Association of periodontal pocket area with type 2 diabetes and obesity: a cross-sectional study

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ABSTRACT
Introduction The aim was to investigate the relationship of full-mouth inflammatory parameters of periodontal disease with diabetes and obesity.

Research design and methods This cross-sectional study conducted diabetes-related examinations and calculated periodontal inflamed and epithelial surface area (PISA and PESA) of 71 Japanese patients with type 2 diabetes. Multiple linear regression analyses were performed to evaluate associations between PISA or PESA and diabetes and obesity parameters.

Results Median value of body mass index (BMI), hemoglobin A1c (HbA1c) level, fasting plasma glucose (FPG) level, and visceral fat area (VFA) were 25.7 kg/m², 9.1%, 151 mg/L, and 93.3 cm², respectively. PISA and PESA were significantly associated with HbA1c after adjusting for age, sex, BMI, smoking status, and full-mouth plaque control level (PISA: coefficient=38.1, 95% CI 8.85 to 67.29, p=0.001; PESA: coefficient=66.89, 95% CI 21.44 to 112.34, p=0.005).

PISA was also significantly associated with the highest tertile of fasting plasma glucose (PISA: coefficient=167.0, 95% CI 48.60 to 285.4, p=0.006). PISA and PESA were not significantly associated with BMI or VFA.

Conclusion PISA was associated with FPG and HbA1c, but not with obesity parameters, independent from confounders such as full-mouth plaque control level in patients with type 2 diabetes.

INTRODUCTION
Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia. Elevated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) are critical markers of diabetes. Obesity is associated with prediabetes and is a risk factor for developing diabetes.1–3 Both diabetes and obesity are recognized as systemic inflammatory conditions.4 Hyperglycemia and dyslipidemia increase oxidative stress, which activates inflammatory mediators.5–7 In adipose tissue in obesity, macrophages secrete a large amount of adipokine that includes inflammatory cytokines such as tumor necrosis factor-α.8 It is known that visceral fat induces chronic, low-level systemic inflammation.9

Evidence for associations between diabetes, obesity, and periodontal disease has been accumulating in recent years.10–15 It is recognized that elevated systemic inflammation levels lead to an increase in local inflammation in the periodontal tissue. Inflammatory markers in gingival crevicular fluid (GCF) are elevated

Significance of this study

What is already known about this subject?
► There is already only one report showing the association between periodontitis and diabetes using periodontal inflamed surface area (PISA). However, the plaque control that primarily causes periodontal disease has not been fully evaluated in the previous investigation.
► The association between obesity and periodontal disease has been reported using various clinical indexes, but the analysis with specific tests for obesity such as visceral fat area (VFA) is quite limited.

What are the new findings?
► PISA and periodontal epithelial surface area (PESA) were significantly associated with hemoglobin A1c using multiple linear regression analysis independent from confounders such as full-mouth plaque control level in patients with diabetes.
► PISA was significantly associated with the highest tertile of fasting plasma glucose, independent of possible confounders.
► PISA and PESA were not significantly correlated with VFA<100 cm² and body mass index ≥25 kg/m² in patients with type 2 diabetes.

How might these results change the focus of research or clinical practice?
► This study suggested that inflammation of periodontal tissue may be affected by diabetes, independent of oral hygiene.
► In the management of patients with diabetes, PISA and PESA may be incorporated as one of the oral clinical endpoints of glycemic control in patients with type 2 diabetes.
in patients with diabetes and patients who were obese.\textsuperscript{16,17} Higher inflammatory marker levels in GCF following initial periodontal treatment might indicate an increase in local inflammation in patients with type 2 diabetes.\textsuperscript{18}

Periodontitis is diagnosed by the presence of periodontal pocket depth $\geq 4$ mm with alveolar bone loss and bleeding on probing (BOP) in the periodontal pocket examination. Within the periodontal pocket, the dental biofilm has accumulated as subgingival plaque and formed numerous microucers on the surface of epithelium. Because periodontal inflammation was caused by microbiological challenge in the periodontal pockets, the evaluation of total periodontal pocket area is required. To quantify and describe the inflammation of full-mouth periodontal tissue as a single parameter, periodontal epithelial surface area (PESA) and periodontal inflammatory surface area (PISA) were developed as parameters of periodontitis.\textsuperscript{19,20} PISA describes the surface area of bleeding pocket epithelium in square millimeters to quantify the amount of inflamed periodontal tissue. To the best of our knowledge, there are few reports investigating the relationship between PISA and diabetic parameters\textsuperscript{20} and no reports investigating the relationship between PISA and obesity parameters. Therefore, the aim of this study was to investigate the relationship between PISA and PESA and the parameters of diabetes and obesity.

**RESEARCH DESIGN AND METHODS**

**Study participants**

This study enrolled 71 Japanese patients hospitalized for diabetes-related problems at the Medical Hospital of Tokyo Medical and Dental University (Tokyo, Japan) who received a dental examination between October 2013 and April 2015. The exclusion criteria were as follows: (a) aged under 20 years, (b) edentulous jaw, and (c) severe renal impairment, which defined as those with an estimated glomerular filtration rate of $< 15$ mL/min/1.73 m$^2$ or those undergoing renal replacement therapy and those with a severe infection or serious trauma. This study was an exploratory study and did not include sample size calculations in advance. This study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 2013. This trial was registered in the University Hospital Medical Information Network (UMIN; https://www.umin.ac.jp/), clinical trial number: UMIN000040218. All participants gave written informed consent to participate in this study and for the result of it to be published.

**Clinical data collection**

Medical interviews and examinations related to diabetes and diabetic complications were performed. Briefly, blood tests for FPG and HbA1c, and measurement of body mass index (BMI) and visceral fat area (VFA) were performed as described previously.\textsuperscript{21} VFA was measured at the level of the umbilicus by a dual bioelectrical impedance analyzer (DUALSCAN, Omron Healthcare, Kyoto, Japan).\textsuperscript{22} After comprehensive examinations, physicians made a diagnosis of type 2 diabetes based on the classification and diagnostic criteria of diabetes mellitus by the Committee of the Japan Diabetes Society.\textsuperscript{23} Oral hygiene status using the O’Leary plaque control record,\textsuperscript{24} and periodontal examination that included tooth mobility, periodontal probing pocket depth (PPD), clinical attachment level (CAL), and BOP at six sites on all residual teeth were conducted by an experienced periodontist. Periodontal pocket measurement was calibrated to reduce intraexaminer error and to ensure reliability and consistency. The intraexaminer agreement was calculated with intraclass correlations coefficients and showed an agreement of 0.89 (95% CI 0.79 to 0.94). Periodontal case classification was used to diagnose periodontal health, gingivitis, and periodontitis stage I, II, III, and IV.\textsuperscript{25,26} Further, to quantify the spread of inflammation in the whole periodontal tissue, PISA and PESA were used as periodontal indicators and were calculated at six sites per tooth. The PESA was calculated using equations determined for each tooth type with CAL and PPD, and the PISA was calculated using BOP, CAL, and PPD. In this study, the PISA and the PESA were derived from the calculation sheet of a previous report.\textsuperscript{19}

**Statistical analysis**

All variables are expressed as numbers and percentages for categorical data or as medians (25th, 75th percentiles) for continuous data. To analyze the association between PISA or PESA and diabetes or obesity, we used HbA1c and FPG as diabetic parameters and BMI and VFA as obesity parameters. HbA1c and FPG were applied as continuous or categorical variables with tertiles as thresholds. BMI was applied as a continuous or categorical variable with the threshold 25 kg/m$^2$ according to the definition of obesity for Japanese population.\textsuperscript{27} VFA was applied as a continuous or categorical variable with the threshold of 100 cm$^2$ according to the definition of visceral fat accumulation, which is an obesity-related cardiovascular risk factor irrespective of BMI.\textsuperscript{28} Differences between groups were calculated with the Mann–Whitney test and correlations were assessed using Spearman’s correlation. Multiple linear regression analysis was performed to investigate the association between PISA or PESA and diabetes or obesity. The multivariate models adjusted for age, sex, BMI, smoking habits, and plaque control record, to which the variance inflation factor (VIF) was added to detect multicollinearity between independent variables. Statistical analyses were performed using STATA software (V.15.0; Stata, College Station, Texas, USA), and $p<0.05$ was considered statistically significant.

**RESULTS**

**Clinical characteristic and periodontal parameters of study participants**

The demographic characteristics of the participants are described in *table 1*. The median age was 62 (51, 69)
years. Of the 71 participants, 47 (66.2%) were men. The median BMI, VFA, HbA1c, and FPG were 25.7 (23.7, 28.6) kg/m², 93.3 (74.6, 128.8) cm², 9.1 (8.0, 10.4) %, and 151 (113, 186) mg/dL, respectively. There were 28 patients with BMI ≥25 kg/m² and 40 patients with VFA ≥100 cm². The number of non-smokers, past smokers, and current smokers was 34 (47.9%), 28 (39.4%), and 9 (12.7%), respectively.

The median number of remaining teeth was 24 (21, 27). The proportions of periodontal health, gingivitis, and periodontal disease stage I, II, III, and IV were 4.2, 0, 1.4, 12.7, 33.8, and 47.9%, respectively. The median full-mouth plaque control record was 45.5 (29.5, 62.5) %. The median PISA and PESA were 190.3 (61.2, 379.9) mm² and 910.4 (684.7, 1142.7) mm², respectively (table 1). Histograms of PISA and PESA are shown in online.

### Table 1 Characteristics of study patients

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Dental health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Number of teeth</td>
</tr>
<tr>
<td>47 (66.2%)</td>
<td>22.4±6.8</td>
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<tr>
<td>Age, years</td>
<td>59.6±13.0</td>
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<tr>
<td>Smoking</td>
<td>Periodontal diagnosis*</td>
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<tr>
<td>Never</td>
<td>Healthy</td>
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<tr>
<td>34 (47.9%)</td>
<td>3 (4.2%)</td>
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<tr>
<td>Former</td>
<td>Gingivitis</td>
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<tr>
<td>28 (39.4%)</td>
<td>0 (0%)</td>
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<tr>
<td>Current</td>
<td>Periodontitis stage I</td>
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<tr>
<td>9 (12.7%)</td>
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<td>BMI (kg/m²)</td>
<td>Periodontitis stage II</td>
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<td>≥25</td>
<td>9 (12.7%)</td>
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<tr>
<td>&lt;25</td>
<td>Periodontitis stage III</td>
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<td>28 (39.4%)</td>
<td>24 (33.8%)</td>
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<td>VFA (cm²)</td>
<td>Periodontitis stage IV</td>
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<td>≥100</td>
<td>34 (47.9%)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>98.9±46.3</td>
</tr>
<tr>
<td>≥100</td>
<td>40 (56.3%)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>31 (43.7%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>PPD≤7 mm (%)</td>
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<tr>
<td>9.4±1.9</td>
<td>1.2±3.1</td>
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<tr>
<td>FPG (mg/dL)</td>
<td>PPD 4–6mm (%)</td>
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<tr>
<td>158.7±55.4</td>
<td>10.0±10.4</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>BOP (%)</td>
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<tr>
<td>11.1±8.4</td>
<td>22.8±17.2</td>
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<tr>
<td>Nephropathy</td>
<td>Full-mouth plaque control record (%)</td>
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<tr>
<td>Normoalbuminuria</td>
<td>45 (63.4%)</td>
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<td>Microalbuminuria</td>
<td>23 (32.4%)</td>
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<td>Macroalbuminuria</td>
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<tr>
<td>Retinopathy</td>
<td>Non-proliferative retinopathy</td>
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<td>Absence of retinopathy</td>
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<tr>
<td>Proliferative retinopathy</td>
<td>16 (22.5%)</td>
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<td>Angina myocardial infarction</td>
<td>7 (9.9%)</td>
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<tr>
<td>Cerebrovascular disorder</td>
<td>15 (21.1%)</td>
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<tr>
<td>Hypertension</td>
<td>41 (57.8%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>47 (66.2%)</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.0±41.1</td>
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<td>LDL cholesterol (mg/dL)</td>
<td>108.8±33.8</td>
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<td>HDL cholesterol (mg/dL)</td>
<td>45.9±11.3</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>160.8±115.2</td>
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<td>Urine albumin (mg/day)</td>
<td>70.0±220.5</td>
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<td>serum CPR (ng/ml)</td>
<td>1.6±0.8</td>
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<tr>
<td>Urine CPR (µg/day)</td>
<td>71.5±48.0</td>
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<td>C-peptide index</td>
<td>1.1±0.7</td>
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<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>77.6±23.9</td>
</tr>
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</table>

Data are number of subjects (%) or mean±SD.
*Criteria for staging according the description of classification Papapanou et al.²⁵
BMI, body mass index; BOP, bleeding on probing; CPR, connecting peptide immunoreactivity; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density liproprotein; LDL, low-density liproprotein; PESA, periodontal epithelial surface area; PISA, periodontal inflamed surface area; PPD, probing pocket depth; VFA, visceral fat area.
supplemental figure 1). PISA and PESA was significantly increased in stages III compared with the healthy control group (online supplemental figure 2).

**Association of PISA or PESA with diabetes parameters**

PISA and PESA were significantly associated with HbA1c (PISA: Spearman’s rs=0.28, p=0.0195; PESA: Spearman’s rs=0.34, p=0.0035) (figure 1A,B). When splitting patients into two groups based on the tertiles of HbA1c (HbA1c T1 and T2 (10.0% and less) vs HbA1c T3 (10.0% and more)), there was no significant difference in PISA or PESA between the two HbA1c groups (figure 2A,B). Multiple linear regression analysis showed the significant, positive association of HbA1c with both PISA and PESA even after adjusting for age, sex, BMI, smoking status, and full-mouth plaque control record (PISA: coefficient=38.1, 95% CI 8.85 to 67.29, p=0.01; PESA: coefficient=66.9, 95% CI 21.44 to 112.34, p=0.005) (tables 2 and 3). The highest tertile of

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**Figure 1** Scatter plots between PISA, PESA and HbA1c, FPG, BMI, and VFA. (A) Scatter plots between PISA and HbA1c. PISA and HbA1c were positively correlated (Spearman’s correlation coefficient=0.28, p=0.0195). (B) PESA and HbA1c were positively correlated (Spearman’s correlation coefficient=0.34, p=0.0035). (C) Scatter plots between PISA and FPG. PISA and FPG were not correlated (Spearman’s correlation coefficient=0.17, p=0.17). (D) PESA and FPG were not correlated (Spearman’s correlation coefficient=0.21, p=0.07). (E) Scatter plots between PISA and BMI. PISA and BMI were not correlated (Spearman’s correlation coefficient=0.009, p=0.94). (F) Scatter plots between PESA and BMI. PESA and BMI were not correlated (Spearman’s correlation coefficient=0.013, p=0.92). (G) Scatter plots between PISA and VFA. PISA and VFA were not correlated (Spearman’s correlation coefficient=0.02, p=0.87). (H) Scatter plots between PESA and BMI. PESA and VFA were not correlated (Spearman’s correlation coefficient=0.03, p=0.78). BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PESA, periodontal epithelial surface area; PISA, periodontal inflamed surface area; VFA, visceral fat area.

**Figure 2** Boxplot diagram illustrating PISA, PESA by HbA1c, FPG, BMI, and VFA. (A) Boxplot diagram illustrating PISA by tertiles of HbA1c. (B) Boxplot diagram illustrating PESA by tertiles of HbA1c. (C) Boxplot diagram illustrating PISA by tertiles of FPG. *P<0.05. (D) Boxplot diagram illustrating PESA by tertiles of FPG. *P<0.05. (E) Boxplot diagram illustrating PISA with BMI split at 25 kg/m² as a reference point. (F) Boxplot diagram illustrating PESA with BMI split at 25 kg/m² as a reference point. (G) Boxplot diagram illustrating PISA with VFA divided by 100 cm² as a reference point. (H) Boxplot diagram illustrating PESA with VFA divided by 100 cm² as a reference point. Mann-Whitney test for intergroup comparison. ○ represents an outlier value. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PESA, periodontal epithelial surface area; PISA, periodontal inflamed surface area; VFA, visceral fat area.
Epidemiology/Health services research

HbA1c was not significantly associated with PISA and PESA following adjustments for the confounders (PISA: coefficient=102.2, 95% CI −15.90 to 220.3, p=0.09; PESA: coefficient=167.8, 95% CI −17.98 to 353.65, p=0.08) (tables 2 and 3). The VIF was calculated for all the predictors in the multiple regression models (online supplemental tables 1 and 2). In the results of the sensitivity analysis of the group with HbA1c less than 8% (n=16), a similar tendency as the analyses represented in tables 2 and 3 was observed. An HbA1c level of ≥8 was more strongly associated with the PISA and the PESA than an HbA1c level <8, following adjustments for the confounders (online supplemental table 3).

The correlation between PISA or PESA and FPG level was not significant in the Spearman’s correlation analysis (figure 1C,D). However, there was a significant difference in PISA and PESA when comparing FPG split into two groups by tertiles (FPG T1 and T2 (175 mg/dL and less) vs FPG T3 (175 mg/dL and more)), with significantly higher PISA and PESA levels in the highest tertile (T3) (figure 2C,D). In the multiple regression analysis, PISA or PESA and FPG levels were not significant (tables 2 and 3). The highest tertile (T3) of FPG was significantly associated with PISA following adjustment for clinically relevant variables including plaque control.

### Table 2

<table>
<thead>
<tr>
<th>PISA</th>
<th>Crude model</th>
<th>Multivariate analysis model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef. 95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Continuous variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>32.3 3.1 to 61.5</td>
<td>0.03</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>0.8 −0.2 to 1.8</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−4.5 −16.9 to 8.0</td>
<td>0.48</td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td>−0.2 −1.5 to 1.1</td>
<td>0.74</td>
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<tr>
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<tr>
<td>HbA1c T3 (compared with T1,2)</td>
<td>78.1 −41.8 to 198.1</td>
<td>0.20</td>
</tr>
<tr>
<td>FPG T3 (compared with T1,2)</td>
<td>158.1 39.8 to 276.3</td>
<td>0.01</td>
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<tr>
<td>BMI≥25kg/m² (compared with &lt;25kg/m²)</td>
<td>9.3 −108.2 to 126.8</td>
<td>0.88</td>
</tr>
<tr>
<td>VFA≥100cm² (compared with &lt;100cm²)</td>
<td>23.2 −99.8 to 146.1</td>
<td>0.71</td>
</tr>
</tbody>
</table>

HbA1c and FPG were analyzed with categorical variable for the highest tertile. BMI and VFA were analyzed with categorical variable for criteria of BMI=25, VFA=100, respectively.

*Means adjusted for age, sex, smoking status, BMI, and plaque control record.
†Means adjusted for age, sex, smoking status, and plaque control record.

BMI, body mass index; Coef, coefficient; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PISA, periodontal inflamed surface area; T, tertile; VFA, visceral fat area.

### Table 3

<table>
<thead>
<tr>
<th>PESA</th>
<th>Crude model</th>
<th>Multivariate analysis model</th>
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<tbody>
<tr>
<td></td>
<td>Coef. 95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Continuous variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>67.1 21.1 to 113.0</td>
<td>0.01</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>1.3 −0.3 to 3.0</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−9.4 −29.7 to 10.9</td>
<td>0.36</td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td>−0.8 −2.9 to 1.3</td>
<td>0.47</td>
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<tr>
<td>Categorical variable</td>
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<tr>
<td>HbA1c T3 (compared with T1,2)</td>
<td>152.7 −38.1 to 343.6</td>
<td>0.12</td>
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<tr>
<td>FPG T3 (compared with T1,2)</td>
<td>232.4 41.6 to 423.2</td>
<td>0.02</td>
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<tr>
<td>BMI≥25kg/m² (compared with &lt;25kg/m²)</td>
<td>35.0 −148.1 to 218.0</td>
<td>0.80</td>
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<tr>
<td>VFA≥100cm² (compared with &lt;100cm²)</td>
<td>10.8 −186.0 to 207.6</td>
<td>0.91</td>
</tr>
</tbody>
</table>

HbA1c and FPG were analyzed with categorical variable for the highest tertile. BMI and VFA were analyzed with categorical variable for criteria of BMI=25, VFA=100, respectively.

*Means adjusted for age, sex, smoking status, BMI, and plaque control record.
†Means adjusted for age, sex, smoking status, and plaque control record.

BMI, body mass index; Coef, coefficient; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PESA, periodontal epithelial surface area; VFA, visceral fat area.
Association of PISA or PESA with obesity parameters

PISA and PESA were not significantly associated with BMI (figure 1E,F) or VFA (figure 1G,H) with Spearman's correlation. Although the BMI ≥25, compared with BMI <25, and VFA ≥100, compared with VFA <100, groups showed a higher tendency of PISA and PESA, neither PISA nor PESA were significantly different when comparing BMI (figure 2E,F) or VFA (figure 2G,H) split along with their thresholds. In the multiple regression analysis, PISA nor PESA were significantly associated with BMI or VFA (tables 2 and 3). Similarly, following adjustments for clinically relevant variables, PISA nor PESA were significantly associated with BMI ≥25 or VFA ≥100 (tables 2 and 3). There were no significant differences in the values of BMI or VFA between the two groups that were divided based on the level of HbA1c (online supplemental figure 3). The VIF was calculated for all the predictors in the multiple regression models (online supplemental tables 1 and 2).

DISCUSSION

To the best of our knowledge, this study provided the first documentation that full-mouth total area of periodontal pockets with inflammation was associated with HbA1c and FPG, but not BMI or VFA in patients with poorly controlled type 2 diabetes. Interestingly, although poor oral hygiene conditions, such as dental plaque accumulation, are the primary cause of periodontitis, the findings of this study suggested that the periodontal inflammation could be affected by glycemic control alone. PISA may be considered a useful clinical parameter for periodontitis in patients with type 2 diabetes.

Here, both PISA and PESA were significantly associated with HbA1c using multivariate analysis. Increases of 38.61 mm² of PISA and 69.49 mm² of PESA were associated with a 1.0% increase of HbA1c. It is known that HbA1c is associated with the severity of periodontal disease in patients with type 2 diabetes, even before diabetes onset. Nesse et al. reported that PISA was significantly associated with HbA1c in a multiple linear regression analysis in which the outcome variable was HbA1c and PISA was included as a potential predictor. Oral hygiene in that study was assessed using plaque index, which does not reflect full-mouth plaque control. In this study, we showed a significant association between HbA1c and PISA after adjusting for plaque control record, which is a quantitative measure of full-mouth oral hygiene. As PISA and PESA represent full-mouth inflammation levels, using a full-mouth plaque control parameter in the analyses might be more appropriate. The FPG value is essential for the diagnosis of diabetes. However, there are not any reports investigating the association of FPG and PISA or PESA. This study found that PISA was significantly associated with the highest tertile of FPG, independent of possible confounders. PISA, in the highest tertile of FPG, increased 143.42 mm² compared with the lower and middle tertiles of FPG. In this cross-sectional study, the mechanism by which poor glycemic control is associated with a high PISA level could not be clarified. In order to analyze the causal relationship, a longitudinal study is warranted to assess serum inflammation markers, such as C reactive protein.

This is the first study to evaluate the association of VFA or BMI and PISA. VFA and BMI are diagnostic criteria for obesity disease, and visceral fat mass has been reported to increase cardiovascular risk. VFA quantitatively represents the amount of adipose tissue, which has been associated with oxidative stress. Visceral fat may affect periodontal tissue because oxidative stress has been implicated in periodontal inflammation. It has also been reported that the higher the BMI, the more likely patients are to have periodontal pockets of 4 mm or more. Furthermore, increases in BMI were also associated with increases in the community periodontal index (CPI) scores in Japan. This study, PISA and PESA were not significantly correlated with the obesity parameters as continuous variables. Even when VFA and BMI were analyzed as categorical variables, PISA and PESA were not significantly correlated with VFA≥100 cm² and BMI ≥25 kg/m². This finding might be consistent with a previous large-scale study in Japan that found that obesity (BMI ≥25 kg/m²) was not significantly associated with periodontal disease. The previous report also suggested that there was no association BMI and clinical attachment loss among patients with type 2 diabetes. However, another report suggested that there was a relationship between CPI code and VFA in Koreans and that VFA might be a risk factor for periodontitis. That report found that the association between VFA and periodontitis (CPI code of 3–4) was for men. However, CPI score cannot accurately represent the condition of the full-mouth periodontal tissue because the CPI score is examined in a limited number of teeth. Because we did not analyze by CPI score or periodontal pocket depth as categorical variables, but used continuous variables such as PISA and PESA in this study, the inconsistent findings might be observed. PISA and PESA are affected by the number of teeth. The classification of periodontal disease also depends on the number of extracted teeth. Therefore, we considered that there were the inconsistent findings with previous report. In addition, we speculated the effect of periodontal tissue by diabetic drug, but no significant difference was found in this study.

There are some limitations of this study. First, the participants were all Japanese patients with poorly controlled type 2 diabetes. Thus, the associations between PISA and diabetic parameters such as HbA1c and FPG may not apply to other populations. Second, patients who are non-diabetic but obese were required as a control group in this study. The association between PISA and the inflammation induced by obesity itself is unclear. Then, the association PISA and HbA1c were...
limited the precision among poorly controlled diabetes since a sample size calculation was not made. In order to confirm the finding of this study, further research is needed that can set to see if the control group on a large scale. Finally, causality cannot be determined because this was a cross-sectional study. Further intervention studies are needed to determine whether intensive diabetic treatments reduce PISA and PESA via suppression of HbA1c and FPG.

CONCLUSION
In conclusion, both PISA and PESA were significantly associated with HbA1c, but not with parameters of obesity. PISA was also associated with FPG. This study suggested that inflammation of periodontal tissue may be affected by glycemic control, independent of oral hygiene.

REFERENCES
Epidemiology/Health services research


Supplementary Table 1. Variance inflation factors (VIF) and 1/VIF explained by the other independent variables of Table 2 models.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Categorical Variable</th>
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<tr>
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<tr>
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<tr>
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</table>

Abbreviations: PISA, periodontal inflamed surface area; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; VFA, visceral fat area; T, tertile; Coef, Coefficient; SE, standard error; CI, confidence interval; VIF, variance inflation factor.
**Supplementary Table 2. Variance inflation factors (VIF) and 1/VIF explained by the other independent variables of Table 3 models.**

<table>
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<th>PESA Variable</th>
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<tr>
<td>VFA (cm²)</td>
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Abbreviations: PESA, periodontal epithelial surface area; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; VFA, visceral fat area; T, tertile; Coef, Coefficient; SE, standard error; CI, confidence interval; VIF, variance inflation factor.
Supplementary Table 3. Association between PISA or PESA and HbA1c when comparing HbA1c split into two groups by 8%.

<table>
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<td>Coef. 95%CI p-value</td>
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<tr>
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<td><strong>PESA</strong></td>
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<tr>
<td>Continuous variable</td>
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<tr>
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<tr>
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<td>102.2 (-15.90, 220.3) 0.09</td>
<td>HbA1c T3 (compared to T1,2)</td>
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<tr>
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†: Adjusted for, sex, smoking status, BMI, PCR.

Abbreviations; PISA, periodontal inflamed surface area; HbA1c, hemoglobin A1c; Coef, Coefficient; CI, confidence interval

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**Supplementary Figure 1. Histogram illustrating PISA and PESA.** Histogram illustrating PISA (A) and PESA (B).
Supplementary Figure 2. Boxplot diagram illustrating PISA and PESA by periodontitis classification (Papapanou et al. 2018).

(A) Boxplot diagram illustrating PISA by periodontitis classification (● represents an outlier value). (B) Boxplot diagram illustrating PESA by periodontitis classification (● represents an outlier value). *p<0.05
Supplementary Figure 3. Boxplot diagram illustrating BMI and VFA by HbA1c. (A) Boxplot diagram illustrating BMI with HbA1c split at 8% as a reference point (• represents an outlier value). (B) Boxplot diagram illustrating VFA with HbA1c split at 8% as a reference point (• represents an outlier value). HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; VFA, visceral fat area.