Original Article

Periodontal Disease is Associated with Metabolic Syndrome - The Role of Peripheral Total and Differential Leukocyte Count-Related Metabolic Derangements

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Objective: Periodontal disease (PD) is chronic inflammation that produces a local and systemic inflammatory response. PD has been reported to be a possible risk factor for some of the components of the metabolic syndrome (MetS), including obesity, diabetes, and dyslipidemia. The present study aimed to examine the relationship between PD and the MetS in a Chinese population, and also the possible mechanism of PD-related metabolic derangements.

Methods: A total of 1,102 participants aged 54 ± 10 years were enrolled in this cross-sectional study, including 447 participants with PD and 655 participants without PD. The total and differential leukocyte profiles of peripheral blood were measured.

Results: The participants with PD had higher rates of MetS and its components (central obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, and impaired fasting glucose) than the participants without PD. In multiple logistic regression analysis, PD was independently associated with the MetS. In further analysis, the PD group had elevated circulating levels of total white blood cells (7.615 ± 2.781 vs. 7.146 ± 2.818 10^9/L), neutrophils (5303 ± 2929 vs. 4611 ± 2956 10^9/L), monocytes (472 ± 273 vs. 410 ± 265 10^9/L), and lymphocytes (1963 ± 927 vs. 1763 ± 906 10^9/L) than the participants without PD. In addition, total and differential leukocyte counts were significantly associated with PD, MetS, and its components (body mass index and high-density lipoprotein-cholesterol levels).

Conclusions: PD was independently associated with the MetS in a Chinese population. Total and differential leukocyte counts were associated with PD-related metabolic derangements.

Key words: Periodontal disease, metabolic syndrome, total white blood cell count, neutrophil count, monocyte count, lymphocyte count

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Introduction

Periodontitis is a common, chronic, low-grade inflammatory disease of microbial origin, affecting humans and resulting in the destruction of the tooth supporting apparatus. The signs and symptoms of periodontitis include swollen gums, deepening of the gingival crevice leading to the formation of a periodontal pocket, bleeding on brushing, increased spacing between the teeth, loose teeth and teeth loss and edentulism can occur if the patients do not receive periodontal treatment. Recent studies have indicated that periodontal disease (PD) is a risk factor for the complications of type 2 diabetes mellitus[1,2] and poor metabolic contro[1,3] and it has also been associated with an increased risk of cardiovascular disease (CVD) in cross-sectional studies.[4,5] In addition, several studies have reported possible associations and etiological relationships between PD and the metabolic syndrome (MetS).[6,7]

The prevalence of the MetS is increasing globally, including in Taiwan. The MetS is a syndrome characterized by several signs that together seriously compromises the health of an individual. It is clear that a common denominator of the member pathologies of the MetS is oxidative stress and the consequent hyperinflammation that leads to serious systemic complications such as CVD and local complications such as periodontitis. Few studies have examined the relationships between PD and MetS taking into consideration the various factors associated with PD that might lead to MetS. In addition, PD may be associated with increased body fatness and inflammatory markers, higher blood pressure levels, diabetes, and hyperlipidemia, and thereby play an important role in the development of MetS.[8-12]

The detrimental effects of PD on MetS and the induction of inflammatory cytokines and associated factors raise the possibility that PD may increase the risk of MetS. To clarify this hypothesis, we investigated the association between PD and features of National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)-defined MetS.[13] The possible mechanisms by which PD affects MetS were also investigated by measuring inflammatory markers of peripheral total and differential leukocytes in a Chinese population.

Methods

Study design and participants

Consecutive patients who were treated for PD at the Dental Clinics of E-Da Hospital, Taiwan, between January 2010 and December 2016 were evaluated. A total of 1,102 participants (641 males and 461 females) were enrolled, including 655 without PD (351 males and 304 females, aged 23 to 98 years) and 447 with PD (290 males and 157 females, aged 31 to 86 years). All of the patients completed questionnaires regarding personal information and their medical and dental history. The inclusion criteria were: 1) aged ≥ 20 years; 2) the presence of at least four teeth to ensure the measurements necessary to diagnose PD; and 3) laboratory measurement of triglycerides, high-density lipoprotein cholesterol (HDL-C), and fasting glucose made in the previous 90 days before oral and general clinical examinations. The exclusion criteria were: 1) individuals who were pregnant; 2) those who had received periodontal treatment in the 3 months before enrollment; 3) those diagnosed with cancer, human immunodeficiency virus/AIDS, or systemic, urinary, fungal, or tissue infections; and 4) those with whom verbal communication was not possible. Each participant provided written informed consent before enrollment. This study was approved by the Human Research Ethics Committee of Kaohsiung E-Da Hospital, I-Shou University (EDAH IRB No. EMRP-104-092). Written informed consent was obtained from all participants.

Data collection procedures

The participants answered a questionnaire to obtain data related to socioeconomic status, demographics, lifestyle, health condition, and dental history. The following results of laboratory tests were collected from the medical records: 1) triglycerides; 2) HDL-C; 3) fasting glucose; 4) HbA1C; 5) total cholesterol; 6) low-density lipoprotein cholesterol (LDL-C); 7) uric acid; and 8) total and differential leukocyte counts. All test results from the participant's medical records were performed by the Laboratory of E-Da Hospital, Kaohsiung, Taiwan. The serum levels of glucose, HDL-C, and triglycerides were measured with standard commercial methods using a parallel, multi-channel analyzer (Hitachi 7170A, Tokyo, Japan). In addition, HbA1c was measured in whole blood using an ion exchange G8 high-performance liquid chromatography analyzer (Tosoh Bioscience, South San Francisco, CA).

A single examiner reviewed the medical history of the participants and conducted a physical examination, including vital signs, anthropometric measurements (weight, height, and waist circumference), palpation, and auscultation. Subsequently, a single dentist masked to the individuals' medical status conducted an oral clinical examination. Reproducibility was assessed by replicating of periodontal measurements. This was done by using an experienced periodontist for 10% of the samples as a reference. The intraexaminer k index for the means of probing depth and recession were 0.77 and 0.89, respectively, and the interexaminer k index showed concordance rates of 0.88 and 0.85 for these measurements, respectively.

Oral and general clinical examinations

The oral clinical examinations assessed the presence of teeth, caries, and restorations. Furthermore, periodontal status was investigated on all teeth except the third molars. The following clinical parameters were obtained using a Williams probe: probing depth, recession measurements, clinical attachment level (CAL), and bleeding on probing (BOP). PD[14] was measured as the distance from the gingival margin to the most apical depth of the pocket at six sites per tooth (mesio-buccal, mid-buccal, distobuccal, mesio-lingual, mid-lingual, and disto-lingual). At the same six sites, measurements of BOP[15] recession, and CAL were obtained.[16] Recession was measured as the distance between the gingivalmargin and the cemento-enamel junction (CEJ), and CAL was measured as the distance from the CEJ to the base of the pocket. The visible plaque index (PI) was also evaluated using the same probe at four sites per tooth (buccal, lingual,mesial, and distal) measured as the presence of a visible biofilm deposit on the tooth surface.

Body height, weight, and waist circumference were measured, and the body mass index (BMI) was calculated. The waist circumference was measured at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. Blood pressure was measured in the morning (readings were taken twice, at least 2 minutes apart), on the right upper arm in line with the heart using a mercury column sphygmomanometer with the participant in the sitting position after a minimum rest period of 5 minutes.

Definitions

The smoking status of the subjects was classified as never having smoked, former smoker (quit smoking for at least 1 year), or current smoker. Alcohol drinking and betel quid chewing status were classified as never having drunk alcohol or chewed betel quid, former drinker or betel quid chewer (quit drinking or betel quid chewing for at least 1 year), or current drinker or betel quid chewer. In this study, former and current drinkers and betel quid chewers were analyzed as a single group.[17] MetS was defined according to the NCEP-ATP III criteria with a modified defini-

tion of central obesity.[13] MetS was diagnosed when a subject met three or more of the following criteria: (1) arterial blood pressure ≥ 130/85 mmHg; (2) central obesity (waist circumference, males ≥ 90 cm; females ≥ 80 cm); (3) serum triglyceride level ≥ 150 mg/dL; (4) serum HDL-C level < 40 mg/dL in males or < 50 mg/dL in females; and (5) fasting plasma glucose concentration ≥ 100 mg/dL or a previous diagnosis of type 2 diabetes. In addition, the participants were diagnosed as having periodontitis (PD group) if they had at least four teeth with at least one site with a probing depth ≥ 4 mm, CAL ≥ 3 mm, and BOP at the same site.[18] Those participants who did not meet these criteria were considered as not having periodontitis (non-PD group).

Statistical analysis

Data are presented as mean ± standard deviation (SD). All statistical analyses were performed using SAS software (version 8.0; SAS Institute, Cary, NC). Statistical differences between variables were compared using unpaired Student's t-tests for normally distributed variables. Categorical variables were recorded as frequencies and/or percentages, and intergroup comparisons were analyzed using the chi-square test. Multiple regression analysis was used to examine associations between peripheral total white blood cell (WBC) count and the values of other parameters. Furthermore, multiple logistic regression analysis was used to assess independent associations between the variables of interest and the presence of MetS. All statistical analyses were two-sided, and a p-value < 0.05 was considered to be statistically significant. In addition, measured variable path analysis (MVPA), a form of structural equation modeling, was used to test the relationships among PD and leukocytes, and their effect on MetS using AMOS 24.0. Sobel's test was used to examine if leukocytosis serves as the causal intermediate between PD and MetS.

Results

The clinical characteristics of the participants are presented in Table 1. Of the

Table 1. Clinical characteristics of the study subjects

Parameter	Participants with periodontal disease	Participants without periodontal disease	*p* value
Number of participants	447	655	
Age (years) (n, %)			
20 – 40	32 (7.2)	66 (10.1)	0.095
40 – 50	112 (25.1)	176 (26.9)	0.501
50 – 60	177 (39.6)	248 (37.9)	0.561
> 60	126 (28.2)	165 (25.2)	0.268
Male gender (n, %)	290 (64.9)	351 (53.6)	0.0002
Smoking (n, %)	79 (17.7)	84 (12.8)	0.026
Drinking (n, %)	60 (13.4)	61 (9.3)	0.032
Betel quid chewing (n, %)	23 (5.2)	28 (4.3)	0.499
Central obesity (n, %)	112 (25.1)	129 (19.7)	0.035
High BP (n, %)	160 (35.8)	213 (32.5)	0.259
Hypertriglyceridemia (n, %)	146 (32.7)	152 (23.2)	0.001
Low HDL-cholesterol (n, %)	117 (26.2)	128 (19.5)	0.009
IFG (n, %)	141 (31.5)	127 (19.4)	< 0.0001
Metabolic syndrome (n, %)	90 (20.1)	83 (12.7)	0.001

BP: blood pressure; HDL: high-density lipoprotein; IFG: impaired fasting glucose.

1,102 participants, 447 (40.6%) were diagnosed with PD. Compared to the non-PD group, significantly more patients in the PD group were male, and had higher rates of smoking, drinking, central obesity, hypertriglyceridemia, low HDL-C, impaired fasting glucose (IFG), and MetS (all $p < 0.05$). In addition, patients with PD were older, and had higher fasting glucose, triglycerides, and LDL-C levels, and WBC, neutrophil, monocyte, and lymphocyte counts than the non-PD group. Furthermore, the PD group had a lower level of HDL-C and fewer number of teeth present than the non-PD group (Table 2). There were no significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, waist circumference, HbA1C, total cholesterol, uric acid, albumin, aspartate aminotransferase, alanine aminotransferase, and creatinine levels, percentage of participants aged 20 – 40, 40 – 50, 50 – 60, and > 60 years, betel quid chewing, and hypertension between the two groups.

Multiple linear regression analysis adjusted for gender and age revealed that total WBC count was positively associated with BMI (β= 0.13, $p = 0.001$), fasting glucose (β = 0.12, $p = 0.025$), HbA1C (β = 0.14, $p = 0.049$), PD (β = 0.08, $p = 0.041$), and MetS (β = 0.16, $p < 0.0001$). Monocyte count was positively associated with BMI (β = 0.10, $p = 0.044$), PD (β = 0.07, $p = 0.045$), and MetS (β = 0.11, $p = 0.029$). Furthermore, peripheral neutrophil count was well associated with BMI (β = 0.13, $p = 0.024$), fasting glucose (β = 0.12, $p = 0.048$), PD (β = 0.08, $p = 0.043$), and MetS (β = 0.14, $p = 0.009$). Moreover, lymphocyte

Table 2. Biochemical characteristics of the study subjects

Parameter	Participants with periodontal disease	Participants without periodontal disease	*p* value
Number of participants	447	655	
Age (years)	55 ± 10	54 ± 10	0.012
Number of teeth present	24.9 ± 4.4	25.6 ± 4.3	0.013
Systolic blood pressure (mmHg)	130 ± 17	130 ± 18	0.931
Diastolic blood pressure (mmHg)	79 ± 12	79 ± 12	0.750
Body mass index (kg/m^2)	24.5 ± 3.6	24.2 ± 3.7	0.128
Waist circumference (cm)	82.1 ± 10.1	81.5 ± 10.6	0.234
Fasting glucose (mg/dL)	118.0 ± 38.5	110.1 ± 30.6	0.020
HbA1C (%)	7.0 ± 2.3	6.8 ± 1.9	0.446
Total cholesterol (mg/dL)	202.5 ± 40.0	196.8 ± 33.9	0.152
Triglyceride (mg/dL)	121.0 ± 70.6	110.4 ± 56.6	0.006
HDL-cholesterol (mg/dL)	54.8 ± 10.9	57.6 ± 12.7	0.0002
LDL-cholesterol (mg/dL)	120.1 ± 37.9	112.1 ± 32.1	0.042
Uric acid (mg/dL)	7.1 ± 11.4	6.0 ± 1.8	0.236
Albumin (g/dL)	4.3 ± 0.4	4.4 ± 0.4	0.555
AST (U/L)	6.1 ± 1.6	6.0 ± 1.8	0.497
ALT (U/L)	35.9 ± 27.1	31.7 ± 24.2	0.065
Creatinine (mg/dL)	1.3 ± 1.2	1.2 ± 1.1	0.813
WBC count (10^9/L)	7.615 ± 2.781	7.146 ± 2.818	0.030
Neutrophil count (10^9/L)	5303 ± 2929	4611 ± 2956	0.020
Monocyte count (10^9/L)	472 ± 273	410 ± 265	0.018
Lymphocyte count (10^9/L)	1963 ± 927	1763 ± 906	0.038

Data are means ± SD. HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cell.

Table 3. Associations of covariates with peripheral total and differential leukocyte counts

Factor	Total WBC count		Monocyte count		Neutrophil count		Lymphocyte count	
	β-coefficient (95% CI)*	*p* value*	β-coefficient (95% CI)*	*p* value*	β-coefficient (95% CI)*	*p* value*	β-coefficient (95% CI)*	*p* value*
Body mass index	0.13 (0.04 – 0.17)	0.001	0.10 (0.20 – 4.73)	0.044	0.13 (0.83 – 4.33)	0.024	0.13 (0.15 – 1.85)	0.017
Systolic BP	-0.06 (-0.03 – 0.01)	0.255	-0.09 (-3.77 – 0.51)	0.135	-0.09 (-8.06 – 7.02)	0.176	0.03 (-5.37 – 8.55)	0.653
Diastolic BP	-0.02 (-0.03 – 0.02)	0.689	-0.07 (-4.73 – 1.41)	0.288	-0.08 (-3.91 – 6.23)	0.188	0.12 (0.03 – 2.82)	0.049
Fasting glucose	0.12 (0.00 – 0.02)	0.025	0.04 (-0.69 – 1.31)	0.541	0.12 (0.01 – 0.06)	0.048	0.04 (-2.68 – 5.21)	0.528
HbA1C	0.14 (0.00 – 0.35)	0.049	0.03 (-1.59 – 4.70)	0.740	0.16 (-1.67 – 7.96)	0.052	-0.03 (-1.36 – 6.53)	0.722
Total cholesterol	-0.06 (-0.01 – 0.00)	0.256	-0.11 (-1.97 – 0.16)	0.094	-0.10 (-7.56 – 2.85)	0.157	0.02 (-2.71 – 3.90)	0.723
Triglyceride	0.05 (-0.00 – 0.01)	0.183	0.02 (-0.29 – 0.45)	0.661	0.04 (-2.60 – 6.02)	0.436	0.07 (-0.39 – 2.24)	0.166
HDL-cholesterol	-0.11 (-0.04 – -0.01)	0.005	-0.12 (-0.03 – -0.04)	0.041	-0.11(-0.02 – -0.06)	0.033	-0.13 (-5.26 – -1.28)	0.021
LDL-cholesterol	0.02 (-0.01 – 0.01)	0.790	0.02 (-0.89 – 1.25)	0.744	0.04 (-4.47 – 7.62)	0.542	0.11 (-0.57 – 5.24)	0.114
Uric acid	0.01 (-0.04 – 0.04)	0.934	-0.13 (-6.28 – 2.56)	0.079	0.09 (-2.47 – 5.75)	0.256	0.01 (-0.78 – 2.24)	0.877
Periodontal disease	0.08 (0.02 – 0.87)	0.041	0.07 (0.01 – 0.76)	0.045	0.08 (0.01 – 0.12)	0.043	0.10 (0.05 – 1.22)	0.038
Metabolic syndrome (NCEP-ATP III)†	0.16 (0.58 – 1.65)	< 0.0001	0.11 (0.70 – 4.81)	0.029	0.14 (0.64 – 3.65)	0.009	0.10 (0.14 – 2.35)	0.046

*Adjusted for age and gender by multiple linear regression analysis. †The definition and criteria of NCEP-ATP III metabolic syndrome are described in the text. WBC: white blood cell; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 4. Multiple logistic regression analysis with the presence of metabolic syndrome as the dependent variable

	Odds ratio	95% confidence interval	*p* value
Age	1.08	1.02 – 1.14	0.011
Male gender	1.19	0.32 – 4.36	0.794
Albumin	0.12	0.02 – 0.93	0.043
Uric acid	1.33	0.96 – 1.84	0.082
AST	0.95	0.90 – 1.01	0.076
ALT	1.03	0.99 – 1.07	0.141
Creatinine	1.03	0.82 – 1.30	0.781
Alcohol use	2.22	0.57 – 8.74	0.253
Smoking	1.59	0.42 – 6.00	0.494
Betel quid use	0.05	0.01 – 2.70	0.140
Number of teeth present	1.06	0.94 – 1.20	0.329
Periodontal disease	3.78	1.43 – 8.03	0.007

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

count was well associated with BMI (β = 0.13, p = 0.017), DBP (β = 0.12, p = 0.049), PD (β = 0.10, p = 0.038), and MetS (β = 0.10, p = 0.046). Additionally, HDL-C was significantly negatively associated with total WBC count (β = -0.11, p = 0.005), monocyte count (β = -0.12, p = 0.041), neutrophil count (β = -0.11, p = 0.033), and lymphocyte count (β = -0.13, p = 0.021) (Table 3). Multivariate logistic regression analysis showed that the presence of MetS was associated with age, albumin, and PD (Table 4).

In addition, the estimated MVPA with parameters and statistical significance of individual paths is shown in Figure 1. The estimated model demonstrated good model fit, χ^2 = 3.5, p = 0.47, CFI = 0.98, SRMR = 0.02, RMSEA=0.001. As indicated in Figure 1, there were significant positive direct effects from PD (β = 0.07, p < 0.001) to leukocytes, and positive direct effects from PD (β = 0.08, p < 0.001) to MetS. Furthermore, there were significant positive direct paths from leukocytes (β = 0.12, p < 0.001) to MetS. Moreover, mediation analysis by the Sobel's test indicated that leukocytes mediated the impact of PD on MetS.

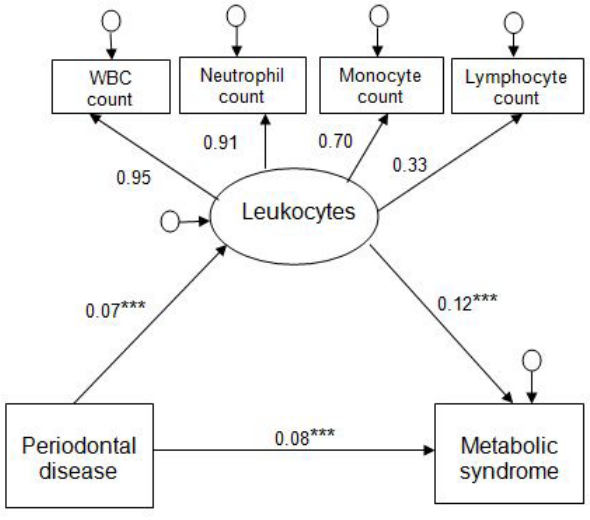

*Fig. 1 Estimated model of the relationship of periodontal disease, leukocytes, and their effect on metabolic syndrome. Note: Coefficients are standardized path coefficients. Overall model fit, χ2=3.5, p=0.47, CFI = 0.98, SRMR = 0.02, RMSEA = 0.001. For tests of significance of individual paths, ***p < 0.001.*

Discussion

The main findings of this study suggested that there is an association between PD and MetS even after adjusting for confounding covariables such as age, sex, albumin, uric acid, aspartate aminotransferase, alanine aminotransferase, creatinine, alcoholic consumption, smoking habit, betel quid use, and number of teeth present. Furthermore, total and differential leukocyte counts were significantly associated with PD, MetS, and its components (BMI and HDL-C levels).

In addition, leukocytes mediated the impact of PD on MetS. These findings support previous studies that described an association between periodontitis and the MetS,[19-21] and that chronic inflammation induced by PD may lead to metabolic dysfunction.[7,22,23]

Periodontitis may predispose individuals to the MetS through mechanisms triggered by the release of products into the blood circulation and/or the translocation of oral bacteria. These bacteria may then provoke inflammatory and immune processes that exacerbate or initiate the MetS.[24,25] The observed increase in the risk of MetS in the patients with PD may be explained by one of the several mechanisms. Periodontitis may cause hyperglycemia or insulin resistance via systemic inflammation. Systemic inflammation has been reported to substantially contribute to insulin resistance in the musculoskeletal system and other peripheral tissues in addition to adipose tissue.[26] Thus, impairment of glucose uptake in tissue leads to sustained hyperglycemia, which in turn induces the expressions of proinflammatory mediators and increases the risk of oral infection and CVD among patients with PD. Furthermore, systemic oxidative stress has been hypothesized to be a potential link between periodontitis and MetS.[27] Increased cytokine concentrations and oxidative stress as a result of periodontitis could lead to reduced insulin sensitivity, and decreased insulin sensitivity is considered to be a significant event in the development of MetS. Moreover, a previous study reported that PD seems to be related to conditions and pathologies characterized by high oxidative stress and by the presence of advanced glycation end (AGE) products, including diabetes and physiologic aging. AGEs can induce chemotaxis and the production of proinflammatory mediators to inhibit osteoblasts and fibroblasts, and to accelerate periodontal damage directly or by binding their receptors.[28] In addition, PD and MetS have a bidirectional association, and systemic diseases have an impact on oral health as oral diseases such as PD have wide ranging systemic effects. In susceptible individuals, periodontal infection acts as an independent risk factor for systemic diseases and may be involved in the basic mechanism of these conditions.[29]

PD is defined as inflammation that is caused by bacteria in dental plaque. Although limited to the oral cavity, this process is responsible for a sustained inflammatory condition that starts with gingivitis in youth and continues to tooth loss at a later age. This disease may be a factor contributing to a high total leukocyte count over an extended period. Yoshida et al.[30] investigated the relationship between dental disease and total leukocyte count in Japanese factory workers, and found significant correlations between total leukocyte count and Community Periodontal Index of Treatment Needs (CPITN) scores. In addition the authors reported that the subjects with severe cases of PD had a significantly high total leukocyte count. Kweider et al.[31] reported that patients with PD had higher mean plaque index, gingival index and CPITN scores, higher levels of fibrinogen, and higher total leukocyte counts. In addition, Pejcić et al.[32] reported a significant relationship between total leukocyte count, neutrophil count and different forms of PD. Taken together, these observations suggest that inflammatory dental disease may be a determinant of fibrinogen level and total leukocyte count in the general population.

In the present study, total and differential leukocyte counts were significantly associated with PD, MetS, and its components (BMI and HDL-C levels). Furthermore, total WBC count was significantly associated with fasting glucose and HbA1C. Moreover, neutrophil count was significantly associated with fasting glucose and lymphocyte count was significantly associated with DBP. Various cell types in the periodontium produce chemokines, including fibroblasts, endothe-

lial cells, macrophages, osteoclasts, epithelial cells, neutrophils, monocytes, lymphocytes and mast cells. Neutrophils, monocytes and other cells produce innate immune cytokines such as interleukin and tumor necrosis factor-alpha (TNF-α) in the diseased periodontal site. These cytokines play an important role in bone resorption and periodontal tissue destruction.[33] In addition, numerous epidemiological and clinical studies have shown that leukocytosis is an independent predictor of insulin resistance, type 2 diabetes, and CVD.[34-36] Elevations in WBC count have been associated with both PD and MetS.[37] The WBC count in patients with PD may be activated by reactive oxygen species or adipocytokines.[38] Activated leukocytes release many kinds of cytokines, including TNF-α, nuclear transcription factor-kappa B, and interleukins, superoxide radicals, and proteases, all of which contribute to insulin resistance, MetS, and atherosclerosis.[39] The elevated peripheral total and differential leukocyte counts in the patients with PD in the present study may suggest a mechanism by which PD induces MetS through inflammatory processes.

There are several limitations to this study. The cross-sectional design limits our ability to infer a causal relationship between PD and MetS. Further longitudinal studies using re-assessed parameters are needed to determine whether PD influences the development of some or all of the components of MetS, or vice versa. Furthermore, we did not consider other confounders that may contribute to the PD-related development of MetS, such as psychosocial stress including income, job, and behavioral stress. Moreover, further investigations are needed to elucidate the mechanisms by which PD impacts the development of MetS and how MetS impacts susceptibility to PD.

In conclusion, our results indicate that PD is independently associated with a higher prevalence of MetS, and that this has a detrimental influence on central obesity, hypertriglyceridemia, low HDL-C, and IFG. Chronic inflammation may contribute to PD-related metabolic derangements. The results of our study raise an important epidemiological issue with regards to MetS, and further large-scale cohort studies are warranted to validate our findings.

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