Received: 13 May 2024 | Revised: 10 July 2024 | Accepted: 11 July 2024

DOI: 10.1111/dom.15835

ORIGINAL ARTICLE

WILEY

Periodontal tissue susceptibility to glycaemic control in type 2 diabetes

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Funding information
Japan Society for the Promotion of Science, Grant/Award Numbers: 20K18827, 21K18281, 22H03300, 22K19622, JP23KJ15250; Japan Agency for Medical Research and Development, Grant/Award Numbers: AMED A154, JP22ym0126809

Abstract

Aim: To assess the direct effect of intensive glycaemic control on periodontal tissues in patients with diabetes mellitus.

Materials and Methods: Twenty-nine patients with type 2 diabetes were enrolled and hospitalized to receive a 2-week intensive glycaemic control regimen. We observed and analysed the systemic and oral disease indicators before and after treatment and clarified the indicators related to periodontal inflammation.

Results: A significant reduction in glycaemic and periodontal parameters, including glycated albumin levels and periodontal inflamed surface area (PISA), was observed after treatment. The changes in PISA per tooth, indicative of periodontal healing, exhibited a bimodal distribution; the patients were divided into two groups on this basis. Correlations were observed between the changes in PISA per tooth and fasting plasma glucose, acetoacetic acid, and beta-hydroxybutyrate levels in the PISA-improved group. Significantly lower levels of C-peptide, coefficient of variation of R-R interval, and ankle-brachial pressure index were observed before treatment in the PISA non-improved group.

Conclusions: Glycaemic control treatment can effectively improve periodontitis in patients with type 2 diabetes, even in the absence of specific periodontal treatments. However, the periodontal responsiveness to glycaemic control treatment depends on the systemic condition of the patient.

KEYWORDS
diabetes complications, glycaemic control, type 2 diabetes, insulin secretion

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1 | INTRODUCTION

Diabetes mellitus is a disease resulting from a relative or absolute deficiency of insulin, leading to hyperglycaemia, inflammation and high oxidative stress. This condition can result in systemic complications, such as cardiovascular disease, retinopathy, and kidney disease.[1] Periodontal disease, a chronic disorder characterized by the inflammatory destruction of periodontal tissues, can lead to tooth loss, thereby affecting the quality of life.[2] A bidirectional relationship has been observed between diabetes mellitus and periodontal disease,[3–6] and it has been reported that worsening of glycaemic control over time and more severe diabetic complications are observed in patients with diabetes who have periodontitis compared with those with mild or no periodontal disease.[4] Recent systematic reviews evaluating the effect of periodontal treatment on diabetes mellitus have revealed a reduction in the levels of glycated haemoglobin (HbA1c), ranging from 0.27% to 1.03%, in patients with diabetes 3–4 months after periodontal treatment.[4] However, diabetes is a known risk factor for periodontal disease, and poor glycaemic control leads to greater destruction of periodontal tissues.[3] Several longitudinal studies have reported that the incidence or number of new cases of periodontitis among patients with type 2 diabetes is two to three times greater than that in those with normal glucose levels.[3,7] Moreover, the severity of periodontitis, the rate of tooth loss and bleeding on probing (BOP), and clinical attachment level (CAL) have been reported to be significantly higher in patients with poor glycaemic control than in those with good glycaemic control.[3,8]

There is a growing body of evidence linking periodontal disease with diabetes mellitus; however, few studies have explored the effect of diabetes treatment, excluding periodontal treatment, on the pathology of periodontal disease.[9] Glycaemic interventions improved glycaemic control and reduced the rate of BOP in 35 patients with type 2 diabetes in a previous multicentre study.[9] However, a reduction in HbA1c levels was not observed in 10 patients (28.6%). This may be attributed to variations in treatment settings across four hospitals and multiple diabetic and dental clinics over a 6-month period, which may have introduced confounding lifestyle factors.

The present study aimed to assess the direct effect of glycaemic control treatment on periodontal tissues in a unique cohort of patients with diabetes accompanied by periodontitis who underwent a 2-week intensive glycaemic control regimen in a controlled hospital setting. Furthermore, the severity of periodontal disease was quantified using the periodontal inflamed surface area (PISA), and the response of the periodontal tissues to diabetes treatment was evaluated. Additionally, the study aimed to identify the clinical indicators that characterize the differences in response to treatment.

2 | MATERIALS AND METHODS

2.1 | Study participants

Patients with type 2 diabetes aged 20–75 years who were hospitalized for 2 weeks (between December 2017 and March 2019) in the Division of Endocrinology and Metabolism, Osaka University Hospital (Suita, Osaka, Japan) with the aim of improving glycaemic control were recruited for this study. Type 2 diabetes was diagnosed based on the criteria outlined by the World Health Organization National Diabetic Group 2006 and/or currently receipt of diabetes treatment. The following patients were excluded: (1) patients who could not achieve strict glycaemic control due to severe hypoglycaemia or advanced diabetic retinopathy where drastic improvement in glucose levels was deemed inappropriate; (2) patients with severe nephropathy, defined by a serum creatinine level greater than 2.0 mg/dL; (3) patients with acute infection, severe trauma, or active cancer; (4) patients undergoing examinations during the pre- and/or postoperative periods; and (5) patients deemed unsuitable for participation by the attending physician. Participants received comprehensive risk management for diabetes at the hospital, which included intensive glycaemic control, blood pressure management, dyslipidaemia control, and body weight management, according to the Japanese treatment guideline for diabetes.[10] Physicians determined the target level of glycaemic control according to the guidelines,[10] typically aiming for a fasting blood glucose level < 7.2 mmol/L (130 mg/dL) and a 2-h postprandial blood glucose level < 10.0 mmol/L (180 mg/dL). Periodontal treatment, including oral hygiene instructions, was not provided in this study.

The Human Ethics Committees of the Osaka University Hospital (no. 16374-6), Osaka University Graduate School of Dentistry, and Osaka University Dental Hospital (no. H28-E40-2) approved this study. This study was conducted in accordance with the Declaration of Helsinki and STROBE guidelines for human observational studies. Written informed consent was obtained from all participants.

2.2 | Clinical indicators

A total of 40 and 29 clinical indicators were assessed on the 2nd and 14th day of hospitalization, respectively. Blood samples were collected in the morning following a 15-h fasting period and analysed using standard techniques. Vital signs and weights were also recorded during these assessments. Blood pressure was measured under stable conditions using an automatic sphygmomanometer. Estimated glomerular filtration rate (mL/min 1.73 m^2) was calculated according to the Statement of the Japanese Society of Nephrology.[11] The C-peptide index was calculated as shown below:[12]

$$100 \times \text{C-peptide immunoreactivity}\,(\text{ng/mL})/\text{fasting plasma glucose}\,(\text{FPG; mg/dL})$$

The R-R intervals were determined, and the coefficient of variation for R-R interval (CVRR) was calculated by dividing the standard deviation (SD) by the mean (M) as shown below:[13]

$$\text{CV}\,(\%) = (\text{SD/M}) \times 100$$

Ankle-brachial pressure index (ABI), calculated as the ratio of ankle systolic pressure (mmHg) to brachial systolic pressure (mmHg),[14]

was measured using an automatic form analyser (BP-203RPE II; Colin, Komaki, Japan). The following equation was used to calculate the pulse wave velocity (PWV):

$$PWV^2 = E * h/r * p$$

where E = elastic modulus, h = vessel wall thickness, r = vessel radius, and p = blood density.[15]

2.3 | Oral examination

A full-mouth general dental survey and detailed periodontal assessment were conducted by four calibrated licensed dentists. These assessments took place in the afternoon on the 2nd and 14th day of hospitalization. All participants were instructed to refrain from eating, drinking, or brushing for at least 1 h before the examination. The number of residual, decayed, and treated teeth, as well as the occlusion, was determined via a general dental survey. Periodontal assessments included the measurement of probing pocket depth (PPD), BOP, gingival recession, and CAL at six sites on all teeth present. In addition, the accumulation of dental plaque at four sites per tooth was assessed in all teeth.

2.4 | PISA, PPD, CAL and plaque index

PISA is an indicator used to quantify the amount of inflamed periodontal tissue associated with periodontal disease. PISA can be calculated using tooth type-specific formulas.[16] PISA calculations were performed using CAL, recession values, and BOP rates based on the method described by Nesse et al.[17] In the present study, PISA per tooth was used for adjusting the number of residual teeth.

The values for each patient were defined as the average of the maximum values among all residual teeth when assessing the changes in PPD and CAL.

Plaque accumulation was assessed using plaque index (PII), evaluated at four specific sites per tooth across all teeth.[18] The PII for each

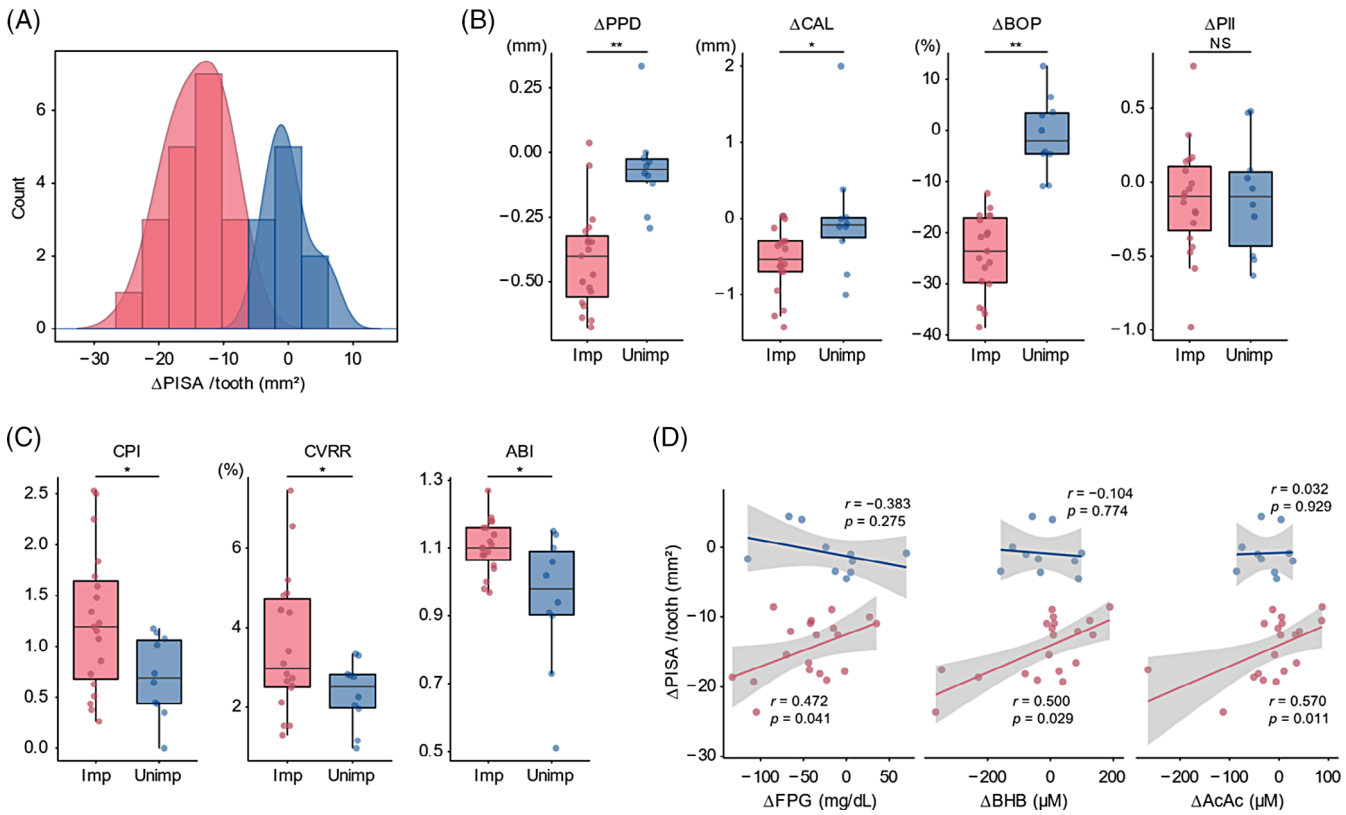

FIGURE 1 Clinical characteristics of the periodontal inflamed surface area (PISA)-improved and non-improved groups. (A) Histogram displaying the changes in PISA per tooth in 29 patients with type 2 diabetes revealed a bimodal distribution, dividing the patients into the PISA-improved (< −5.0 mm^2) and non-improved (≥ −5.0 mm^2) groups. (B) Differences in the changes in the periodontal indicators between the PISA-improved and non-improved groups $^*p < 0.05$, $^{**}p < 0.01$. (C) Significant differences can be observed in the values for clinical indicators before glycaemic control treatment between the PISA-improved and non-improved groups. $^*p < 0.05$. (D) Positive correlations can be observed between the changes in PISA per tooth and systemic indicators in the PISA-improved group. ABI, ankle brachial pressure index; AcAc, acetoacetic acid; BHB, beta-hydroxybutyrate; BOP, bleeding on probing; CAL, clinical attachment level; CPI, C-peptide index; CVRR, coefficient of variation of R-R interval; FPG, fasting plasma glucose; Imp, PISA-improved group; NS, not significant; PII, plaque index; PISA/tooth, periodontal inflamed surface area/number of residual teeth; PPD, probing pocket depth; Unimp, PISA non-improved group.

participant, as an indicator of overall oral hygiene status, was calculated as the average score across these sites.[19]

2.5 | Definition

Values obtained on the 2nd and 14th day of the general and oral examinations were defined as the before and after glycaemic control treatment values, respectively. The values obtained before the glycaemic control treatment were subtracted from the values obtained after the treatment to determine the changes in the values of all indicators.

2.6 | Statistical analysis

Paired samples were analysed to determine the presence of significant differences in glycated albumin (GA) and HbA1c levels, PISA, PISA per tooth, PPD, CAL, BOP rate, and PII before and after glycaemic control treatment. The Shapiro–Wilk test was used to evaluate the normality of the distribution of all variables. Variables with p values ≥0.05 and <0.05 were defined as parametric and nonparametric variables and evaluated using paired t-tests and Wilcoxon signed-rank tests, respectively. The participants were categorized into two groups based on the bimodal distribution of PISA per tooth: the PISA-improved group (< -5.0 mm^2) and the non-improved group (≥ -5.0 mm^2; Figure 1A).

The differences in the changes in PPD, CAL, BOP, and PII between the two groups were assessed. Data with normal distribution were assessed using the Shapiro–Wilk test, and samples were defined as parametric when both had p values of ≥0.05. Levene's test was used to assess homoscedasticity. Student's t-test was used if the variances were equal. Welch's test was used in other cases. The Mann–Whitney U-test was used when the Shapiro–Wilk p values were <0.05.

Parametric variables were analysed using Pearson's correlation coefficients, whereas nonparametric variables were analysed using Spearman's rank correlation coefficients.

The differences in the values of systemic and oral disease indicators were analysed before treatment and compared between the groups, using the Shapiro–Wilk test, Levene's test, Student's t-test, Welch's test, and the Mann–Whitney U-test.

Additionally, differences between the PISA-improved and PISA-non-improved groups were analysed using Fisher's exact test for variables such as sex, smoking history, antidiabetic drugs, diabetic complications (diabetic retinopathy, nephropathy, and neuropathy), and comorbidities (hypertension, dyslipidaemia, diabetic macroangiopathy, coronary arterial disease, cerebral infarction, and peripheral arterial disease).

All statistical analyses were performed using SPSS Statistics ver. 28 (IBM Corporation, NY, USA). Statistical significance was set at a p value of <0.05.

3 | RESULTS

3.1 | Study population

Thirty-one patients with type 2 diabetes aged 41–73 years, who were hospitalized at the Osaka University Hospital's Division of Endocrinology and Metabolism, were initially enrolled in this study. Two patients who declined to undergo oral examination on the 14th day of hospitalization were excluded. Thus, the final analysis included 29 patients. All patients had moderate periodontitis at the outset of the study, with average values of 21.4, 32.9%, and 4.21 mm for the number of residual teeth, BOP rate, and CAL, respectively.

3.2 | Effects of glycaemic control treatment on the clinical parameters of diabetes and periodontitis

Analysis of the clinical changes caused by glycaemic control treatment revealed a significant reduction in GA and HbA1c levels (GA: average decrease 4.32%; HbA1c: median decrease 6.00 mmol/mol [0.500%]) after the intervention. Greater reductions were observed in individuals with higher initial GA and HbA1c levels (Figure 2). Significant reductions were also observed in the periodontal parameters, including BOP rate, PPD, CAL and PISA (BOP: median decrease of 16.7%; PPD: average decrease of 0.291 mm; CAL: median decrease of 0.326 mm; PISA: median decrease of 10.9 mm^2), after the intervention. However, the changes in PII were not significant (Figure 2).

3.3 | Sub-analyses of the effects of glycaemic control treatment on the periodontal parameters

Glycaemic control treatment resulted in a significant reduction in BOP rate, PPD, and CAL in the PISA-improved group compared with that in the PISA-non-improved group; however, no significant differences were observed between the groups in terms of the changes in PII (Figure 1B).

3.4 | Characteristic features of the PISA-improved group

Regarding group differences in systemic and oral disease indicators, statistically significant findings included lower levels of C-peptide ($p = 0.041$), C-peptide index ($p = 0.031$), CVRR during breathing ($p = 0.019$), and ABI ($p = 0.035$) observed in the PISA non-improved group before treatment (Figure 1C Table 1). However, no statistically significant differences were found between the groups in terms of age, sex, smoking history, duration of diabetes, use of antidiabetic drugs before and during glycaemic control treatment, diabetic complications, or comorbidities (Tables 1 and 2).

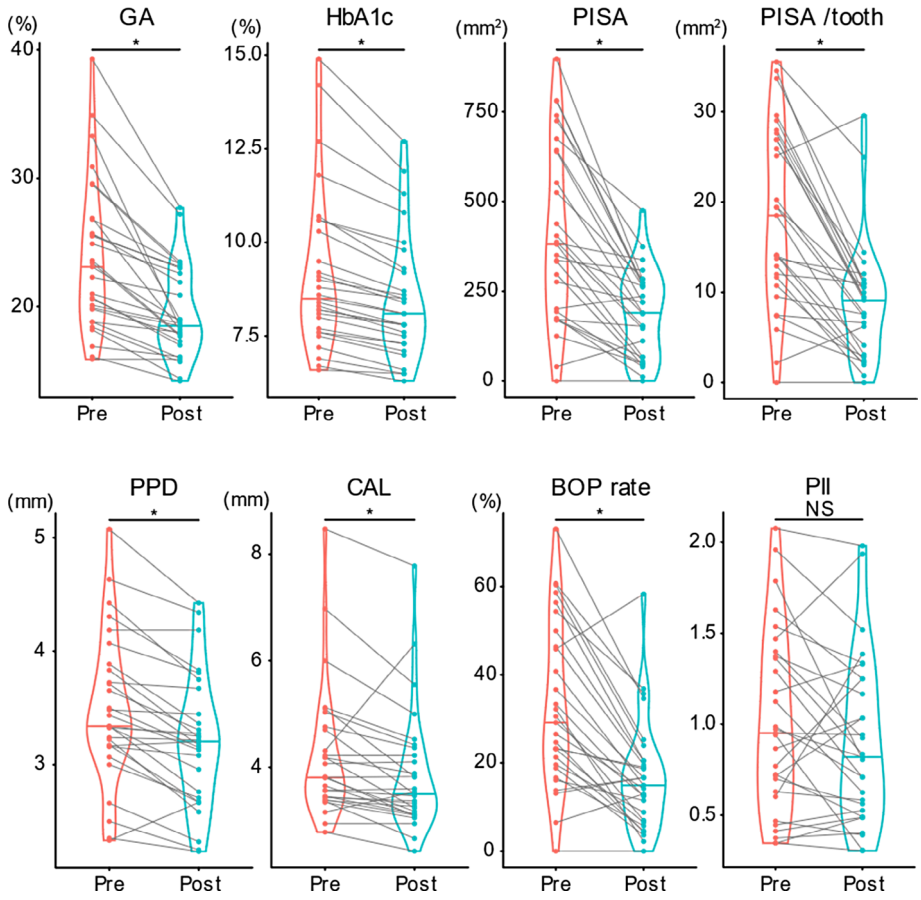

FIGURE 2 Changes of the clinical indicators before and after glycaemic control in 29 patients with type 2 diabetes mellitus. The dots indicate patient values, with lines connecting the pre- and post-treatment data for each individual. $^*p < 0.05$. The central lines on the plots indicate the median. BOP, bleeding on probing; CAL, clinical attachment level; GA, glycated albumin; HbA1c, glycated haemoglobin; NS, not significant; PISA, periodontal inflamed surface area; PISA/tooth, periodontal inflamed surface area/number of residual teeth; PPD, probing pocket depth; PII, plaque index.

Correlation analyses revealed significant positive correlations between changes in PISA per tooth and FPG ($r = 0.472$, $p = 0.041$), acetoacetic acid (AcAc: $r = 0.570$, $p = 0.011$) levels, and beta-hydroxybutyrate (BHB) levels ($r = 0.500$, $p = 0.029$) in the PISA-improved group (Figure 1D, Table 3).

4 | DISCUSSION

The present study demonstrated that comprehensive diabetes treatment effectively improved periodontitis in patients with type 2 diabetes who exhibited poor glycaemic control, even in the absence of specific periodontal treatment. A bimodal treatment response was observed when PISA was used as a quantitating indicator of periodontal disease, with broad range. Positive correlations were observed between the changes in PISA per tooth and FPG, AcAc, and BHB levels in the PISA-improved group. In contrast, smaller changes were observed in BOP rate, PPD and CAL in the PISA non-improved group. Moreover, the pretreatment levels of C-peptide, CVRR, and ABI in the PISA non-improved group were lower than those in the improved group.

In contrast with the findings of a previous study,[9] intensive diabetes treatment was found to improve BOP rates and modestly reduce PPD and CAL in the present study. This finding may be attributed to the hospital-based glycaemic control regimen used in the present study, which minimized lifestyle-related confounders in patients with uncontrolled diabetes and isolated the direct impact of treatment on periodontal health. Notably, there were no significant changes in PII, indicating oral hygiene levels, in both PISA-improved and non-improved groups. This suggests that improvements in periodontal indicators can be primarily attributed to better glycaemic control rather than changes of oral hygiene. Furthermore, while pleiotropic benefits of metformin including anti-inflammatory and immune-modulating effects that may reduce the risk of periodontal disease,[20,21] have been reported, this study found no differences in the use of antidiabetic drugs between the PISA-improved and non-improved groups. Additionally, no significant differences were observed in the changes of inflammatory indicators between metformin users and non-users (not shown), suggesting a negligible effect of antidiabetic drugs on periodontal inflammation during short-term intensive glycaemic control treatment. Thus, the findings indicate that improved glycaemic control alone may effectively reduce inflammation and mitigate periodontal damage in individuals with diabetes.

As mentioned above, no significant changes in oral hygiene were observed in the present study; however, treatment-induced systemic changes might have influenced the oral microbiome.[22] Recent research supports this notion, suggesting that glycaemic control can alter the composition of saliva microbiota in patients with diabetes and periodontitis.[22] Furthermore, there is evidence for diabetes enhancing the pathogenicity of the oral microbiome by promoting inflammation mediated by IL-17, which contributes to bone

TABLE 1 Values of systemic and oral disease indicators before glycaemic control treatment.

Clinical indicators	All participants ($n = 29$)	PISA-improved group ($n = 19$)	PISA non-improved group ($n = 10$)	p value
PII	1.02 ± 0.50	1.10 ± 0.53	0.853 ± 0.395	0.209
PESA,[a] mm^2	1100 ± 424	1160 ± 345	978 ± 546	0.363
Diabetes duration, years	17.6 ± 11.0	15.6 ± 9.4	21.3 ± 13.3	0.192
BW, kg	66.6 ± 8.9	67.5 ± 9.2	64.9 ± 8.5	0.459
BMI, kg/m^2	26.1 ± 3.0	26.0 ± 3.2	26.4 ± 2.7	0.751
Waist, cm	98.1 ± 8.7	98.7 ± 8.5	97.0 ± 9.2	0.622
UA, mg/dL	5.77 ± 1.09	5.87 ± 1.01	5.58 ± 1.26	0.501
eGFR, mL/min/1.73 m^2	67.9 ± 16.8	71.2 ± 13.0	61.7 ± 21.8	0.151
HDL-cho, mg/dL	52.5 ± 12.1	52.1 ± 11.2	53.4 ± 14.2	0.781
GA, %	23.8 ± 5.8	23.8 ± 6.7	23.8 ± 4.1	0.969
HR, bpm	76.5 ± 12.8	77.8 ± 14.6	74.0 ± 8.6	0.459
SBP, mmHg	130 ± 17	129 ± 18	133 ± 14	0.535
DBP, mmHg	73.9 ± 12.0	76.7 ± 12.1	68.4 ± 10.3	0.075
CPR, ng/mL	1.54 ± 0.99	1.81 ± 1.01	1.03 ± 0.73	0.041
CPI	1.06 ± 0.66	1.25 ± 0.70	0.702 ± 0.395	0.031
CVRR-resting, %	2.15 ± 1.00	2.34 ± 0.87	1.81 ± 1.17	0.190
CVRR-breathing,[a] %	3.12 ± 1.57	3.55 ± 1.74	2.34 ± 0.82	0.019
maxIMT, mm	2.07 ± 1.00	1.95 ± 0.78	2.29 ± 1.34	0.396
ABI[a]	1.05 ± 0.15	1.11 ± 0.08	0.946 ± 0.200	0.035
PWV, cm/s	1830 ± 272	1830 ± 281	1830 ± 268	0.990
Age,[b] years	68.0 (65.0–70.0)	68.0 (63.5–70.0)	69.0 (67.0–71.0)	0.403
Cre,[b] mg/dL	0.700 (0.640–0.850)	0.700 (0.640–0.795)	0.725 (0.640–1.080)	0.353
AST,[b] U/L	22.0 (17.0–27.0)	23.0 (19.0–37.5)	21.0 (17.0–25.0)	0.195
ALT,[b] U/L	22.0 (17.0–37.0)	23.0 (18.0–41.0)	17.5 (15.0–22.0)	0.138
γ-GTP,[b] U/L	27.0 (19.0–47.0)	34.0 (20.5–50.5)	25.5 (18.0–36.0)	0.353
CPK,[b] U/L	93.0 (71.0–129.0)	92.0 (73.0–118.0)	98.5 (57.0–129.0)	0.769
TC,[b] mg/dL	200 (174–215)	207 (181.5–233.5)	185.5 (160–205)	0.115
TG,[b] mg/dL	125 (83–235)	140 (83.5–247)	110.5 (79.0–203)	0.403
LDL-cho,[b] mg/dL	117 (91–137)	123 (104.5–141)	102 (78–129)	0.077
FPG,[b] mg/dL	135 (113–171)	135 (115–172)	135 (93–171)	0.604
HbA1c[b] mmol/mol	69.0 (61.0–89.0)	70.0 (61.0–92.0)	67.5 (61.0–75.0)	0.636
%	8.50 (7.70–10.30)	8.60 (7.75–10.60)	8.35 (7.70–9.00)	
AcAc,[b] μmol/L	66.0 (41.0–101.0)	60.0 (34.0–87.5)	92.5 (74.0–139.0)	0.077
BHB,[b] μmol/L	103 (46–208)	82.0 (43.0–190.5)	152 (79–231)	0.266
hs-CRP,[b] ng/mL	710 (436–1170)	516 (316.5–1465)	820 (518–1170)	0.403
CRP,[b] mg/dL	0.0600 (0.0400–0.1100)	0.0400 (0.0400–0.1450)	0.0800 (0.0500–0.1100)	0.512
uAlb/Cr,[b] mg/gCr	12.5 (3.4–40.0)	6.75 (2.95–36.67)	13.9 (3.8–40.0)	0.636
Glucagon,[b] pg/mL	26.5 (16.5–43.5)	25.0 (16.5–34.0)	34.0 (24.0–47.0)	0.383
Sex: Female/Male[c]	16 (55.2)/ 13 (44.8)	10 (52.6)/ 9 (47.4)	6 (60.0)/4 (40.0)	0.507
Smoking history[c]	14 (48.3)	10 (52.6)	4 (40.0)	0.400
Diabetic retinopathy[c]	13 (44.8)	8 (42.1)	5 (50.0)	0.493
Diabetic nephropathy[c]	10 (34.5)	6 (31.6)	4 (40.0)	0.478
Diabetic neuropathy[c]	19 (65.5)	11 (57.9)	8 (80.0)	0.221
Hypertension[c]	22 (75.9)	14 (73.7)	8 (80.0)	0.541
Dyslipidaemia[c]	25 (86.2)	16 (84.2)	9 (90.0)	0.571
Diabetic macroangiopathy[c]	11 (37.9)	6 (31.6)	5 (50.0)	0.283

TABLE 1 (Continued)

Clinical indicators	All participants ($n = 29$)	PISA-improved group ($n = 19$)	PISA non-improved group ($n = 10$)	p value
Coronary arterial disease[c]	7 (24.1)	4 (21.1)	3 (30.0)	0.459
Cerebral infarction[c]	5 (17.2)	3 (15.8)	2 (20.0)	0.576
Peripheral arterial disease[c]	2 (6.9)	0 (0.0)	2 (20.0)	[d]
Insulin[c]	15 (51.7)	8 (42.1)	7 (70.0)	0.150
SUs[c]	7 (24.1)	4 (21.1)	3 (30.0)	0.459
BGs[c]	12 (41.4)	8 (42.1)	4 (40.0)	0.615
TZDs[c]	1 (3.4)	1 (5.3)	0 (0.0)	[d]
DPP-4 inhibitors[c]	9 (31.0)	5 (26.3)	4 (40.0)	0.364
Glinides[c]	0 (0.0)	0 (0.0)	0 (0.0)	[d]
α-GIs[c]	2 (6.9)	2 (10.5)	0 (0.0)	[d]
SGLT2 inhibitors[c]	6 (20.7)	4 (21.1)	2 (20.0)	0.669
GLP-1RAs[c]	6 (20.7)	5 (26.3)	1 (10.0)	0.302

Note: No symbol = Data are given as average of all participants' values (one standard deviation) using Student's t-test. The p value indicates the result of comparing PISA-improved and non-improved groups.
Abbreviations: ABI, minimum value of ankle brachial pressure index; AcAc, acetoacetic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, biguanide; BHB, beta hydroxybutyrate; BMI, body mass index; BW, body weight; CPI, C-peptide index; CPK, creatine phosphokinase; CPR, C-peptide immunoreactivity; Cre, creatinine; CRP, C-reactive protein; CVRR-breathing, coefficient of variation of R-R interval on breathing; CVRR-resting, coefficient of variation of R-R interval on resting; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GA, glycated albumin; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL-cho, high-density lipoprotein cholesterol; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL-cho, low-density lipoprotein cholesterol; max IMT, maximum value of intima-media thickness from common carotid artery to internal carotid artery; PESA, periodontal epithelial surface area; PII, plaque index; PWV, maximum value of brachial-ankle pulse wave velocity; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea; TC, total cholesterol; TG, triglycerides; TZD, thiazolidinedione; UA, uric acid; uAlb/Cr, urine albumin/creatinine ratio; α-GI, alpha-glucosidase inhibitor; γ-GTP, γ-glutamyl transpeptidase.
[a]Data are given as average of all participants' values (one standard deviation) using Welch's test.
[b]Data are given as median of all participants' values (interquartile range) using Mann–Whitney U-test.
[c]Data are given as counts (percentages) using Fisher's exact test.
[d]No p value. Fisher's exact test could not be analysed because no patients had peripheral arterial disease and used TZDs, Glinides and α-GIs in PISA-improved or non-improved groups.

TABLE 2 Antidiabetic drugs during the glycaemic control treatment.

	All participants ($n = 29$)	PISA-improved group ($n = 19$)	PISA non-improved group ($n = 10$)	p value
Insulin	22 (75.9)	14 (73.7)	8 (80.0)	0.541
SUs	2 (6.9)	1 (5.3)	1 (10.0)	0.579
BGs	18 (62.1)	13 (68.4)	5 (50.0)	0.283
TZDs	1 (3.4)	1 (5.3)	0 (0.0)	[a]
DPP-4 inhibitors	8 (27.6)	5 (26.3)	3 (30.0)	0.581
Glinides	0 (0.0)	0 (0.0)	0 (0.0)	[a]
α-GIs	2 (6.9)	2 (10.5)	0 (0.0)	[a]
SGLT2 inhibitors	7 (24.1)	6 (31.6)	1 (10.0)	0.206
GLP-1RAs	10 (34.5)	6 (31.6)	4 (40.0)	0.478

Note: No symbols = Data are presented as numbers (percentages) using Fisher's exact test. The p value indicates the result of comparing PISA-improved and non-improved groups.
Abbreviations: BG, biguanide; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea; TZD, thiazolidinedione; α-GI, alpha-glucosidase inhibitor.
[a]No p value. Fisher's exact test couldn't be analysed because no patients used TZDs, Glinides and α-GIs.

resorption.[23] Thus, the improvement in periodontitis observed in the present study was likely due to the changes in oral microbiota composition and reduced pathogenicity. Additionally, metformin has been shown to influence changes in oral and gut microbiota.[20,24] Further studies are needed to further investigate how glycaemic control treatment impacts the subgingival microbiome in patients with type 2 diabetes.

TABLE 3 Correlation coefficient of PISA per tooth and other clinical indicators in the PISA-improved and non-improved groups.

Clinical indicators	Correlation coefficient (PISA-improved group)	*p* value (PISA-improved group)	Correlation coefficient (PISA non-improved group)	*p* value (PISA non-improved group)
ΔBW	0.236	0.331	0.347	0.325
ΔBMI	0.240	0.322	0.292	0.413
ΔUA	0.065	0.791	−0.204	0.572
ΔeGFR	−0.002	0.994	0.127[a]	0.726
ΔAST	−0.014	0.956	0.279	0.435
ΔALT	−0.217	0.372	0.138	0.703
Δγ-GTP	0.242	0.317	0.043[a]	0.907
ΔCPK	−0.358	0.132	0.150	0.680
ΔHDL-cho	−0.149	0.541	−0.495	0.146
ΔFPG	0.472	0.041	−0.383	0.275
ΔHR	−0.297	0.218	−0.502	0.139
ΔSBP	0.243	0.317	0.152	0.676
ΔCPR	−0.018	0.942	−0.301	0.397
ΔCPI	−0.086	0.728	−0.292	0.413
ΔCre	−0.095[a]	0.699	−0.385	0.272
ΔTC	−0.216[a]	0.374	−0.392	0.263
ΔTG	−0.024[a]	0.923	−0.201[a]	0.578
ΔLDL-cho	−0.154[a]	0.530	−0.118	0.744
ΔHbA1c	0.186[a]	0.446	0.092[a]	0.800
ΔGA	0.179[a]	0.463	−0.375	0.286
ΔAcAc	0.570[a]	0.011	0.032	0.929
ΔBHB	0.500[a]	0.029	−0.104	0.774
Δhs-CRP	0.263[a]	0.276	0.345[a]	0.328
ΔCRP	0.390[a]	0.099	0.121	0.738
ΔuAlb/Cr	0.251[a]	0.300	0.527[a]	0.117
ΔDBP	−0.329[a]	0.170	0.149	0.681

Note: No symbol = Data are given as Pearson's correlation coefficient. It was used when both were parametric variables.
Abbreviations: AcAc, acetoacetic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BHB, beta hydroxybutyrate; BMI, body mass index; BW, body weight; CPI, C-peptide index; CPK, creatine phosphokinase; CPR, C-peptide immunoreactivity; Cre, creatinine; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GA, glycated albumin; HbA1c, glycated haemoglobin; HDL-cho, high-density lipoprotein cholesterol; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL-cho, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, uric acid; uAlb/Cr, urine albumin/creatinine ratio; γ-GTP, γ-glutamyl transpeptidase.
[a]Data are given as Spearman's rank correlation coefficient, used when both were nonparametric variables.

The lower levels of C-peptide, CVRR and ABI observed before glycaemic control treatment in the PISA non-improved group likely reflect several interconnected factors. These lower levels suggest the β-cell dysfunction and more severe neuropathy and atherosclerosis.[12,13,25,26] Decreased insulin secretion exacerbates poor glycaemic control, which promotes the accumulation of advanced glycation end products (AGEs) in tissues and cells.[27] AGE accumulation is known to play a pivotal role in the pathogenesis of diabetic vascular complications, including neuropathy and atherosclerosis, through mechanisms involving oxidative stress and vascular endothelial dysfunction.[27,28] Moreover, endothelial dysfunction and neuropathy can further delay wound healing.[29] AGEs are also known to affect the functional properties of several matrix molecules (e.g., type I collagen and laminin) crucial for maintaining the integrity of the junctional epithelium and achieving periodontal healing.[30,31] Some reports suggest that AGEs impair insulin secretion.[27,32] We speculated that patients with severe diabetic complications likely experience more pronounced vascular damage, hindering periodontal wound repair. C-peptide, CVRR and ABI could potentially predict how periodontal tissues respond to glycaemic control treatment. Although this mechanism appears to explain the results observed in the PISA non-improved group in this study, the levels of HbA1c and GA before glycaemic control treatment were not significantly higher in this group. Average HbA1c values over several years are generally more reflective of the long-term accumulation of AGEs in tissues compared to single-point measurements such as HbA1c and GA values at admission. Unfortunately, obtaining these

long-term data was not feasible owing to ethical restrictions, which represents a limitation of our study.

Nevertheless, the concept of 'metabolic memory' provides insight into how persistent hyperglycaemia impacts inflammation and complications in patients with diabetes over time. The mechanisms underlying metabolic memory primarily involve epigenetic modifications that have been implicated in the progression of diabetic complications.[33] These modifications may contribute to vascular dysfunction and impact the improvement of periodontal inflammation. Early diabetes intervention is crucial for improving both diabetes management and periodontal health.

The changes in FPG, AcAc, and BHB were positively correlated with improvements in PISA per tooth in the PISA-improved group. This finding aligns with recent research linking CAL with impaired fasting glucose.[34] Considering that improved glycaemic control enhances insulin secretion and sensitivity,[35] the 2-week intensive glycaemic control regimen implemented in this study likely improved insulin function, mitigated glucotoxicity, and reduced AcAc and BHB levels. Recently, there has been growing interest in the direct effects of ketone bodies, such as AcAc and BHB, on tissues and cells. AcAc and BHB have been reported to modulate inflammation and immune cell function, albeit through different mechanisms. AcAc is associated with proinflammatory signalling, whereas BHB tends to exert anti-inflammatory effects.[36] In our study (Figure 1D), some patients showed an increase in AcAc and/or BHB levels, while others exhibited a decrease; however, all patients experienced a decrease in PISA per tooth. This suggests that the balance between AcAc and BHB levels may be associated with improvements in periodontal inflammation. Further research is needed to elucidate the specific roles of these ketone bodies in the context of periodontal health and inflammation and deepen our understanding of the intricate relationship between blood glucose levels, ketone bodies, and periodontal inflammation.

The correlation between changes in PISA per tooth and other systemic indicators was observed only in the PISA-improved group. Conversely, as mentioned above, patients in the PISA non-improved group exhibited a more diverse range of disadvantageous factors affecting periodontal tissue recovery. This suggests that patients in the PISA-improved group had narrower variations in systemic conditions, which may have contributed to the correlation between changes in PISA per tooth and other systemic indicators.

The present study had some limitations. First, owing to our focus on patients undergoing intensive care in hospitalization and the extensive, time-consuming nature of the examinations performed before and after treatment, the sample size was relatively small. This restricted our ability to utilize multivariate models to identify factors associated with improvements in PISA. Additionally, some participants had poorly controlled diabetes before glycaemic control treatment, hindering its applicability to patients with diabetes encountered in routine clinical practice. Nevertheless, the present study provides a valuable starting point for further investigations into the impact of diabetes treatment on periodontal health. Further studies with larger sample sizes must be conducted in the future to clarify the relationship between systemic metabolic changes and oral microbiota.

In conclusion, the findings of the present study indicate that glycaemic control treatment improved periodontal inflammatory destruction in patients with uncontrolled diabetes; however, the effectiveness varied depending on the systemic condition of individual patients. The C-peptide levels, CVRR and ABI were identified as potential biomarkers for predicting the response of periodontal tissues. The direct impact of diabetes treatment on periodontal health was determined in the present study, thereby offering new insights into the interplay between improved glycaemic control and periodontal conditions. Given the link between diabetes and periodontal disease, the findings of the present study advocate for enhanced collaboration between physicians and dentists beginning at the early stage of diabetes for more effective management of patients with diabetes and periodontitis.

AUTHOR CONTRIBUTIONS

Moe Inoue, contributed to design, data analysis and interpretation, and drafted and revised the manuscript. Akito Sakanaka, contributed to design, data acquisition and interpretation, and critically revised the manuscript. Naoto Katakami, contributed to design, data acquisition and interpretation, and critically revised the manuscript. Masahiro Furuno contributed to design, data acquisition, and critically revised the manuscript. Hitoshi Nishizawa, Kazuo Omori, Naohiro Taya, Asuka Ishikawa, Shota Mayumi, Emiko Tanaka Isomura and Hiroki Takeuchi contributed to design, data acquisition, and critically revised the manuscript. Atsuo Amano contributed to design, data interpretation, and critically revised the manuscript. Iichiro Shimomura and Eiichiro Fukusaki, contributed to conception, design, critically revised the manuscript; Masae Kuboniwa contributed to conception, design, data acquisition and interpretation, and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

The authors thank Miho Kakiuchi and Harumi Aoki for their skilled technical assistance in processing the samples, and Eriko Nakamura and Shunsuke Yamaga of the Department of Preventive Dentistry, Osaka University Graduate School of Dentistry, DDS, PhD, for helpful discussions during the development of this study. None of the participants received any financial support. This study was supported by grants from the Japan Agency for Medical Research and Development (AMED A154; no. JP22ym0126809), and JSPS KAKENHI grant number 22H03300, 22K19622, 21K18281, 20K18827 and JP23KJ15250.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15835.

DATA AVAILABILITY STATEMENT

Unfortunately, we cannot share the datasets used and/or analyzed during the current study by archiving them in a public repository, as we did not obtain consent from the subjects for public disclosure, nor did we receive approval from the ethical committee. However, we will respond sincerely to any requests from the editorial office.

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How to cite this article: Inoue M, Sakanaka A, Katakami N, et al. Periodontal tissue susceptibility to glycaemic control in type 2 diabetes. *Diabetes Obes Metab*. 2024;1-10. doi:10.1111/dom.15835