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ORIGINAL ARTICLE

The number of microvascular complications is associated with an increased risk for severity of periodontitis in type 2 diabetes patients: Results of a multicenter hospital-based cross-sectional study

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ABSTRACT

Aims/Introduction: To explore the relationships between periodontitis and microvascular complications as well as glycemic control in type 2 diabetes patients.

Materials and Methods: This multicenter, hospital-based, cross-sectional study included 620 patients with type 2 diabetes. We compared the prevalence and severity of periodontitis between patients with ≥1 microvascular complication and those without microvascular complications. We also compared the prevalence and severity of periodontitis among patients with different degrees of glycemic control.

Results: After adjusting for confounding factors, multiple logistic regression analysis showed that the severity of periodontitis was significantly associated with the number of microvascular complications (odds ratio 1.3, 95% confidence interval 1.1–1.6), glycated hemoglobin ≥8.0% (64 mmol/mol; odds ratio 1.6; 95% confidence interval 1.1–2.3), and older age (≥50 years; odds ratio 1.7; 95% confidence interval 1.1–2.6). However, the prevalence of periodontitis was not significantly associated with the number of microvascular

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complications, but was associated with male sex, high glycated hemoglobin (≥8.0% [64 mmol/mol]), older age (≥40 years), longer duration of diabetes (≥15 years) and fewer teeth (≤25). Furthermore, propensity score matching for age, sex, diabetes duration and glycated hemoglobin showed that the incidence of severe periodontitis was significantly higher among patients with microvascular complications than among those without microvascular complications ($P < 0.05$).

Conclusions: The number of microvascular complications is a risk factor for more severe periodontitis in patients with type 2 diabetes, whereas poor glycemic control is a risk factor for increased prevalence and severity of periodontitis.

INTRODUCTION

Periodontitis is a chronic infectious disease triggered by a bacterial biofilm of dental plaque. This biofilm leads to pocket formation, which progresses to inflammation-mediated loss of connective tissue attachment and alveolar bone destruction, eventually resulting in tooth loss[1,2]. Many studies have shown that both type 1 and type 2 diabetes mellitus increase the prevalence and severity of periodontitis, and that the effects are more evident in type 2 diabetes patients[3–6].

Poor glycemic control has been considered an important risk factor for periodontitis. The prevalence and severity of periodontitis in type 2 diabetes patients have been reported to be increased[7–14], because chronic hyperglycemia (long-term poor glycemic control) increases host susceptibly to infectious bacteria in the periodontium. Diabetic microangiopathic change has been also considered as a risk factor for periodontitis[15]. However, evidence for microangiopathy as a risk factor for periodontitis has so far been insufficient.

Long-term poor glycemic control causes microangiopathic changes, such as retinopathy, nephropathy and neuropathy, as morphological alterations, in type 2 diabetic patients[16,17]. Similarly, such changes to the periodontal tissue[18] can increase host susceptibility to infectious bacteria in the periodontium. Therefore, we hypothesized that microangiopathy might increase the risk of periodontitis in type 2 diabetes patients, because microangiopathic capillary changes in the periodontal tissue could be similar to those observed in retinopathy, nephropathy or neuropathy.

Few studies have shown that microvascular complications, including retinopathy[19–23], nephropathy[22,24,25] and neuropathy[22,26], are associated with periodontitis in type 2 diabetes patients. However, these studies investigated the associations individually, rather than comprehensively evaluating whether all microvascular complications are related to periodontitis.

The aim of the present multicenter, hospital-based, cross-sectional study was to systematically and comprehensively explore the relationships between microvascular complications and periodontitis in type 2 diabetes patients by comparing the prevalence and severity of periodontitis between patients with ≥1 microvascular complication and those without any complications. This study also explored the relationship between glycemic control status and periodontitis by comparing the prevalence and severity of periodontitis among type 2 diabetes patients with different degrees of glycemic control.

METHODS

Participants

A total of 635 type 2 diabetes patients aged 25–81 years were recruited from among those who presented to diabetes clinics at 21 institutions; the list of institutions is presented in Appendix S1. All medical histories of the participants were documented, and physical and biochemical examinations, followed by dental examinations, were carried out at each facility. Ultimately, 620 patients were included in the analysis after excluding those with missing data.

The study protocol was approved by the ethics committee at each institution. Written informed consent was obtained from each participant at the respective diabetes and dental clinics.

Diagnosis of diabetic microvascular complications and stratification of glycemic control status

Retinopathy was diagnosed based on the presence of characteristic microvascular changes in the retina, such as hemorrhage, exudate, edema and fibrous proliferation, as detected by ophthalmoscopy through dilated pupils[27]. The diagnosis of diabetic nephropathy was based on the presence of proteinuria or microalbuminuria in 24-h urine samples (≥30 mg/24 h)[27]. Neuropathy was diagnosed based on the presence of at least two positive findings among abnormal sensation, vibration abnormality on both sides of the ankle and ankle tendon reflex abnormality on both sides[27].

Glycemic control was stratified into the following four grades: 'poor,' glycated hemoglobin (HbA1c) ≥8.0% (64 mmol/mol); 'fair,' HbA1c ≥7.0% (53 mmol/mol) and <8.0% (64 mmol/mol); 'good,' HbA1c ≥6.0% (42 mmol/mol) and <7.0% (53 mmol/mol); and 'excellent,' HbA1c <6.0% (42 mmol/mol).

Measurements

The HbA1c level was measured to estimate the glycemic control status. Total cholesterol and high-density lipoprotein (HDL) cholesterol levels in the serum were measured as

systemic markers of lifestyle-related diseases. The HbA1c level was measured using high-performance liquid chromatography (Kyotokagaku Co, Kyoto, Japan), whereas total cholesterol and HDL cholesterol levels were measured with enzyme-linked immunosorbent assay using an automated device (Hitachi Co., Tokyo, Japan).

Intraoral examinations

The number of teeth (excluding the third molars) was recorded. An examination for periodontitis was carried out using the simple World Health Organization Community Periodontal Index (CPI) codes[28]. In this examination, the right central incisor in the maxilla and the left central incisor in the mandible were considered as representative teeth among the anterior teeth, whereas the first and second molars on the right and left sides of the maxilla and mandible, respectively, were considered as representative teeth among the posterior teeth. The dentition (excluding the third molars) was divided into sextants according to the World Health Organization protocol. The following CPI codes were used: code 0, no signs of periodontal disease; code 1, gingival bleeding after gentle probing; code 2, supragingival or subgingival calculus; code 3, 4–5 mm deep pathological pockets; code 4, 6-mm or deeper pathological pockets; and code X, missing index teeth. The participants with CPI codes 0, 1 and 2 were considered to have healthy periodontal tissue, gingivitis and supragingival or subgingival calculus, respectively. Participants with CPI code 3 were considered to have mild periodontitis, whereas participants with CPI codes 4 and X were considered to have severe periodontitis[28]. The maximum code in each sextant was recorded.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. The unpaired *t*-test, Mann–Whitney *U*-test or Pearson's χ^2-test was used to evaluate differences in demographic data between patients with and those without microvascular complications. Pearson's χ^2-test or the Mann–Whitney *U*-test with Bonferroni's correction were carried out to assess the associations of the prevalence and severity of periodontitis with microvascular complications or glycemic control status.

Multiple logistic regression analysis was carried out to determine the odds ratios and 95% confidence intervals for microvascular complications or glycemic control status with respect to the prevalence and severity of periodontitis. In the present analysis, variables without a normal distribution were treated as categorical data. Explanatory variables were selected using a stepwise approach with the Akaike information criterion involving correction for finite sample sizes, and were entered into the regression model. The Cochrane–Armitage trend test was carried out to assess the presence of an association between the prevalence of periodontitis and the number of microvascular complications/glycemic control. To reduce the confounding effects of covariates, we used propensity scores to match patients with microvascular complications to patients without microvascular complications. The following four covariates related to periodontitis were taken into account for matching: age, sex, diabetes duration and HbA1c level. Statistical analyses were carried out using the JMP version 9.0 software (SAS Institute Inc., Cary, NC, USA) and SPSS 22.0 (IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the diabetes patients with or without microvascular complications

The study included 620 diabetes patients. Demographic data and characteristics of the patients are shown in Table 1. Age, body mass index (BMI), HbA1c level, diabetes duration and number of teeth did not show normal distribution. Mean age, HbA1c level, maximum CPI, prevalence of periodontitis, prevalence of severe periodontitis, systolic blood pressure, diastolic blood pressure and diabetes duration were significantly greater in diabetes patients with microvascular complications than in patients without complications. However, the number of teeth was significantly lower in patients with microvascular complications than in patients without complications. Sex, BMI, smoking status, total cholesterol level and HDL cholesterol level did not differ significantly between the two patient groups.

Of the 620 study patients, 214 (34.5%) had retinopathy, 160 (25.8%) had nephropathy and 185 (29.8%) had neuropathy. A total of 313 (50.5%) patients had at least one microvascular complication (24 had retinopathy and nephropathy, 34 had retinopathy and neuropathy, 26 had nephropathy and neuropathy, and 81 had all three complications).

Additionally, of the 620 patients, 293 (47.2%) had poor glycemic control, 152 (24.5%) had fair glycemic control, 135 (21.8%) had good glycemic control and 40 (6.5%) had excellent glycemic control (Table 1).

Characteristics of the diabetes patients categorized by the number of microvascular complications

Demographic data and characteristics of the patients categorized by number of microvascular complications are shown in Table 2. Distributions of maximum CPI, number of teeth, systolic blood pressure and diabetes duration were different among the patients categorized by the number of microvascular complications.

Number of microvascular complications and prevalence of periodontitis in type 2 diabetic patients

The prevalence of periodontitis was significantly higher in patients with all three microvascular complications than in those without microvascular complications ($P < 0.01$); however, the prevalence of periodontitis was not significantly different between patients with one or two microvascular complications and those without microvascular complications (Figure 1a). The Cochrane–Armitage trend test showed a significant association between the prevalence of periodontitis and the number of microvascular complications ($P < 0.01$).

Table 1 | Characteristics of the diabetes patients with and those without microvascular complications

Variables	Microvascular complications		*P*-value
	+	−	
n	313	307	
Age (years)	55.1 ± 9.3	52.4 ± 10.3	0.0006
Sex (male/female)	198/115	181/126	0.27
HbA1c, % (mmol/mol)	8.7 ± 1.8 (72 ± 19)	7.7 ± 1.5 (61 ± 16)	<0.0001
BMI (kg/m^2)	24.0 ± 3.9	23.9 ± 3.9	0.67
Maximum CPI, *n* (0/1/2/3/4/X)	7/43/42/94/104/23	16/49/57/101/77/7	0.002
Periodontitis (CPI ≥3), *n* (%)	221 (70.6)	185 (60.3)	0.0067
Severe periodontitis (CPI ≥4) *n* (%)	127 (40.6)	84 (27.4)	0.0005
Smoking (%)	42.6	38	0.26
Present teeth (*n*)	20.6 ± 8.1	23.1 ± 6.3	<0.0001
Total cholesterol (mg/dL)	205.7 ± 45.4	204.8 ± 42.2	0.81
HDL cholesterol (mg/dL)	54.5 ± 19.2	54.3 ± 16.6	0.90
Systolic blood pressure (mmHg)	137.3 ± 17.8	129.5 ± 16.8	<0.0001
Diastolic blood pressure (mmHg)	80.1 ± 11.2	78.0 ± 11.0	0.02
Diabetes duration (years)	12.3 ± 8.5	6.9 ± 5.6	<0.0001
Retinopathy only (*n*)	75	0	
Nephropathy only (*n*)	29	0	
Neuropathy only (*n*)	44	0	
Retinopathy + nephropathy (*n*)	24	0	
Retinopathy + neuropathy (*n*)	34	0	
Nephropathy + neuropathy (*n*)	26	0	
Retinopathy + nephropathy + neuropathy (*n*)	81	0	
Poor glycemic control (*n*)	192	101	
Fair glycemic control (*n*)	67	85	
Good glycemic control (*n*)	45	90	
Excellent glycemic control (*n*)	9	31	

Data are presented as mean ± standard deviation. *P*-values are based on the *t*-test/Mann–Whitney *U*-test for continuous variables, and the χ^2-test for categorical variables. Glycemic control status was stratified into the following four grades: 'poor,' glycated hemoglobin (HbA1c) ≥8.0%; 'fair,' HbA1c ≥7.0% and <8.0%; 'good,' HbA1c ≥6.0% and <7.0%; and 'excellent,' HbA1c <6.0%. BMI, body mass index; CPI, community periodontal index; HDL, high-density lipoprotein cholesterol.

Number of microvascular complications and severity of periodontitis in type 2 diabetes patients

The proportion of patients with each maximum CPI code with respect to the number of microvascular complications is shown in Figure 1b. Severe periodontitis was present in 37.8% of patients with one microvascular complication, 36.9% of patients with two microvascular complications and 49.4% of patients with three microvascular complications. The severity of periodontitis was greater in patients with one, two or three microvascular complications than in those with no microvascular complications ($P < 0.05$, $P < 0.05$ and $P < 0.01$). Additionally, the severity of periodontitis was greater in patients with three microvascular complications than in those with one microvascular complication ($P < 0.05$).

HbA1c values and prevalence of periodontitis in type 2 diabetes patients

The prevalence of periodontitis was significantly higher in patients with poor glycemic control (71.0%) than in those with excellent glycemic control (50.0%; $P < 0.01$; Figure 2a). However, the prevalence of periodontitis was not significantly different between patients with fair glycemic control (62.5%) or good glycemic control (61.5%) and those with excellent glycemic control (50.0%). There was a significant association between the prevalence of periodontitis and glycemic control ($P < 0.01$).

HbA1c values and severity of periodontitis in type 2 diabetes patients

Severe periodontitis was present in 40.6% of patients with poor glycemic control, 28.3% of patients with fair glycemic control, 28.1% of patients with good glycemic control and 28.0% of patients with excellent glycemic control. The incidence of severe periodontitis was significantly higher in patients with good, fair and poor glycemic control than in those with excellent glycemic control ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively; Figure 2b).

Multiple logistic regression analysis

To evaluate the association between diabetic microvascular complications and the prevalence or severity of periodontitis,

Table 2 | Characteristics of the diabetes patients categorized by the number of microvascular complications

Variables	No. microvascular complications			*P*-value
	1	2	3	
n	148	84	81	
Age (years)	54.9 ± 9.5	54.7 ± 10.2	55.8 ± 7.8	0.81
Sex (male/female)	87/61	52/32	59/22	0.10
HbA1c, % (mmol/mol)	8.5 ± 1.8 (69 ± 20)	8.6 ± 1.7 (70 ± 19)	9.0 ± 2.0 (75 ± 22)	0.22
BMI (kg/m^2)	24.3 ± 3.4	24.2 ± 4.9	23.5 ± 3.4	0.14
Maximum CPI (*n*) (0/1/2/3/4/X)	3/23/22/44/50/6	3/12/11/27/24/7	1/8/9/23/30/10	0.04
Periodontitis (CPI ≥ 3), *n* (%)	100 (67.6)	58 (69.1)	63 (77.8)	0.25
Severe periodontitis (CPI ≥4), *n* (%)	56 (37.8)	31 (36.9)	40 (49.4)	0.17
Smoking (%)	40.6	40.8	48	0.54
Present teeth (*n*)	21.8 ± 7.6	20.8 ± 7.9	18.4 ± 9.0	0.01
Total cholesterol (mg/dL)	205.9 ± 41.5	203.0 ± 42.6	208.1 ± 54.6	0.77
HDL cholesterol (mg/dL)	56.4 ± 22.3	52.4 ± 13.8	53.1 ± 17.7	0.28
Systolic blood pressure (mmHg)	134.3 ± 17.3	136.2 ± 18.7	144.2 ± 16.2	0.0003
Diastolic blood pressure (mmHg)	79.6 ± 11.4	78.7 ± 10.9	82.7 ± 10.7	0.051
Diabetes duration (years)	9.9 ± 7.9	12.7 ± 8.9	16.2 ± 7.4	<0.0001
Retinopathy only (*n*)	75	0	0	
Nephropathy only (*n*)	29	0	0	
Neuropathy only (*n*)	44	0	0	
Retinopathy + nephropathy (*n*)	0	24	0	
Retinopathy + neuropathy (*n*)	0	34	0	
Nephropathy + neuropathy (*n*)	0	26	0	
Retinopathy + nephropathy + neuropathy (*n*)	0	0	81	
Poor glycemic control (*n*)	89	50	53	
Fair glycemic control (*n*)	27	21	19	
Good glycemic control (*n*)	24	12	9	
Excellent glycemic control (*n*)	8	1	0	

Data are presented as mean ± standard deviation. *P*-values are based on the ANOVA/Kruskal–Wallis test for continuous variables, and the χ^2-test for categorical variables. Glycemic control status was stratified into the following four grades: 'poor,' glycated hemoglobin (HbA1c) ≥8.0%; 'fair,' HbA1c ≥7.0% and <8.0%; 'good,' HbA1c ≥6.0% and <7.0%; and 'excellent,' HbA1c <6.0%. BMI, body mass index; CPI, community periodontal index; HDL, high-density lipoprotein cholesterol.

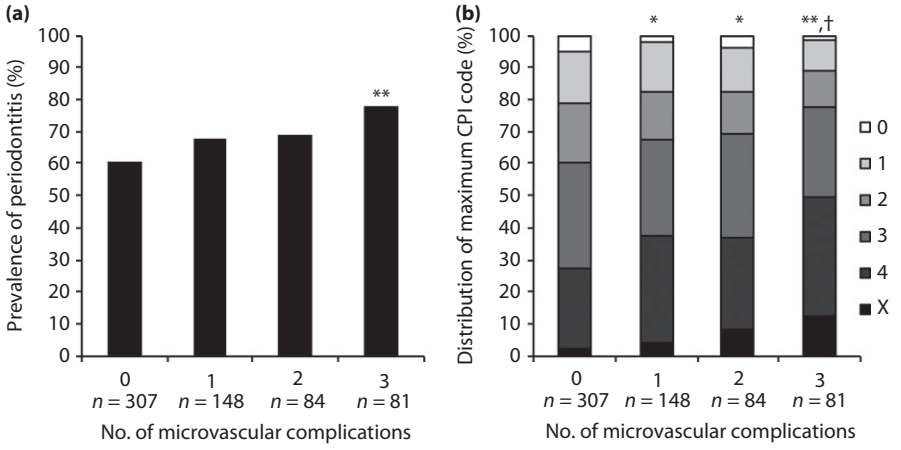

Figure 1 | (a) Prevalence of periodontitis and (b) distribution of maximum Community Periodontal Index (CPI) code in type 2 diabetes patients according to the number of microvascular complications. *P < 0.05, **P < 0.01 vs patients without microvascular complications. †P < 0.05 vs patients with a single microvascular complication.

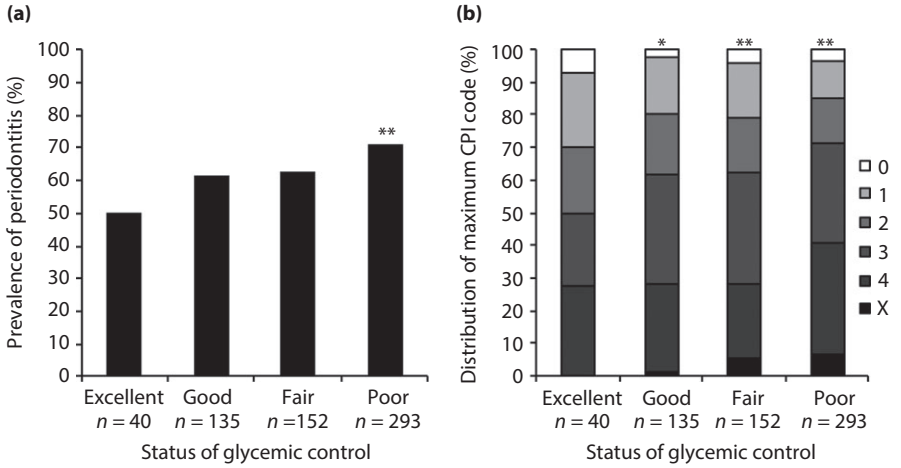

Figure 2 | (a) Prevalence of periodontitis and (b) distribution of maximum Community Periodontal Index (CPI) code in type 2 diabetes patients according to glycemic control status. Glycemic control status was stratified into the following four grades: 'poor,' glycated hemoglobin (HbA1c) ≥8.0%; 'fair,' HbA1c ≥7.0% and <8.0%; 'good,' HbA1c ≥6.0% and <7.0%; and 'excellent,' HbA1c <6.0%. *$P < 0.05$ **$P < 0.01$ vs patients with HbA1c <6.0%

multiple logistic regression analysis was carried out. Sex, age, BMI, HbA1c level, diabetes duration, number of teeth, total cholesterol level, HDL cholesterol level, smoking status and number of microvascular complications were used as explanatory variables. As age, BMI, HbA1c level, diabetes duration and number of teeth did not have a normal distribution, these variables were categorized into textiles or quartiles. Age was divided into four categories: ≥60 years, ≥50 and <60 years, ≥40 and 50 years, and <40 years; BMI into three categories: ≥30 kg/m^2, ≥25 and <30 kg/m^2, and <25 kg/m^2; HbA1c into four categories: ≥8.0% (64 mmol/mol), ≥7.0% (53 mmol/mol) and <8.0% (64 mmol/mol), HbA1c ≥6.0% (42 mmol/mol) and <7.0% (53 mmol/mol), and <6.0% (42 mmol/mol); diabetes duration into four categories: ≥15 years, ≥10 and <15 years, ≥5 and <10 years, and <5 years; and number of teeth into four categories: ≤19, 20–25, 26–27 and 28.

In the analyses, male sex, age ≥40 years, diabetes duration ≥15 years, HbA1c ≥8.0% (64 mmol/mol) and number of teeth ≤25 were significantly associated with the prevalence of periodontitis (Table 3), whereas age ≥50 years, HbA1c ≥8.0% (64 mmol/mol) and the number of microvascular complications were significantly associated with the severity of periodontitis (Table 3).

Table 3 | Multiple logistic regression analysis for the risk of periodontitis and severe periodontitis in type 2 diabetes patients

Dependent variable	Independent variable		Adjusted OR	95% CI	*P*-value
Periodontitis	Sex	Female	1		
		Male	1.6	(1.1–2.4)	0.01
	Age (years)	<40	1		
		≥40	1.5	(1.1–2.1)	0.02
	Diabetes duration (years)	<15	1		
		≥15	1.3	(1.0–1.7)	0.03
	HbA1c	<8.0%	1		
		≥8.0%	1.2	(1.0–1.5)	0.03
	No. present teeth	≥26	1		
		≤25	1.4	(1.2–1.7)	<0.01
Severe –periodontitis	Age (years)	<50	1		
		≥50	1.7	(1.1–2.6)	0.02
	HbA1c	<8.0%	1		
		≥8.0%	1.6	(1.1–2.3)	0.02
	No. microvascular complications		1.3	(1.1–1.6)	0.01

CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

Propensity score matching

We carried out one-to-one patient matching based on propensity scores. Propensity score matching resulted in the selection of 324 patients (162 patients with microvascular complications and 162 patients without microvascular complications). The incidence of severe periodontitis was significantly higher among patients with microvascular complications than among those without microvascular complications ($P < 0.05$), although there were no significant differences in smoking status, number of teeth, total cholesterol level and HDL cholesterol level between the patient groups (Table 4).

DISCUSSION

The present study had some important findings. First, in type 2 diabetes patients, the number of microvascular complications was associated with the severity of periodontitis, but not its prevalence. Second, poor glycemic control was associated with both the prevalence and severity of periodontitis.

Table 4 | Characteristics of the diabetes patients with and those without microvascular complications after matching for age, sex, diabetes duration and glycated hemoglobin by propensity scores

Variables	Microvascular complications		*P*-value
	+	−	
n	162	162	
Age (years)	53.8 ± 9.4	53.7 ± 9.9	0.89
Sex (male/female)	103/59	101/61	0.91
HbA1c, % (mmol/mol)	8.1 ± 1.7 (65 ± 19)	8.1 ± 1.5 (65 ± 17)	0.92
BMI (kg/m^2)	24.1 ± 4.0	24.0 ± 4.4	0.87
Maximum CPI, *n* (0/1/2/3/4/X)	6/27/18/50/54/7	5/24/27/60/41/5	0.17
Periodontitis (CPI ≥3), *n* (%)	111 (68.5)	106 (65.4)	0.35
Severe periodontitis (CPI ≥4), *n* (%)	61 (37.7)	46 (28.4)	0.049
Smoking (%)	44.3	38.5	0.31
Present teeth (*n*)	21.7 ± 7.1	22.6 ± 6.9	0.21
Total cholesterol (mg/dL)	200.0 ± 43.0	204.7 ± 3 9.9	0.57
HDL cholesterol (mg/dL)	54.3 ± 21.3	55.4 ± 17.8	0.62
Systolic blood pressure (mmHg)	135.7 ± 17.5	130.6 ± 16.9	0.013
Diastolic blood pressure (mmHg)	79.9 ± 11.1	77.9 ± 10.6	0.09
Diabetes duration (years)	8.3 ± 5.6	8.3 ± 5.8	0.96
Retinopathy only (*n*)	41	0	
Nephropathy only (*n*)	18	0	
Neuropathy only (*n*)	30	0	
Retinopathy + nephropathy (*n*)	13	0	
Retinopathy + neuropathy (*n*)	16	0	
Nephropathy + neuropathy (*n*)	17	0	
Retinopathy + nephropathy + neuropathy (*n*)	27	0	
Poor glycemic control (*n*)	80	71	
Fair glycemic control (*n*)	39	51	
Good glycemic control (*n*)	35	33	
Excellent glycemic control (*n*)	8	7	

Data are presented as mean ± standard deviation. *P*-values are based on the *t*-test/Mann–Whitney *U*-test for continuous variables, and the χ^2-test for categorical variables. Glycemic control status was stratified into the following four grades: 'poor,' glycated hemoglobin (HbA1c) ≥8.0%; 'fair,' HbA1c ≥7.0% and <8.0%; 'good,' HbA1c ≥6.0% and <7.0%; and 'excellent,' HbA1c <6.0%. BMI, body mass index; CPI, community periodontal index; HDL, high-density lipoprotein cholesterol.

Bacterial microflora at the site of periodontal diseases in diabetes patients is similar to that in non-diabetic individuals[29,30]. Therefore, susceptibility to periodontitis in type 2 diabetes patients is mainly associated with the conditions of the host.

There is strong evidence that poor glycemic control is a risk factor for an increase in the prevalence and severity of periodontitis in type 2 diabetes patients as a result of chronic hyperglycemia-induced abnormalities that involve multiple and synergistic adverse events, such as neutrophil dysfunction[31], induced inflammation[32], formation of advanced glycation end-products[33], increased oxidative stress[34], elevated growth factor levels[35] and activation of protein kinase C[36]. In the present study, we found that poor glycemic control, as detected by a high HbA1c value (≥8.0%), was associated with increases in the prevalence and severity of periodontitis.

With respect to previous reports on the relationship between glycemic control status and periodontitis in type 2 diabetic patients, several cross-sectional[7–13] and longitudinal studies[9,14] showed significant associations between poor glycemic control and increased prevalence and severity of periodontitis. Additionally, we recently reported that effective glycemic control using antihypoglycemic agents and/or insulin treatment improved bleeding on gingival probing in type 2 diabetes patients in a short-term (3 months) longitudinal study[37]. These results were consistent with the concept that poor glycemic control contributes to an increase in both the prevalence and severity of periodontitis in type 2 diabetes patients. The results of the present study regarding the positive relationship between poor glycemic control and periodontitis are confirmatory. We clearly showed that poor glycemic control (HbA1c >8.0%) was associated with increases in the prevalence and severity of periodontitis.

Thickening of the capillary basement membrane and appearance of microaneurysms are morphological hallmarks of diabetic microvascular complications. Thickening of the capillary basement membrane has been observed in the gingiva[38,39],

muscle[40] and heart[41], and capillary microaneurysms have been noted in the hearts[42] of diabetes patients and in the gingivae of type 2 Goto-Kakizaki diabetic rats[43].

In 1988, Hiller *et al.*[44] hypothesized that general microangiopathy affects not only the retina, but also other organs, such as the heart, independent of atherosclerotic coronary disease. This was based on a significant positive association between diabetic retinopathy and cardiovascular disease events in the youngest age group, no association in the middle age group, and a significant negative association in the oldest group of type 2 diabetes patients in the Framingham Heart and Framingham Eye Studies. More recently, Hujoel and Stott-Miller[21] similarly found that gingival hemorrhages at several sites were significantly associated with retinal hemorrhages, and both shared chronic hyperglycemia as an explanatory marker in type 2 diabetes patients. This result supports the hypothesis of Hiller *et al.*[44] that microangiopathic changes in the retina are reflective of systemic microvascular changes, such as those in the periodontal tissue[38,39], as well as in the muscle[40] and heart[41,42]. Consequently, we hypothesized that such microvascular morphological changes in the periodontal tissues render the host susceptible to infectious bacteria in the periodontium among type 2 diabetes patients. However, previous studies that investigated the relationship between diabetic microvascular complications and periodontitis focused on single microvascular complications, but did not explore the relationship between multiple diabetic microvascular complications and periodontitis comprehensively[19–26].

In the present study, we investigated this relationship in a large number of participants ($n = 620$) using a multicenter, hospital-based, cross-sectional design. Our results showed that type 2 diabetes patients with microvascular complications had more severe periodontitis than those without microvascular complications, and that multiple microvascular complications further increased the severity of periodontitis. In contrast, the presence of one or more microvascular complications did not increase the prevalence of periodontitis. These results support our hypothesis, and suggest that microangiopathy is a risk factor for severe periodontitis in type 2 diabetes patients.

We identified seven cross-sectional studies and one retrospective study that investigated whether microangiopathic change contributes to the severity of periodontitis in patients with retinopathy, nephropathy, or neuropathy[19–26]. Seven of these reports[19,20,22–26] found a significant association between the presence of microangiopathy and periodontitis in diabetes patients, and four were on type 2 diabetes patients[19,20,25,26]. As our finding that microvascular complications in individual tissues, such as the retina, kidney and nerve, contribute to the severity of periodontitis has been already reported, the novelty of our data is the finding that microvascular complications in multiple organs together can contribute to an additive increase in the severity of periodontitis in type 2 diabetes patients.

The different effects of poor glycemic control and microvascular complications on periodontal tissue are unclear. However, it is likely that both the physiological and biochemical effects of poor glycemic control, including those aforementioned quotations[31–36], have a more potent adverse impact on the periodontal tissue than only the morphological effect of microangiopathic change.

Diabetes mellitus and periodontitis have recently been found to have a bidirectional relationship[3,45]; that is, the presence of periodontitis adversely affects glycemic control in patients with diabetes mellitus, and effective periodontal treatment improves glycemic control in type 2 diabetes patients, without changes in the treatment for glycemic control[46,47]. Conversely, the presence of diabetes increases the risk of periodontitis, and we recently found that effective glycemic control ameliorated periodontitis in type 2 diabetes patients without periodontal treatment by reducing inflammation at the gingiva[37]. Therefore, glycemic and periodontal treatments should be administered simultaneously to diabetes patients with periodontitis, as this approach can improve glycemic control and ameliorate periodontitis, and might also inhibit the development and progression of diabetic microvascular complications.

The present study had several limitations. First, this was a cross-sectional study; thus, the causal relationship between diabetic microangiopathic changes and periodontitis cannot be explained. In the present cross-sectional study, multiple logistic analyses showed a clear association between microvascular changes and the severity of periodontitis. Longitudinal or prospective studies are required to substantiate the relationship between microvascular changes and the severity of periodontitis. However, it might be difficult to investigate the relationship between microangiopathy and periodontitis in a longitudinal study, because appropriately effective agents for advanced microangiopathic disorders in diabetes patients are not presently available. However, interestingly, one previous report mentioned that severe periodontitis predicted the development of overt nephropathy and end-stage renal disease[25]. Second, we applied the CPI assessment for periodontitis, which is simple to use and enables a unanimous diagnosis by reducing measurement error during community-based examinations. However, the validity of the CPI, including hierarchical concepts of progression of periodontitis, close concordance between periodontal inflammation and lack of estimation for alveolar bone loss, has been challenged[48]. The results of the present and previous studies[19,20,26] show that additional information about alveolar bone loss will be required to clarify the context in which the severity of periodontitis is affected by microangiopathic changes in the periodontium. Third, HbA1c values were converted to internationally used units defined by the National Glycohemoglobin Standardization Program by adding 0.4% to the HbA1c values of the Japan Diabetes Society[49]. This might have introduced some bias into the present results.

The number of microvascular complications, including neuropathy, nephropathy and retinopathy, in type 2 diabetes patients is associated with more severe periodontitis than in patients without microvascular complications after adjustment

for potential confounders. Multiple manifestation of microvascular complications further progresses the severity of periodontitis. Thus, microvascular complications could be designated as a risk factor for periodontitis in type 2 diabetes in addition to poor glycemic control. The number of diabetic microvascular complications is associated with an increased risk of severity of periodontitis in type 2 diabetic patients.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 |The list of institutions that participated in this study.