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ORIGINAL ARTICLE

Association of periodontitis with increased white blood cell count and blood pressure

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Abstract

This study aimed to examine the association of periodontitis with white blood cell (WBC) count and blood pressure (BP). In 2002, 424 subjects (manufacturing workers) were investigated for periodontitis by a general dentist. All were Japanese. Among them, 364 subjects (269 men and 95 women) who also attended the next year's (2003) screening were enrolled for this study. Of the 364 subjects, 55 (15.1%) had periodontitis. We also measured the BP and WBC count in periodontitis and non-periodontitis subjects at baseline and 1-year later follow-up. The WBC count was higher in subjects with periodontitis than in subjects without periodontitis, both at baseline [mean ± standard error (SE) $6.6 \times 10^3 \pm 0.2 \times 10^3$/ml vs $5.8 \pm 0.3 \times 10^3$/ml; $p < 0.001$] and follow-up ($7.0 \pm 0.3 \times 10^3$/ml vs $6.5 \pm 0.1 \times 10^3$/ml; $p = 0.03$). The systolic BP was higher in subjects with periodontitis than in subjects without periodontitis, both at the baseline (128.8 ± 2.1 mmHg vs 120.8 ± 0.8 mmHg; $p < 0.001$) and follow-up (129.2 ± 2.3 mmHg vs 123.0 ± 0.8 mmHg; $p = 0.011$), and so was the diastolic BP both at baseline (76.1 ± 1.5 mmHg vs 71.2 ± 0.6 mmHg; $p = 0.003$) and follow-up (80.5 ± 1.7 mmHg vs 75.4 ± 0.7 mmHg; $p = 0.004$). Periodontitis is associated with increased BP and WBC count. This finding may provide one underlying pathway linking periodontitis and cardiovascular disease.

Key Words: *Atherosclerosis, blood pressure, inflammation, periodontitis, white blood cell*

Introduction

Periodontitis results in local destruction of connective tissues in which bacterial products penetrate periodontal tissues, initiating an inflammatory response. This common infection has been suggested as a novel risk factor for cardiovascular disease in a number of studies. Epidemiological studies have reported the association between periodontal disease and (i) coronary heart disease (1–3), (ii) cerebrovascular disease (4,5) and (iii) peripheral vascular disease (6). On the other hand, some studies found no relationship (7–9), and the topic remains controversial. Previous investigations of the periodontitis and cardiovascular disease relationship have focused on clinical vascular events.

Periodontitis and hypertension share common risk factors, such as increasing age, smoking, stress and socio-economic status. These risk factors may confound the association of the two diseases. Therefore, the question whether periodontitis relates to the pathogenesis of subclinical atherosclerosis is crucial for the elucidation of a causal relationship. However, it was seldom studied. If it is true that periodontitis is independently related with blood pressure (BP), its clinically importance as evidence in connecting periodontitis and atherosclerosis would be raised.

A white blood cell (WBC) is the principal component of the immune system and inflammatory response. Several studies have reported the relation of elevated WBC count and coronary heart disease (10,11), stroke (10), and subclinical atherosclerosis (12,13). In addition, an elevated WBC count is associated with higher BP (14). This information

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supports a certain role of WBC in the chronic process of atherosclerosis. However, chronic inflammatory states are not associated with an elevation of WBC count, and it is unknown whether this association between WBC count and atherosclerosis reflects ongoing chronic subclinical infection (12).

A few previous studies have reported an association between periodontitis and BP (15–17). However, none has examined an association between both systolic BP (SBP) and diastolic BP (DBP) and periodontitis, and simultaneously taken inflammatory markers into account. Thus, this study examined the association between SBP/DBP and periodontitis as well as WBC count in apparently healthy subjects.

Materials and methods

Study participants

The subjects were apparently healthy workers who had been currently working at a factory making writing materials. The subjects underwent investigations as a part of an annual comprehensive health screening in accordance with the Occupational Safety and Health Law. During 2 days in April 2002, an invited dentist performed dental health checks, during the ordinary screening of 424 workers. Of the 424 workers at baseline, 364 (91%) who also attended the next year's (April 2003) screening were enrolled for the study. All were Japanese. The study was approved by the ethical review board and performed in accordance with applicable regulatory requirements of the factory.

Data collection

The health screening was performed by the Japan Preventive Medicine Association, except the dental examination. Information included medical examination, medical interview, medical history and laboratory tests. Demographic and clinical characteristics included age, gender, current history of medically treated hypertension and diabetes, family history of medically treated hypertension (siblings, parents and grandparents), current smoking and alcohol intake, daily work and sleep hours, and physical activity. The medical examination included height, weight, laboratory data, SBP and DBP. BP was measured in the right arm using a normal mercury sphygmomanometer in accordance with the guideline of the health screening (18). For the BP readings, participants were required to sit on chairs at least 5 min before the reading in a room prepared for the health check, which was kept around at 25°C. The first and the fifth phase of the Korotkoff sounds were recorded as SBP and DBP. The follow-up information included SBP, DBP and WBC count that were taken at the same health screening on April 2003. All the procedures were the same as in 2002.

Periodontal examination

To assess the periodontal condition, we used the WHO's community periodontal index for treatment needs (CPITN). The condition of each subject was divided into sextants, and for each sextant we recorded the highest index found according to the following scores: 0, periodontal health; 1, gingival bleeding; 2, calculi detected during probing; 3, pocket depth 4–5 mm; and 4, pocket depth$\geqslant$6 mm. The periodontal condition of every patient was reported as the worst sextant CPITN condition. Participants with CPITN 3 and 4, namely having gingival pockets 4 mm or more, were classified as periodontitis cases.

Statistical analysis

We used SPSS, release 11.5 (SPSS Inc.) for statistical analysis. Descriptive parameters were shown as the mean, standard deviation and percentiles. In univariate analysis, the *t*-test was used for a comparison of the mean values. Categorical variables were analyzed by using the chi-square test or Fisher's exact test when appropriate. Baseline and 1-year later follow-up information of WBC count and BP between low CPITN (non-periodontitis) and high CPITN (periodontitis) groups were compared by analysis of variance (ANOVA) and analysis of covariance (ANCOVA) with adjustment of the possible confounders. In multivariate analysis, age was categorized as a binary variable at the median, because of its asymmetrical distribution. A significant difference was defined as $p < 0.05$.

Results

Among the 364 participants, 271 (74.5%) were male. Average age (mean$\pm$SD) was 39.8$\pm$11.1 years, ranging between 20 and 59 years. The basic characteristics stratified by the presence of periodontitis are shown in Table I. Among the study participants, subjects with periodontitis were predominantly male and smokers. There were no statistical differences between the two groups in the other characteristics, including age. Four subjects (7.3%) with periodontitis and 16 (5.2%) subjects without periodontitis had current history of treated hypertension. However, the

Table I. Basic characteristics stratified by periodontal status.

	Periodontitis		
	No	Yes	
	(n=309)	(n=55)	p
Age, years, mean (SD)	39.5 (10.9)	41.7 (11.8)	0.17
Male gender, n (%)	224 (72.5)	47 (85.5)	0.04
Height, cm, mean (SD)	166.0 (8.6)	166.3 (8.3)	0.81
Weight, kg, mean (SD)	63.3 (11.2)	64.5 (11.7)	0.48
Body mass index, kg/m^2, mean (SD)	22.9 (3.3)	23.2 (3.4)	0.49
Total cholesterol, mmol/l, mean (SD)	5.2 (0.9)	5.2 (0.8)	0.71
Triglycerides, mmol/l, median (SD)	1.3 (1.2)	1.5 (1.2)	0.30
Hypertension, n (%)	16 (5.2)	4 (7.3)	0.52
Diabetes, n (%)	6 (1.9)	2 (3.6)	0.35
Familial history of hypertension, n (%)	104 (33.7)	19 (34.5)	0.90
Current alcohol intake, n (%)	175 (56.6)	35 (63.6)	0.33
Current smoking, n (%)	119 (38.5)	31 (56.4)	0.02
Exercise $\leqslant$1/week, n (%)	49 (15.9)	9 (16.4)	0.92
Sleep $<$7 h/day, n (%)	112 (36.2)	34 (43.6)	0.30
Labor $>$9 h/day, n (%)	186 (60.2)	35 (63.6)	0.63
Lost teeth $\geqslant$3, n (%)	39 (12.6)	8 (14.5)	0.70

Probability values are for two-group comparison of means (unpaired t-test) or percentages (chi-square test or Fisher's exact test). SD, standard deviation.

prevalence was low in the both groups and the difference did not reach statistical significance. Duration of hypertension ranged between 0 and 23 years, and was 3.5 ± 3.7 years in periodontitis subjects and 5.9 ± 6.5 years in non-periodontitis subjects (p=0.28 in t-test).

In the analysis that treated WBC count as a linear variable (Table II), subjects with periodontitis had higher WBC counts than those without. This trend was consistent through the analysis, and was significant, except for the adjustment at the follow-up. As for the covariates in the adjusted analysis, body mass index and smoking were associated with WBC count both at the baseline and the follow-up.

The analysis that treated SBP and DBP as linear variables is shown in Table III. At baseline, subjects with periodontitis had significantly higher SBP than those without it. This trend was consistent even after possible confounders were taken into consideration. At the follow-up results, there was a similar trend, although the two ANCOVA results did not reach statistical significance. The differences of SBP between subjects with and without periodontitis were 8.0 (unadjusted), 6.1 (adjusted 1) and 6.0 (adjusted 2) mmHg at the baseline, and 6.2, 4.2 and 3.7 mmHg at follow-up, respectively. At both the baseline and the follow-up analysis, subjects with periodontitis had significantly higher DBP than those without. The difference of DBP between subjects with and without periodontitis were 4.9 (unadjusted), 3.6 (adjusted 1) and 3.4 (adjusted 2) mmHg at the baseline, and 5.1, 3.7 and 3.7 mmHg at the follow-up, respectively.

Table IV shows an example that shows statistical significance and non-significance of covariables in ANCOVA (shown in Table III) between periodontitis and non-periodontitis. As shown in Table IV, male gender, age, hypertension and

Table II. Association between periodontitis and white blood cell count.

	White blood cell count (10^3/ml, Mean $\pm$ SE)			
	Baseline		Follow-up (1-year later)	
Periodontitis	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
No (n=309)	5.8 ± 0.1	5.8 ± 0.1	6.5 ± 0.1	6.5 ± 0.1
Yes (n=55)	6.6 ± 0.3	6.4 ± 0.2	7.0 ± 0.3	6.9 ± 0.2
F for trend	12.7	8.1	4.8	2.4
p	$<$0.001	0.005	0.03	0.12

[a]For gender, age, body mass index, smoking, drinking, hypertension and diabetes.

Table III. Association between periodontitis and blood pressure.

	Systolic blood pressure (mmHg, mean ± SE)					
	Baseline			Follow-up (1-year later)		
Periodontitis	Unadjusted	Adjusted 1[a]	Adjusted 2[b]	Unadjusted	Adjusted 1	Adjusted 2
No (n=309)	120.8 ± 0.8	121.1 ± 0.8	121.1 ± 0.8	123.0 ± .9	123.3 ± 0.8	123.4 ± 0.8
Yes (n=55)	128.8 ± 2.1	127.2 ± 1.8	127.1 ± 1.8	129.2 ± 2.3	127.5 ± 2.0	127.1 ± 2.0
F for trend	13.4	9.7	8.9	6.5	3.7	3.1
p	<0.001	0.002	0.003	0.011	0.054	0.081
	Diastolic blood pressure (mmHg, mean ± SE)					
No (n=309)	71.2 ± 0.6	71.4 ± 0.5	71.5 ± 0.5	75.4 ± 0.7	75.6 ± 0.6	75.6 ± 0.6
Yes (n=55)	76.1 ± 1.5	75.0 ± 1.3	74.9 ± 1.3	80.5 ± 1.7	79.3 ± 1.5	79.3 ± 1.5
F for trend	9.1	6.3	5.7	8.6	5.5	5.4
p	0.003	0.013	0.017	0.004	0.020	0.021

[a]For gender, age, body mass index, smoking, drinking, hypertension, and diabetes. [b]For gender, age, body mass index, smoking, drinking, hypertension, diabetes and WBC count.

body mass index reached statistical significance as covariables, and the others (diabetes, smoking, alcohol intake and WBC count) did not in most ANCOVA results. The statistical significance and non-significance of the covariables were consistent in all the ANCOVA analyses for SBP and DBP, except age in the follow-up DBP values.

Discussion

This study addressed an association of periodontitis with higher BP, and indicated that BP may be one of underlying pathways linking periodontitis and cardiovascular disease. Subjects with periodontitis had higher BP, even after one year. We found that both SBP and DBP were higher in subjects with periodontitis than in those without periodontitis, even after adjustment for major known confounding factors. Quite expectedly, male gender, age, hypertension and body mass index were also associated with higher BP in multivariate analysis.

We did not find a significant association between periodontitis and treatment of hypertension in a categorical analysis. There are two possible reasons for this. First, the period of hypertension treatment varied considerably, so the baseline periodontitis might occur hereafter. Second, the prevalence to treated hypertension may be too small to detect statistical significance in this sample size, which eventually requires a larger scale of study.

There are several biological mechanisms proposed to explain that a higher WBC count may lead to atherogenesis and hypertension. For example, monocyte-derived macrophages can induce endothelial cell injury and thrombus formation by oxidant formation (19). Activated WBC may have rheological abnormalities such as aggregation and adherence to microvessels resulting tissue ischemia (20). Several studies have investigated systemic inflammatory markers such as WBC, C-reactive protein and interleukin 6 in periodontal disease. As for WBC, a few studies (21,22) have reported patients with periodontal disease that had a higher WBC count, but the persistent relation is unknown and a question remains as to whether a high WBC count really participates as mediator in causal pathways, or exists merely as a

Table IV. Significance of covariables in one-way analysis of covariance between periodontitis and non-periodontitis.

Covariables	F for trend	p
Male gender	28.9	<0.001
Age	6.2	0.013
Hypertension	22.6	<0.001
Diabetes	0.7	0.41
Body mass index	22.2	<0.001
Smoking	0.01	0.94
Alcohol intake	0.2	0.63
White blood cell count	0.4	0.54

These covariables were used in the adjusted 2 model in Table III.

concomitant risk factor. Of note, alveolar bone loss around posterior teeth has been reported to be associated with serum C-reactive protein level and WBC count (23). Alveolar bone loss indicates present or past history of severe periodontitis, and CRP is a significant indicator of cardiovascular risk (24,25). In this study, the WBC count was elevated in subjects with periodontitis after adjusting possible confounders including smoking, as shown in Table II. However, the WBC count was not associated with BP in the ANCOVA analyses. Thus, the result of this study may indicate that the WBC elevation is one of the clinical markers of inflammatory process or, at most, one of numerous causal mediators, in the BP–chronic inflammation (such as periodontitis) relationship.

The underlying mechanism linking higher BP to periodontitis remains speculative. The anatomic closeness of periodontium to blood flow can facilitate bacteremia and systemic spread of bacterial products, components and immunocomplex (26), which precipitates to vascular pathology leading to atherosclerosis (27–31). Atherosclerosis causes an increase of resistance to blood flow and therefore an increase of BP, which may explain the periodontitis–BP relationship.

This study has several limitations. First, the periodontal status was measured only at the baseline of this study. Those who had no periodontitis at the baseline might develop the disease hereafter, and vice versa. This possibility, however, dilutes the strength of an association in the follow-up analysis. Second, we did not measure causal oral pathogens *per se*, and could not evaluate the interaction of the infectious burden of specific pathogens on the host response. It is of note that animal model studies have shown that *Porphyromonas gingivalis* (the most prominent pathogen in periodontitis) infection accelerates atherosclerosis (32,33). Third, we did not collect some information that might relate to periodontitis. These include WBC count differential, highly sensitive C-reactive protein level and oral health care. Fourth, differences in DBP measurements between baseline and follow-up analysis appear to be large (shown in Table III). Thus, there might be some inter-observer bias of BP reading between baseline and follow-up. However, this study focused on the comparison of BP between subjects with periodontitis and without at each observation. Thus, this influence of inter-observer bias would be minimal.

This study has some significance. First, aging was a strong risk factor both for periodontitis and high BP, with potential confounding effect. We adjusted age in multivariate analysis, and moreover, the age difference between periodontitis and non-periodontitis subjects was not substantial, so the possibility of misleading results due to aging will be minimal. Second, the participants were employed in a single factory and were of a single ethnicity, and assumed to be in small variance in socio-economic and health status. These facts are important in this kind of study that aimed to compare BP differences in a small range. Third, we measured the BP and WBC count at both baseline and 1-year later follow-up. Therefore, we could indicate that periodontitis had a persistent association with BP and WBC count.

In this study, the observed association between periodontitis and BP may have clinical strength. The magnitudes of the difference between periodontitis and non-periodontitis subjects were approximately 8 mmHg/5 mmHg (SBP/DBP) at baseline. For example, effect of diet and weight reduction on BP showed that BPs fell 6.0 mmHg/3.0 mmHg with dietary fish alone, 5.5 mmHg/2.2 mmHg with weight reduction alone and 13.0 mmHg/9.3 mmHg with fish and weight loss combined (34). Since early dental care can reverse periodontal inflammation, the question whether early intervention can equally prevent BP elevation has much clinical relevance.

In summary, periodontitis is persistently associated with higher BP, accompanied by an elevation of WBC count. Periodontitis may be a significant component of chronic inflammatory–vascular pathogenesis. It has an important implication for preventive services, in that prevention and treatment of periodontitis may contribute to prevention of hypertension and related vascular complications.

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