse the association, whereas the other study [28] contained only age, gender, smoking, TG, cholesterol and BMI. Analysis of tooth loss and WBC counts might be explained in the same manner. Tooth extraction of patients who suffered from periodontal disease has an effect on the reduction of inflammatory burden [29]. Therefore, systemic inflammation might be reduced in patients with multiple tooth loss. Another possible explanation is that total WBC counts were used in investigating the association, and only the neutrophil count showed statistical significance. It might have been significantly different if differential WBC counts were used in analysis.

There are some limitations in this study. First, a cross-sectional design cannot reveal the causal relationship between periodontal disease and the two biomarkers. Second, the dental history of periodontal treatment and the reason for tooth extraction were not inspected. Further longitudinal studies are recommended to consider dental history into the analysis.

Conclusions

Within our results, clinical parameters of periodontal disease and tooth loss were associated with CRP and WBC in adults aged 50 and over. This association implies the potential significance of periodontal inflammatory burden for systemic inflammation.

Conflict of Interest

The authors declare that they have no competing interests.

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References

1. Burt B. Position paper: epidemiology of periodontal diseases. J Periodontol 2005;76:1406-1419. doi: 10.1902/jop.2005.76.8.1406.
2. Demmer RT, Squillaro A, Papapanou PN, Rosenbaum M, Friedewald WT, Jacobs DR, Desvarieux M. Periodontal infection, systemic inflammation, and insulin
resistance: results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2004. Diabetes care 2012;35:2235-2242. doi: 10.2337/dc12-0072.
3. Xu F, Lu B. Prospective association of periodontal disease with cardiovascular and all-cause mortality: NHANES III follow-up study. Atherosclerosis 2011;218:536-542. doi: 10.1016/j.atherosclerosis.2011.07.091.
4. Yao Z, Yang J, Pan L, Chen Z. Periodontal treatment: potential to reduce cardiovascular morbidity and/or mortality. Med hypotheses 2009;73:33-35. doi: 10.1016/j.mehy.2009.01.051.
5. Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, Roberts WC. The American Journal of Cardiology and Journal of Periodontology editors?? consensus: periodontitis and atherosclerotic cardiovascular disease. J Periodontol 2009;80:1021-1032. doi:10.1902/jop.2009.097001.
6. Bokhari H, Syed A, Khan AA, Butt AK, Azhar M, Hanif M, Tatakas DN. Non-surgical periodontal therapy reduces coronary heart disease risk markers: a randomized controlled trial. J Clin Periodontol 2012;39:1065-1074. doi: 10.1111/j.1600-051X.2012.01942.x.
7. Buhlin K, Hultin M, Norderyd O, Persson L, Pockley AG, Rabe P, Klinge B, Gustafsson A. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol 2009;36:541-549. doi: 10.1111/j.1600-051X.2009.01430.x.
8. Chen YW, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, Iwai T, Izumi Y, Ishikawa I. Periodontitis may increase the risk of peripheral arterial disease. Euro J Soc Vasc Surg 2008;35:153-158. doi: 10.1016/j.ejvs.2007.08.016.
9. Paquette DW, Brodala N, Nichols TC. Cardiovascular disease, inflammation, and periodontal infection. Periodontol 2000 2007;44:113-126. doi: 10.1111/j.1600-0757.2006.00196.x.
10. Seymour GJ, Ford PJ, Cullinan MP, Leishman S, West MJ, Yamazaki K. Infection or inflammation: the link between periodontal and cardiovascular diseases. Future Cardiol 2009;5:5-9. doi: 10.2217/14796678.5.1.5.
11. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76:2106-2115. doi:10.1902/jop.2005.76.11-S.2106.
12. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35:277-290. doi: 10.1111/j.1600-051X.2007.01173.x.
13. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JI, Nardin ED. Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol 2001;72:1221-1227. doi:10.1902/jop.2000.72.9.1221.
14. Linden GJ, McClean K, Young I, Evans A, Kee F. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. J Clin Periodontol 2008;35:741-747. doi: 10.1111/j.1600-051X.2008.01288.x.
15. D’Aiuto F, Ready D, Tonetti MS. Periodontal disease and C-reactive protein-associated cardiovascular risk. J Periodontol Res 2004;39:236-241. doi: 10.1111/j.1600-0765.2004.00731.x.
16. Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US population. J Dent Res 2000;79:49-57.
17. Saito T, Murakami M, Shimazaki Y, Oobayashi K, Matsumoto S, Koga T. Association between alveolar bone loss and elevated serum C-reactive protein in Japanese men. J Periodontol 2003;74:1741-1746. doi: 10.1902/jop.2003.74.12.1741.
18. Gustafsson A, Ito H, Asman B, Bergstrom K. Hyper-reactive mononuclear cells and neutrophils in chronic periodontitis. J Clin Periodontol 2006;33:126-129. doi: 10.1111/j.1600-051X.2005.00883.x.
19. Kweider M, Lowe GD, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count; links with myocardial infarction? Scott Med J 1993;38:73-74.
20. Kweon SS, Shin MH, Jeong SK, Nam HS, Lee YH, Park KS, Ryu SY, Choi SW, Kim BH, Rhee JA, Zheng W, Choi JS. Cohort Profile: The Namwon Study and the Dong-gu Study. Int J Epidemiol 2014;43:558-567. doi: 10.1093/ije/dys244.
21. Pitiphat W, Savetsirl W, Wara-Aswapati N. C-reactive protein associated with periodontitis in a Thai population. J Clin Periodontol 2008;35:120-125. doi: 10.1111/j.1600-051X.2007.01179.x.
22. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511. doi: 10.1161/01.CIR.0000052939.59093.45.
23. Hussain Bokhari SA, Khan AA, Tatakas DN, Azhar M, Hanif M, Izhar M. Non-surgical periodontal therapy lowers serum inflammatory markers: a pilot study. J Periodontol 2009;80:1574-1580. doi:10.1902/jop.2009.090001.
24. Graziani F, Cei S, Tonetti M, Paolantonio M, Serio R, Sammartino G, Gabriele M, D’Aiuto F. Systemic inflammation following non-surgical and surgical periodontal therapy. J Clin Periodontol 2010;37:848-854. doi: 10.1111/j.1600-051X.2010.01585.x.
25. Meisel P, Wilke P, Biffin R, Holtfreter B, Wallaschofski H, Kocher T. Total tooth loss and systemic correlates of inflammation: role of obesity. Obesity 2012;20:644-650.
doi: 10.1038/oby.2011.218.
26. Ajwani S, Mattila KJ, Narhi TO, Tilvis RS, Ainamo A. Oral health status, C-reactive protein and mortality and a 10 year follow-up study. Gerodontol 2003;20:32-40. doi: 10.1111/j.1741-2358.2003.00032.x.
27. Wakai K, Kawamura T, Umemura O, Hara Y, Machida J, Anno T, Ichihara Y, Mizuno Y, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Associations of medical status and physical fitness with periodontal disease. J Clin Periodontol 1999;26:664-672. doi: 10.1034/j.1600-051X.1999.261006.x.
28. Fredriksson MI, Figueredo CM, Gustafsson A, Bergstrom KG, Asman BE. Effect of periodontitis and smoking on blood leukocytes and acute-phase proteins. J Periodontol 1999;70:1355-1360. doi: 10.1902/jop.1999.70.11.1355.
29. Khader YS, Al Habashneh R, Al Malalheh M, Bataineh A. The effect of full-mouth tooth extraction on glycemic control among patients with type 2 diabetes requiring extraction of all remaining teeth: a randomized clinical trial. J Periodontal Res 2010;45:741-747. doi: 10.1111/j.1600-0765.2010.01294.x.