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ORIGINAL ARTICLE

Severe periodontal disease in Japanese patients with high HbA1c levels: a cross-sectional study

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Abstract

Objective This study aimed to investigate the relationship between plasma glucose profiles and periodontal disease (PD) severity in men and women

Methods We conducted a cross-sectional cohort study, enrolling all eligible patients with type 2 diabetes mellitus (T2DM) who regularly visited the outpatient department

Results Patients were divided into severe and non-severe PD groups. The severe PD group showed a male predominance and significantly higher hemoglobin A1c (HbA1c) levels than the non-severe PD group. The optimal HbA1c cutoff value on the receiver operating characteristic curve for predicting severe PD was 7.3% [56 mmol/mol] (sensitivity, 52%; specificity, 73%; $P = 0.01$). Multivariate logistic regression revealed that male sex (odds ratio [OR], 2.75; 95% confidence interval [CI], 1.19–6.34; P = 0.01) and higher HbA1c levels (OR, 3.09; 95% CI, 1.42–6.70; $P < 0$ .01) were independently and significantly associated with the presence of severe PD. The prevalence rates of severe PD in patients with HbA1c levels < 7.3% [56 mmol/mol] and HbA1c levels ≥ 7.3% [56 mmol/mol] were 17.4% and 53.3% in women, and 50.0% and 66.7% in men, respectively.

Conclusions Men with T2DM had a high risk of severe PD independent of HbA1c levels. Plasma glucose management may be crucial for maintaining periodontal health in T2DM patients, particularly in women.

Keywords Periodontal disease · Sex characteristics · Type 2 diabetes mellitus · Oral health · Remaining teeth · Community periodontal index

Introduction

Evidence of a close bidirectional relationship between periodontal disease (PD) and type 2 diabetes mellitus (T2DM) has confirmed the importance of screening for severe PD [1]. Severe PD increases hemoglobin A1c (HbA1c) levels [2]; accordingly, PD treatment improves glycemic control [3]. Mechanistic studies have shown that T2DM increases the inflammatory response to bacteria involved in periodontal disease and inhibits the resolution of inflammation, thus accelerating periodontal tissue destruction [4]. Furthermore, periodontal disease promotes systemic inflammatory mediators that exacerbate insulin resistance [5], leading to the worsening of T2DM.

Plasma glucose profiles influence the status and severity of PD. High HbA1c values (> 7.0% [52 mmol/mol]) accelerate PD progression in patients with T2DM [6]. Additionally, patients with T2DM and elevated HbA1c levels (≥ 9.0% [75 mmol/mol]) have a higher risk of alveolar bone resorption

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than those without T2DM or with T2DM accompanied by low HbA1c levels (< 9.0% [75 mmol/mol]) [7]. Hyperglycemia in T2DM drives the irreversible formation of AGEs, which have direct pro-inflammatory and pro-oxidant effects on gingival tissues [8]. Additionally, persistent hyperglycemia, which leads to exaggerated immune-inflammatory responses induced by periodontal pathogens, is responsible for the greater risk and severity of periodontal disease in patients with DM [9].

However, no definitive cutoff HbA1c level has been proposed to predict the risk of developing severe PD. Furthermore, the influence of sex and glucose profiles on the development of severe PD remains unclear.

We previously reported that regular check-ups contribute to the oral health of T2DM patients [10]. In this study, we investigated the relationship between plasma glucose profiles and PD severity. Confirmation of the optimal HbA1c cutoff value for predicting severe PD may help clinicians manage PD in patients with T2DM.

Subjects and methods

Subjects and protocol

A non-interventional observational cohort study of patients treated for T2DM was conducted in an outpatient service at Kurinami Clinic, Saga, Japan, between April 1, 2021 and April 30, 2022. The inclusion criterion was regular visits to the outpatient department for T2DM treatment. Participants were enrolled consecutively, excluding patients with cancer or acute diseases including infectious diseases. The primary outcome was the presence of PD. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Human Ethics Review Committee of Jinnouchi Hospital, Kumamoto, Japan (2024-4-1). This study was registered under the UMIN protocol registration system (ID: UMIN000054481).

Evaluation of the oral environment

To evaluate the oral environment, a dentist or dental hygienist assessed the periodontal condition and counted the remaining teeth in the dental consultation room of Kurinami Clinic. Periodontal examinations were performed in accordance with the World Health Organization (WHO) Community Periodontal Index (CPI) [11] proposed by Oral health surveys: basic methods—4th ed. The periodontal inflamed surface area (PISA) [12] reflects the surface area of inflammation (ulceration) in the pocket and is calculated on the basis of the probing depth and bleeding on probing. It provides a relatively accurate representation of the current state of inflammation in the oral cavity but, together with the 2013 revision of the CPI [13], assesses the condition of all teeth and was thus not used in this study. The measurements were performed using the WHO perio probe (Shioda, Tochigi, Japan). Ten representative teeth were evaluated, and six six blocks of CPI values were obtained for the upper and lower jaws of the anterior teeth and molars; the highest value was used as the "individual value." A CPI value of 0 indicates healthy gingiva, a value of 1 indicates a periodontal pocket < 4 mm and bleeding on probing, a value of 2 indicates a periodontal pocket < 4 mm and tartar adherence, a value of 3 indicates a periodontal pocket > 4 mm but < 6 mm (with or without bleeding or tartar), and a value of 4 indicates a periodontal pocket > 6 mm (with or without bleeding or tartar). In this study, we assigned patients with a CPI of 4 to the severe PD group, in accordance with the previous literature [14]. Simultaneously, questionnaires were administered to the study participants regarding their history of tooth loss within the previous year, history of gingival swelling, number of tooth brushings per day, regular interdental cleaning, and regular dental consultations (at least once a year).

Blood sampling and measurement of clinical parameters

Blood and urine samples were collected and analyzed at each hospital visit. Blood analyses were conducted in the hospital laboratory to determine glycosylated hemoglobin (HbA1c) levels (National Glycohemoglobin Standardization Program (NGSP) values followed by International Federation of Clinical Chemistry (IFCC) values in square brackets).

Statistical analysis

The normality of the distribution of continuous data was assessed using the Shapiro–Wilk test. Normally distributed data are expressed as mean ± standard deviation, and data with a skewed distribution are described as medians and interquartile ranges. Categorical data are presented as frequencies and percentages. Differences in categorical variables between the two groups were tested using Fisher's exact test, and differences in continuous variables were analyzed using an unpaired t-test or the Mann–Whitney U test.

Receiver operating characteristic (ROC) curve analysis was used to calculate the optimal HbA1c cutoff value for identifying severe PD. Based on the optimal cutoff (≥ 7.3% [56 mmol/mol]), we performed a logistic regression analysis to identify factors predicting the presence of severe PD. A history of gingival swelling was excluded from the logistic regression analysis because it is a symptom of PD. Thus, seven factors considered to be potentially associated with severe PD were entered into the regression model: age, sex, body weight, number of remaining teeth, smoking status, regular check-ups with dentists, and

management of diabetes mellitus. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Tokyo, Japan).

Results

Subjects

In total, 162 consecutive patients with T2DM were enrolled in this study. The participants' characteristics are presented in Table 1. The median age was 71 years, and 76 patients (46.9%) were men. In total, 62 (38.2 %) and 82 (50.6 %) patients were diagnosed with severe PD (CPI = 4) and non-severe PD (CPI = 4), respectively, and 18 (11.1%) had an unmeasurable CPI.

Comparison of clinical characteristics between the severe and non-severe PD groups

The baseline clinical characteristics of the severe and non-severe PD groups are presented in Table 1. The proportion of males, body weight, proportion of patients with a history of gingival swelling, and HbA1c levels (non-severe PD group, 7.1% [53 mmol/mol]; severe PD group, 7.4% [57 mmol/mol]) were significantly higher in the severe PD group than in the non-severe PD group. Dot plots of HbA1c levels in the severe and non-severe PD groups are shown in Figure 1.

ROC curve analysis

We calculated the optimal cutoff value of HbA1c for predicting the presence of severe PD using ROC curve analysis, which was 7.3%. The area under the curve was 0.62 (sensitivity, 52%; specificity, 73%; $P = 0.014$) (Figure 2). When the ROC analysis of HbA1c as a predictor of severe PD was limited to women, the optimal cutoff value of HbA1c was

Table 1 Clinical characteristics of participants (n = 162)

	Overall (n = 162)	Non-severe (n = 82)	Severe (n = 62)	P-value
Physical parameters				
Age (years)	71 (63–77)	68 (61–77)	72 (64–77)	0.0853
Male; n, (%)	76 (46.9)	30 (36.6%)	38 (61.3%)	0.0042
Height (cm)	157 (151–165)	156 (152–162)	162 (152–167)	0.1103
Weight (kg)	60.5 (53.3–69.2)	58.4 (53.3–67.2)	64.1 (54.1–73.2)	0.0476
Body mass index (kg/m^2)	24.2 (21.9–26.9)	24.4 (21.8–26.8)	24.3 (21.6–27.5)	0.2807
Periodontal disease-associated parameters				
Community Periodontal Index				
0; n, (%)	3 (1.9%)	3 (3.7%)		
1; n, (%)	4 (2.5%)	4 (4.9%)		
2; n, (%)	7 (4.3%)	7 (8.5%)		
3; n, (%)	68 (42.0%)	68 (82.9%)		
4; n, (%)	62 (38.3%)		62 (100%)	
Not measurable; n, (%)	18 (11.1%)			
Number of remaining teeth	22 (11–26)	23 (16–26)	24 (19–27)	0.2432
Lifestyle				
Current smoking; n, (%)	29 (17.9%)	11 (13.4%)	15 (24.1%)	0.1257
History of tooth loss within the previous year; n (%)	29 (17.9%)	14 (17.1%)	13 (21.0%)	0.6671
History of gingival swelling; n, (%)	62 (38.3%)	26 (31.7%)	33 (53.2%)	0.0108
Number of times teeth brushed per day	1.93 ± 0.90	2.05 ± 0.75	1.94 ± 0.96	0.4273
Regular interdental cleaning (yes); n, (%)	44 (27.1%)	26 (31.7%)	17 (27.4%)	0.7133
Regular dental consultation (yes), n, (%)	36 (22.2%)	24 (29.3%)	11 (17.7%)	0.1212
Diabetes mellitus and its comorbidities				
Hemoglobin A1c (%)	7.2 ± 0.8	7.1 ± 0.7	7.4 ± 0.9	0.0143
Diabetes duration (years)	12 (6–18)	11 (5–17)	14 (6–20)	0.2591
Hypertension; n, (%)	102 (63.0%)	49 (59.8%)	40 (64.5%)	0.6060
Hyperlipidemia; n, (%)	108 (66.6%)	55 (67.1%)	42 (67.8%)	1.0000

Data are represented as the mean ± SD, median [25–75th percentile range]

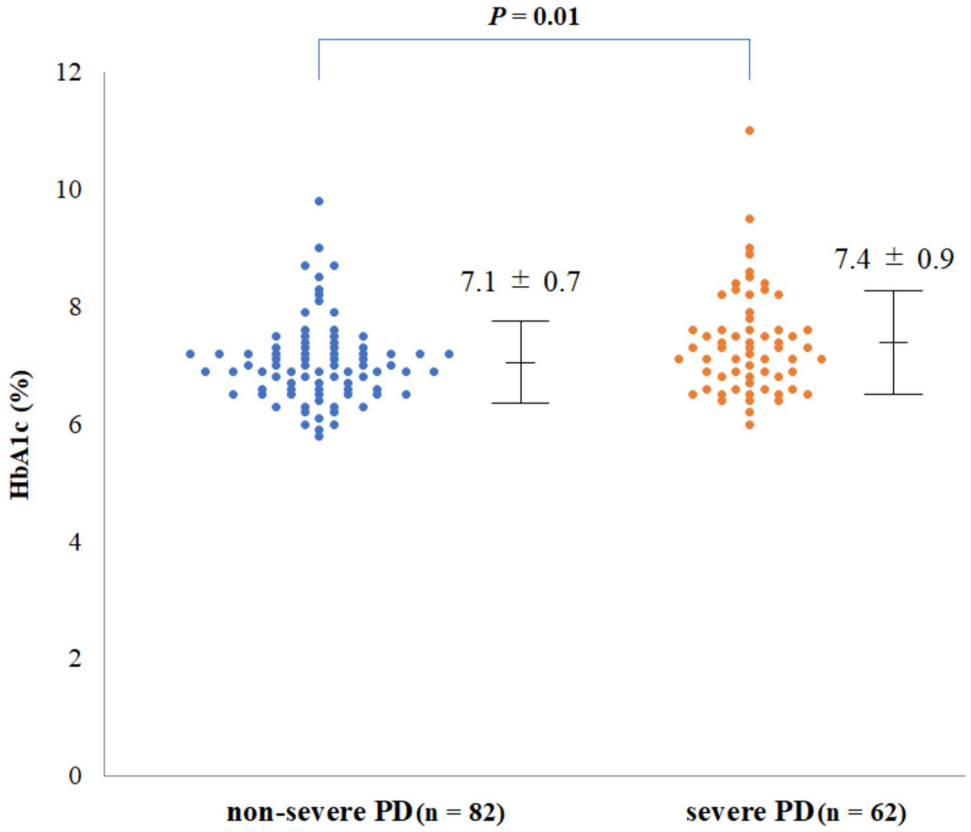

Fig. 1 Dot plot of HbA1c values in the non-severe and severe PD groups. Data are presented as the mean ± standard deviation and were analyzed using an unpaired *t*-test. *PD* periodontal disease, *HbA1c* glycated hemoglobin

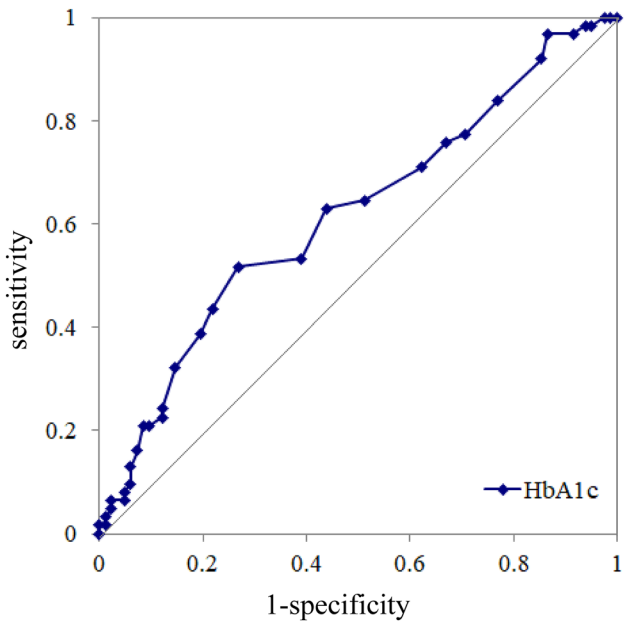

Fig. 2 Receiver operating characteristic curve analysis was used to identify the optimal HbA1c value for predicting severe PD. The optimal HbA1c cutoff value for predicting the presence of severe PD, defined based on the sensitivity and specificity values, was 7.3% (National Glycohemoglobin Standardization Program) (AUC, 0.62; standard error, 0.05; 95% confidence interval, 0.52–0.71; $P = 0.01$). *AUC* area under the curve, *PD* periodontal disease, *HbA1c* glycated hemoglobin

7.3% (AUC = 0.68; sensitivity, 67%; specificity, 73%; $P = 0.015$).

Logistic regression analysis of the presence of severe PD

Logistic regression analysis was performed to identify predictors of the presence of severe PD (Table 2). Simple regression analysis identified male sex (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.39–5.42; $P < 0.01$) and high HbA1c levels (OR, 2.90; 95% CI, 1.45–5.84; $P < 0.01$) as significant predictors. Similarly, male sex (OR, 2.75; 95% CI, 1.19–6.34; $P = 0.02$) and high HbA1c levels (OR, 3.09; 95% CI, 1.42–6.70; $P < 0.01$) were independently and significantly associated with the presence of severe PD in multivariate logistic regression analysis.

Prevalence of severe PD stratified by gender and presence of high HbA1c levels (≥ 7.3% [56 mmol/mol])

The prevalence rates of severe PD in women with HbA1c levels < 7.3% and HbA1c levels ≥ 7.3% [56 mmol/mol] were 17.4% and 53.3%, respectively. The OR for severe PD in women with HbA1c levels ≥ 7.3% [56 mmol/mol] (vs. women with HbA1c levels < 7.2% [55 mmol/mol]) was 5.42

Table 2 Results of logistic regression analysis for the presence of severe periodontal disease (n = 144)

	Simple regression			Multivariate regression		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Physical parameters						
Age (per 1.0 year)	0.97	0.94–1.01	0.087	1.00	0.95–1.04	0.92
Sex (male)	2.74	1.39–5.42	0.004	2.75	1.19–6.34	0.018
Height (per 1.0 cm)	1.03	0.99–1.06	0.11			
Weight (per 1.0 kg)	1.03	1.00–1.05	0.051	1.00	0.97–1.03	0.94
Body mass index (per 1.0 kg/m^2)	1.04	0.97–1.13	0.29			
Periodontal disease-associated parameters						
Number of remaining teeth	1.03	0.98–1.08	0.24	1.04	0.98–1.10	0.23
Current smoking (yes)	2.12	0.89–5.03	0.088	1.23	0.45–3.37	0.69
Number of times teeth brushed per day (per 1.0)	0.85	0.57–1.27	0.43			
Presence of regular interdental cleaning (yes)	0.81	0.39–1.68	0.58			
Presence of regular dental consultation (yes)	0.52	0.23–1.17	0.11	0.55	0.22–1.35	0.19
Diabetes mellitus and its comorbidities						
Presence of elevated hemoglobin A1c (≥ 7.3%)	2.90	1.45–5.84	0.003	3.09	1.42–6.70	0.004
Diabetes duration (years)	1.02	0.98–1.07	0.26			
Hypertension (yes)	1.22	0.62–2.42	0.56			
Hyperlipidemia (yes)	0.99	0.49–2.02	0.98			

Hosmer–Lemeshow goodness-of-fit χ^2 was 12.864 with a P value of 0.117 *OR* odds ratio, *CI* confidence interval

(95% CI, 1.91–15.46). Additionally, the prevalence of severe PD was 50.0% in men with HbA1c levels of < 7.3% [56 mmol/mol] and 66.7% in those with HbA1c levels of ≥ 7.3% [56 mmol/mol]. The OR for severe PD in men with HbA1c levels ≥ 7.3% [56 mmol/mol] (vs. women with HbA1c levels < 7.2% [55 mmol/mol]) was 2.00 (95% CI, 0.71–5.63).

Discussion

We determined that the optimal HbA1c cutoff value for predicting severe PD in patients with T2DM was 7.3% [56 mmol/mol] (NGSP). Male patients with elevated HbA1c levels had a higher risk of developing severe PD than those with non-elevated HbA1c levels. Additionally, female patients with elevated HbA1c levels had a higher risk of severe PD than those with lower HbA1c levels.

Male predominance was observed in severe PD, as reported in large-scale epidemiological investigations [15, 16]. Male predominance in patients with PD has also been reported in Japan [17]. Sex- and sex-related factors, including genetics, lifestyle factors (e.g., high rates of smoking and poor oral hygiene), and health-related factors (e.g., high prevalence of diabetes mellitus and atherosclerosis), have been investigated as risk factors for PD development in men [18]. High total testosterone level has also been investigated as a factor potentially associated with the development of PD in men [19].

In this study, severe PD was more closely related to the glucose profile in female patients than in male patients. Notably, high HbA1c levels increased the risk of severe PD more in women than in men. Furthermore, sex-specific associations with the development of diabetic complications have recently been highlighted; hyperglycemia has a greater impact on cardiovascular disease events and malignancies in women than in men [20, 21]. Thus, the management of plasma glucose profiles may be more effective in preventing severe PD in female patients than in male patients.

We suggest that the appropriate management of plasma glucose profiles is key to maintaining a better periodontal environment in patients with T2DM. Furthermore, effective management of T2DM may decrease the risk of cardiac and renal mortality, which is elevated 3.2fold by severe PD in patients with T2DM [22].

In this study, severe PD was not associated with the number of remaining teeth. Patients with DM reportedly have more severe PD [23] and greater tooth loss [24] compared with those without DM. Glycemic profiles are known to affect the severity of PD and the number of remaining teeth [25]. A bidirectional association exists between T2DM and severe PD [26], and a high HbA1c level is a risk factor for severe PD. One reason for the lack of association between severe PD and the number of remaining teeth in this study was that the mean HbA1c level was relatively favorable (7.2%, NGSP [55 mmol/mol, IFCC]). A surveillance study of periodontal status in patients with DM and relatively good glycemic

management (mean HbA1c level: 7.1%, NGSP [53 mmol/mol, IFCC]) also failed to find an association between the presence of PD and a decrease in the number of remaining teeth [27]. In contrast, topical antibiotics for PD reduce high-sensitivity C-reactive protein and HbA1c levels [3], although an association between T2DM and mild PD has not been observed [26]. These findings suggest that regular dental consultations for patients with T2DM, regardless of HbA1c values, are important for early diagnosis of PD, including mild PD. Additionally, early intervention for PD improves T2DM outcomes, whereas neglecting PD may exacerbate T2DM and decrease the number of remaining teeth [10]. In this context, regular dental consultations for patients with DM are important for PD management, retention of remaining teeth, and effective DM treatment. However, neither the regularity of dental consultations for patients with DM [28] nor the skills of certified diabetes educators regarding the oral management of patients with T2DM have reached high levels in Japan [29]. Thus, patients and healthcare professionals should be more aware of the importance of oral healthcare and regular dental consultations to maintain the oral health of patients with DM. However, as well as PD, other possible reasons for tooth extraction include caries [30, 31], root fracture, and the dentist's judgment. Additionally, although the main reason for tooth extraction in Japan is PD from approximately 55 years of age onward, prior to that it is tooth decay [32]. The variety of reasons for tooth extraction in patients with DM could explain why severe PD was not associated with the number of remaining teeth in this study.

This study has several limitations strengths and limitations. First, we did not exclude patients who had not undergone dental consultation. Second, we evaluated PD using the 2007 revision of the CPI [7] instead of the latest (2013) version [13] or the periodontal inflamed surface area (PISA) [12]. Third, given the small sample size, we cannot exclude the influence of confounding factors. Finally, this study was conducted at a single institution; therefore, future multicenter studies are required to validate our results.

In conclusion, we identified the optimal HbA1c cutoff value (7.3%, NGSP [56 mmol/mol, IFCC]) for predicting severe PD in patients with T2DM. Our results confirmed a male predominance in severe PD, and the cutoff value of HbA1c of 7.3% may be particularly useful in women. Notably, the glucose profile was more strongly associated with an increased risk of severe PD in female patients than in male patients. Management of plasma glucose profiles is key for maintaining periodontal health and improving the prognosis of patients with T2DM.

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Data availability All data supporting the findings of this study are available within the paper.

Declarations

Conflict of interest HJ has received honoraria from Novo Nordisk, Sanofi, AstraZeneca Pharmaceuticals, Astellas Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Takeda, and Novartis Pharmaceuticals. SS has received honoraria from AstraZeneca Pharmaceuticals and Ono Pharmaceutical. The authors declare no other potential conflicts of interest relevant to this study.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Human Ethics Review Committee of Jinnouchi Hospital, Kumamoto, Japan (2024-4-1). Informed consent or substitute for it was obtained from all patients for being included in the study.

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