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Effect of non-surgical periodontal therapy on insulin resistance and insulin sensitivity among individuals with borderline diabetes: A randomized controlled trial

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ABSTRACT

Objective: To investigate the effect of non-surgical periodontal therapy on insulin resistance and sensitivity among individuals with borderline diabetes not receiving medications.
Methods: A crossover, randomized controlled trial was conducted among participants with borderline diabetes diagnosed by a 75-g oral glucose tolerance test. Participants were randomly assigned to either an early or later intervention group. The early intervention group underwent non-surgical periodontal therapy of scaling and root planing during the first 6 months, followed by a 6-month non-intervention period. The order was reversed in the later intervention group. Primary outcomes included: fasting or post-load serum glucose and insulin, body mass index (BMI), HOMA-IR, HOMA-β, and Matsuda Index.
Results: Seventy-four participants were randomized, and 71 participants completed the trial. There were no significant differences between groups in glucose and insulin concentrations during the intervention and non-intervention periods. When analyzed within groups by median-split of bleeding on probing (BOP) levels before intervention, the lower BOP group showed improved changes in BMI, HOMA-IR, HOMA-β, and Matsuda Index ($P < 0.05$). Further, we observed a positive correlation between baseline BOP and change in BMI ($P = 0.06$). Change in BMI was positively correlated with changes in HbA_{1c}, HOMA-IR, and HOMA-β ($P < 0.05$), and inversely correlated with change in Matsuda Index ($P = 0.001$).
Conclusions: Periodontal therapy had no significant effect on markers related to insulin and glucose metabolism among individuals with borderline diabetes. However, participants with a lower BOP (%) showed significant improvements in BMI, fasting serum insulin, HOMA-IR, HOMA-β and Matsuda Index.
Clinical significance: Among individuals diagnosed with borderline diabetes, those who had < 37% of a lower BOP (%) showed potential improvements in BMI, fasting serum insulin, HOMA-IR, HOMA-β and Matsuda Index following non-surgical periodontal therapy.

1. Introduction

While several observational studies have reported that periodontal disease was associated with the prevalence of diabetes mellitus [1,2], the results from clinical trials of non-surgical periodontal therapy among patients with diabetes have been inconsistent. Some studies showed an improvement in serum glucose or HbA1c [3,4] and insulin resistance [5,6] associated with non-surgical periodontal therapy, whereas other studies found no improvement in HbA1c levels [7,8]. However, previous clinical trials examined patients with type 2 diabetes that were undergoing medical treatment, so that the effect of non-surgical periodontal therapy could not be distinguished from that of the

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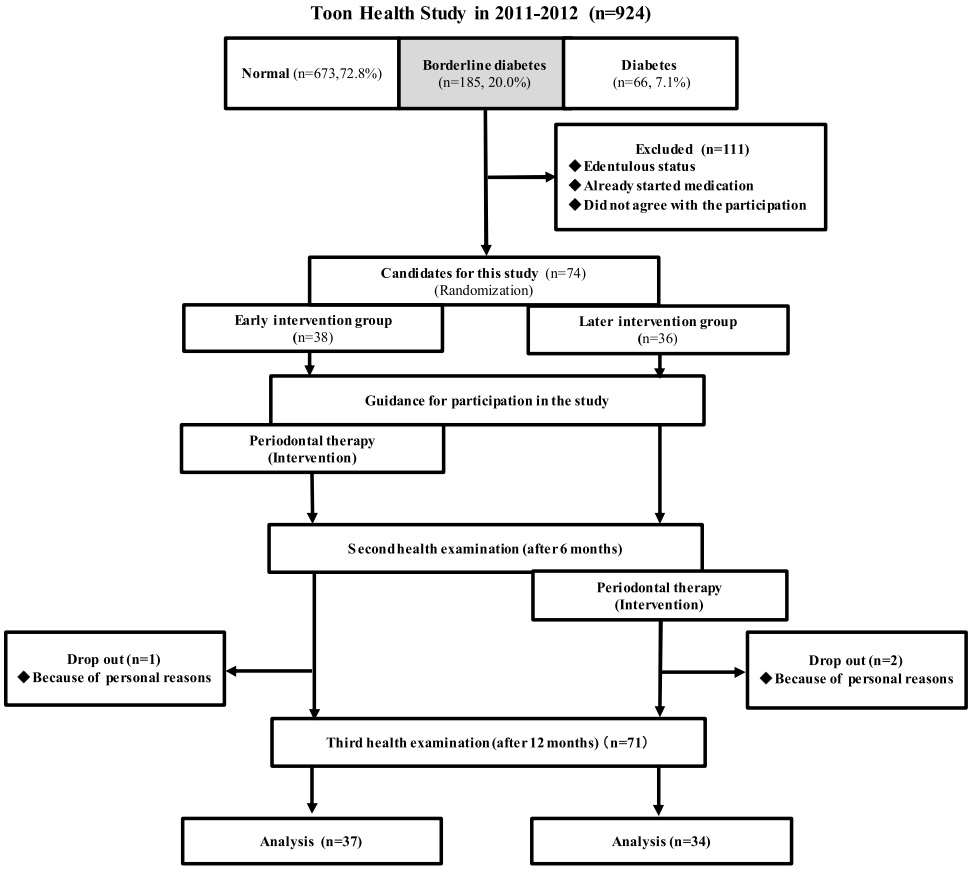

Fig. 1. Study design.

Table 1
Baseline characteristics.

	Early intervention group			Later intervention group		
Number of subjects	37			34		
Age (years)	66.3	±	7.5	66.9	±	8.1
Male sex (%)	37.8			38.2		
BMI (kg/m^2)	23.3	±	3.3	23.7	±	3.0
HbA_{1c} (%)	5.6	±	0.3	5.7	±	0.3
Fasting serum glucose (mmol/L)[a]	5.3	(4.9, 5.8)		5.3	(4.7, 5.9)	
1-h serum glucose (mmol/L)[a]	9.5	(7.6, 12.0)		9.7	(7.9, 11.9)	
2-h serum glucose (mmol/L)[a]	8.7	(7.6, 10.1)		8.9	(8.0, 9.9)	
Fasting serum insulin (μU/mL)[a]	5.5	(3.3, 9.5)		5.7	(2.8, 11.3)	
1-h serum insulin (μU/mL)[a]	46.5	(23.5, 92.2)		53.0	(27.1, 103.9)	
2-h serum insulin (μU/mL)[a]	54.5	(32.1, 92.5)		65.9	(37.0, 117.7)	
HOMA-IR[a]	1.3	(0.7, 2.3)		1.3	(0.6, 2.8)	
HOMA-β[a]	62.6	(36.5, 107.5)		67.8	(40.1, 114.6)	
Matsuda Index[a]	5.6	(3.3, 9.6)		5.2	(2.7, 10.1)	
Current drinker (%)	51.4			52.9		
Current smoker (%)	8.1			2.9		
Habitual exercise (%)	59.5			55.9		
No. of teeth	24.4	±	5.6	24.4	±	4.5
No. of treated teeth	8.7	±	5.7	6.8	±	4.3
No. of untreated teeth	7.2	±	4.5	8.7	±	4.6
BOP (%)	31.5	±	18.6	31.1	±	15.6
Mean PPD (mm)[a]	3.32	(2.8, 3.9)		3.20	(2.9, 3.6)	

[a] Variables are expressed as geometric mean.

diabetes medication. Therefore, it is unclear what effect non-surgical periodontal therapy has only glycemic control among individuals with borderline diabetes, i.e., those that do not require medication.

Periodontal treatment is associated with changes in adipocytokines, such as adiponectin and leptin [9,10]. However, few studies have examined body weight change [11] and its relation with the effects of periodontal therapy on glycemic control. Therefore, to consider the effect of body weight change, we investigated the effect of non-surgical periodontal therapy on insulin resistance and sensitivity among individuals with borderline diabetes in a randomized controlled trial (RCT).

Table 2
Comparison of measurements between the early and later intervention groups at baseline and at 6 months and 12 months.

	Baseline	6 months	12 months
BMI (kg/m^2)			
Early intervention group (n = 37)	23.3	22.7	22.5
Later intervention group (n = 34)	23.7	23.4	23.3
P value	0.58	0.36	0.30
HbA_{1c} (%)			
Early intervention group (n = 37)	5.6	5.7	5.6
Later intervention group (n = 34)	5.7	5.7	5.7
P value	0.60	0.36	0.28
Fasting serum glucose (mmol/L)[a]			
Early intervention group (n = 37)	5.3	5.3	5.4
Later intervention group (n = 34)	5.3	5.3	5.3
P value	0.66	0.98	0.71
1-h serum glucose (mmol/L)[a]			
Early intervention group (n = 37)	9.5	10.6	10.4
Later intervention group (n = 34)	9.7	9.5	9.8
P value	0.78	0.02	0.25
2-h serum glucose (mmol/L)[a]			
Early intervention group (n = 37)	8.7	8.0	8.0
Later intervention group (n = 34)	8.9	7.6	8.5
P value	0.43	0.29	0.31
Fasting serum insulin (μU/mL)[a]			
Early intervention group (n = 37)	5.5	5.4	5.7
Later intervention group (n = 34)	5.7	5.7	6.0
P value	0.90	0.67	0.65
1-h serum insulin (μU/mL)[a]			
Early intervention group (n = 37)	46.5	52.2	50.6
Later intervention group (n = 34)	53.0	51.3	55.4
P value	0.42	0.90	0.53
2-h serum insulin (μU/mL)[a]			
Early intervention group (n = 37)	54.5	52.9	58.2
Later intervention group (n = 34)	65.9	59.2	73.3
P value	0.15	0.36	0.09
HOMA-IR[a]			
Early intervention group (n = 37)	1.3	1.3	1.4
Later intervention group (n = 34)	1.3	1.3	1.4
P value	0.96	0.69	0.73
HOMA-β[a]			
Early intervention group (n = 37)	62.6	61.3	63.2
Later intervention group (n = 34)	67.8	63.7	68.9
P value	0.53	0.73	0.46
Matsuda Index[a]			
Early intervention group (n = 37)	5.6	5.5	5.3
Later intervention group (n = 34)	5.2	5.4	4.9
P value	0.57	0.93	0.55
BOP (%)			
Early intervention group (n = 37)	31.5	18.3	26.9
Later intervention group (n = 34)	31.1	43.0	19.5
P value	0.91	< 0.001	0.02
Mean PPD (mm)[a]			
Early intervention group (n = 37)	3.32	2.70	2.90
Later intervention group (n = 34)	3.20	3.30	2.80
P value	0.29	< 0.001	0.08

Abbreviations: BMI = body mass index; BOP = bleeding on probing; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β-cell function; PPD = probing pocket depth.
The continuous variables are expressed as mean.
[a] Variables are expressed as geometric mean.

2. Subjects, materials and methods

2.1. Study design

This study was a crossover RCT. Ethical approval was obtained from the Human Ethics Review Committee of the Ehime University Graduate School of Medicine (approval number 1609015). Written informed consent was obtained from all participants before the baseline examination, and this study conformed to the Declaration of Helsinki guidelines. This study was registered at the University Hospital Medical Information Network Center and has the identifier UMIN000014585.

2.2. Study participants

Participants included men and women aged 30–79 years with borderline diabetes. Inclusion criteria were defined according to the criteria of the Japan Diabetes Society (serum fasting glucose of 6.1–7.0 mmol/L [110–125 mg/dL] and/or 2-h postprandial glucose levels of 7.8–11.1 mmol/L [140–199 mg/dL], as measured by the 75 g oral glucose tolerance test [OGTT]). Participants (n = 924) were recruited from the Toon Health Study from June to November in 2011 and 2012. Details of the Toon Health Study were previously reported [12,13]. Exclusion criteria included: participants who were edentulous, those who had already started medication for diabetes, and those who did not agree to participate in this study.

2.3. Intervention

A dentist performed non-surgical periodontal therapy, including scaling and root planing (SRP), under the appropriate treatment plan according to oral conditions once during the first month of the study. All participants were treated by the same dentist, and in a similar manner. Hygienists instructed patients regarding gargling using antiplaque mouthwash [14,15] containing chlorhexidine gluconate. Any non-preservable teeth were extracted during the intervention period. In addition to dental therapy, the dentist and the dental hygienist provided dental health instructions to the study participants. To maintain oral hygiene, participants also underwent professional mechanical tooth cleaning once per month.

2.4. Outcomes

Study outcomes included both blood glucose and insulin levels in accordance with the 75-g OGTT, HbA_{1c}, homeostasis model assessment index of insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function (HOMA-β), and Matsuda Index. Primary outcomes were: HOMA-IR, HOMA-β and Matsuda Index; secondary outcomes were: blood glucose and insulin levels. Probing pocket depth (PPD) and bleeding on probing (BOP) were also evaluated as indices of oral condition and periodontal therapy.

2.4.1. 75-g OGTT, insulin resistance, and insulin sensitivity

Overnight fasting blood samples were drawn from the antecubital vein into vacuum tubes containing a serum separator gel (for glucose and blood chemistry). These serum tubes were centrifuged immediately at 3000 rpm (1670*g*) for 15 min, and the separated serum samples were sent to the laboratory for analyses. Participants underwent an OGTT and 1 h- and 2 h-postload glucose and insulin concentrations were measured by standard laboratory methods. Serum glucose was measured by the hexokinase method (Sysmex, Kobe, Japan), using an automatic analyzer (7600-D; Hitachi Co., Tokyo, Japan). Insulin was measured using the electrochemiluminescence method in ECLusys (Roche Diagnostics, Tokyo, Japan). HbA1c was measured using the latex immuno-agglutination method (Determiner hemoglobin A1c; Kyowa Medex Co., Ltd., Tokyo, Japan), and presented in terms of the National Glycohemoglobin Standardization Program value. The HOMA-IR was calculated as fasting serum insulin (FSI) [μU/mL] × fasting serum glucose (FSG) [mg/dL]/405. The HOMA-β was calculated as 360 × FSI [μU/mL] / (FSG [mg/dL] − 63). The Matsuda Index, which has been highly correlated with euglycemic insulin-clamp-derived insulin sensitivity, was calculated as [10000/√((FSG × FSI) × (mean OGTT glucose concentration × mean OGTT insulin concentration))].

2.4.2. Periodontal examination (full-mouth examination)

2.4.2.1. Probing pocket depth: PPD. PPD was measured at 6 points on a tooth, by a dentist and a dental hygienist using an automated probe with a constant force (20 g) at baseline and by the dentist at 6 months and 12 months. The efforts of the dentist and the dental hygienist were

Table 3
Changes in each measurement during the intervention and non-intervention periods.

	Intervention period (n = 71)			Non-intervention period (n = 71)			P value
BMI (kg/m^2)	−0.36	±	0.81	−0.27	±	0.65	0.50
HbA_{1c} (%)	0.01	±	0.21	0.01	±	0.27	0.96
Fasting serum glucose (mmol/L)	0.01	±	0.43	0.06	±	0.45	0.61
1-h serum glucose (mmol/L)	0.65	±	2.23	−0.18	±	2.00	0.06
2-h serum glucose (mmol/L)	0.14	±	2.03	−0.58	±	2.28	0.12
Fasting serum insulin (μU/mL)	0.06	±	2.16	0.05	±	2.29	0.97
1-h serum insulin (μU/mL)	2.81	±	28.9	−1.03	±	29.9	0.51
2-h serum insulin (μU/mL)	6.63	±	35.1	0.14	±	29.6	0.31
HOMA-IR	0.04	±	0.61	0.01	±	0.61	0.78
HOMA-β	−0.78	±	24.0	0.22	±	26.7	0.84
Matsuda Index	−0.43	±	2.85	−0.18	±	3.89	0.73
BOP (%)	−18.1	±	16.1	10.2	±	14.9	< 0.001
Mean PPD (mm)	−0.60	±	0.33	0.15	±	0.27	< 0.001

Abbreviations: BMI = body mass index; BOP = bleeding on probing; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β-cell function; PPD = probing pocket depth.
Values are expressed as mean ± standard deviation.

Table 4
Changes in each measurement during the intervention period according to median-split BOP (%) prior to intervention.

	BOP (%) prior to intervention						P value
	< 37%			≥ 37%			
Number of subjects	36			35			
BMI (kg/m^2)	−0.60	±	0.88	−0.11	±	0.65	0.01
HbA_{1c} (%)	0.02	±	0.19	−0.01	±	0.23	0.61
Fasting serum glucose (mmol/L)	−0.01	±	0.48	0.03	±	0.38	0.66
1-h serum glucose (mmol/L)	0.61	±	2.54	0.70	±	1.89	0.86
2-h serum glucose (mmol/L)	−0.29	±	1.77	0.58	±	2.20	0.07
Fasting serum insulin (μU/mL)	−0.57	±	1.84	0.70	±	2.31	0.01
1-h serum insulin (μU/mL)	−0.27	±	31.6	5.98	±	25.9	0.37
2-h serum insulin (μU/mL)	4.60	±	37.6	8.70	±	32.7	0.62
HOMA-IR	−0.12	±	0.52	0.20	±	0.65	0.03
HOMA-β	−6.72	±	27.2	5.33	±	18.7	0.03
Matsuda Index	0.32	±	2.14	−1.19	±	3.29	0.03

Abbreviations: BMI = body mass index; BOP = bleeding on probing; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β-cell function.
Values are expressed as mean ± standard deviation.

Table 5
Pearson's partial correlation coefficients of BOP (%) prior to intervention and the change in BMI during intervention with the changes of each measurement during the intervention period.

	BOP (%) prior to intervention		Change in BMI	
	r[a]	P value	r[a]	P value
BMI	0.23	0.06	–	–
HbA_{1c}	0.01	0.92	0.26	0.03
Fasting serum glucose	−0.08	0.54	0.16	0.19
1-h serum glucose	0.03	0.82	0.12	0.34
2-h serum glucose	0.33	0.005	0.23	0.06
Fasting serum insulin	0.16	0.18	0.48	< 0.001
1-h serum insulin	−0.03	0.82	0.24	0.05
2-h serum insulin	0.12	0.32	0.36	0.002
HOMA-IR	0.12	0.32	0.45	< 0.001
HOMA-β	0.19	0.12	0.34	0.004
Matsuda Index	−0.12	0.33	−0.32	0.007

Abbreviations: BMI = body mass index; BOP = bleeding on probing; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β = homeostatic model assessment of β-cell function.
[a] Age- and sex-adjusted Pearson's partial correlation coefficient.

calibrated; and the kappa value for agreement of probing depth between them was 0.88, which was considered a strongly positive association, thereby assuring the quality of the calibration [12].

2.4.2.2. Bleeding on probing: BOP. BOP was evaluated at 4 points of each tooth: the proximal, distal, buccal, and lingual sides. The total number of the bleeding points divided by the total measuring points was calculated and evaluated as oral inflammation. BOP (%) was calculated as follows:

BOP (%) = (total number of bleeding points/total number of teeth × 4) × 100.

2.4.3. Other measurements

Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg)/height (m)^2. A self-administrated questionnaire was used to assess smoking, alcohol drinking, and exercise habits. We asked the participants about alcohol habits (current/nondrinker) and smoking habits (current/nonsmoker). Habitual physical activity status was defined as more than 30 min of physical activity per day more than twice per week for more than 1 year, or more than 1 h of walking or equivalent physical activity per day in daily life.

2.5. Sample size, randomization, and blinding

Sample size was determined by a power calculation based on previous reports regarding fasting and 2-h serum glucose levels after OGTT stratified by the severity of periodontal status in a Japanese population [16]. In the study, the mean difference in fasting serum glucose after

OGTT was 6 mg/dl for the non- to light-periodontal group (pocket depth < 1.9 mm) and 20 mg/dl for the moderate-to heavy-periodontal group (pocket depth ≥ 1.9 mm). As the average pocket depth in the community was assumed to be approximately 3 mm, we presumed the improvement in serum glucose level in the intervention group to be approximately 9–10 mg/dL, which was larger than that observed in the previous study. With a mean difference, standard deviation, significance level, and number of study subjects of 9, 13, 0.05, and 34, respectively, the power of this study was calculated to be 80.3%.

Study participants were randomized by the lottery method. Allocation was carried out without information on the participants, and independent of the dentist and the study researchers. Study participants were randomized 1:1 into 2 groups: an early intervention group (1–6 m), in which participants underwent periodontal treatment and dental health instruction during the first sixth months from baseline, and a later intervention group (7–12 m), in which participants underwent the same intervention during the seventh to the twelfth month from baseline.

All participants were informed of the study structure. Therefore, it was ethically impossible to blind participants from the dental intervention because they visited a dentist and were treated during the intervention period.

2.6. Statistics

We compared mean values and prevalence rates of the baseline characteristics for the early (n = 37) and later (n = 34) intervention groups. Mean values at baseline, 6 months, and 12 months between the two groups were compared by a *t*-test. We tested differences in BMI, HbA_{1c}, fasting and 1-h and 2-h postload glucose and insulin concentrations, HOMA-IR, HOMA-β, Matsuda Index, BOP (%), and mean PPD between the intervention period (1–6 m in the early intervention group plus 7–12 m in the later intervention group) and the non-intervention period of each group, and differences were compared (i.e., after intervention-before intervention) by a *t*-test. We further stratified the participants by median pre-intervention values of BOP (< 37% and ≥37%), and compared changes in measurements within groups by a *t*-test. We also calculated the age-and sex-adjusted Pearson's partial correlation coefficients of the BOP (%) before intervention and the BMI change during the intervention with change of the measurements during intervention. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc.). All P values were two-tailed, and P values < 0.05 were regarded as statistically significant.

3. Results

The numbers of randomly assigned participants in the early and later groups were n = 38 and n = 36, respectively. A couple that insisted on participating together after allocation joined the same group. Guidance for participation in the study was conducted in October of 2011 and 2012, and in January of 2012 and 2013. The first follow-up examination (6-month follow-up) was held in April and July of 2012 and 2013, and the second follow-up examination (12-month follow-up) was held in October of 2012 and 2013 and in January of 2013 and 2014. During the follow-up, one participant in the early intervention group and two participants in the later intervention group dropped out of the trial because for personal reasons. Therefore, we analyzed 37 subjects in the early intervention group (1–6 m) and 34 subjects in the later intervention group (7–12 m) (Fig. 1).

Baseline characteristics of the early (n = 37) and later (n = 34) intervention groups are shown in Table 1. Baseline glucose and insulin concentrations were similar between the two groups. Oral health conditions of BOP (%) and PPD were also similar.

Table 2 shows a comparison of the measurements between the early and later intervention groups at baseline, 6 months, and 12 months. There were no significant differences in primary outcomes, except for 1-h serum glucose levels at 6 months. Regarding oral health conditions, BOP (%) and mean PPD were significantly improved following the periodontal therapy.

Table 3 shows the differences in each measurement between the intervention and non-intervention periods. The BOP (%) and mean PPD were significantly improved for the intervention period compared with the non-intervention period (P < 0.001). However, the differences in the other measurements were not statistically significant.

Table 4 shows changes in each measurement during the intervention according to the median-split BOP (%) prior to intervention. Compared to the higher BOP (%) group (≥ 37%, n = 35), the lower BOP (%) group (< 37%, n = 36) showed significantly improved changes in BMI (P = 0.01), fasting serum insulin (P = 0.01), HOMA-IR (P = 0.03), HOMA-β (P = 0.03), and Matsuda Index (P = 0.03).

We calculated the age- and sex-adjusted Pearson's partial correlation coefficients of BOP (%) before the intervention and the change in BMI during the intervention period with the changes of each measurement during the intervention period (Table5). We observed a borderline significant correlation between the BOP (%) before the intervention and the change in BMI (r = 0.23, P = 0.06), and a significant positive correlation between the BOP (%) before the intervention and the change in the 2 h serum glucose levels (r = 0.33, P = 0.005). We also observed that change in the BMI was positively correlated with changes in the HbA1c (r = 0.26, P = 0.03), HOMA-IR (r = 0.45, P < 0.001), HOMA-β (r = 0.34, P = 0.004), and serum insulin levels (fasting (r = 0.48, P < 0.001), 1 h (r = 0.24, P = 0.05) and 2 h (r = 0.36, P = 0.002)), and was inversely correlated with change in the Matsuda Index (r = −0.32, P = 0.007).

4. Discussion

In this RCT, we found that periodontal therapy had no significant effect on the markers related to insulin and glucose metabolism among individuals with borderline diabetes who were not taking medication for their diabetes. However, we found that the participants with a lower BOP (%) showed significant improvements in their BMI, fasting serum insulin, HOMA-IR, HOMA-β and Matsuda Index. The benefit in this subgroup might be associated with weight reduction, since decrease in BMI was positively correlated with favorable changes in markers representing insulin and glucose metabolism during the intervention.

SRP therapy for all participants was performed by the same dentist. Both BOP (%) and mean PPD were improved following the intervention, suggesting that the therapy was effective at treating periodontitis. Non-preservable teeth were extracted during the intervention period. The mean number of teeth extracted were 0.6 and 0.4 in the early and later intervention groups, respectively. Treatment planning did not influence the outcomes.

Two meta-analyses examining the relationship of non-surgical periodontal treatment, including SRP, with glycemic control among patients with type 2 diabetes showed reductions in HbA_{1c} [3,4] and fasting plasma glucose [4] levels. However, another meta-analysis assessing SRP plus oral doxycycline showed no effect on the change of HbA1c compared with control (SRP only) in patients with diabetes [8]. The different results may be explained by the severity of periodontal disease in the respective study populations. The mean PPDs at baseline in the successive studies were 2.24–2.67 mm [17–19], which were lower than that of our participants and that of another large clinical trial failing to show an improvement of HbA1c; in the latter trial, the mean PPD was 3.3 mm. Oral high BOP levels indicate the presence of inflammation and maintain the growth of periodontal bacteria, because oral bleeding due to periodontitis increases hemoglobin concentrations in gingival crevicular fluid, which in turn stimulates the secretion of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 [20]. The increase in inflammatory cytokines could impair the intracellular signaling of insulin in relation to insulin resistance [21]. Considering the inflammatory status in severe periodontal disease, the periodontal

treatment may not have been sufficient to improve insulin resistance. In that case, high oral BOP levels may mask the effect of the treatment, which could account for the negative results observed in the present study. Indeed, in this study, the mean value of the higher BOP group after 6 months of intervention (23.1 ± 10.3%) was higher than that of the lower BOP group prior to intervention (22.7 ± 10.5%). Thus, improved changes in BMI, fasting serum insulin, HOMA-IR, HOMA-β, and Matsuda Index were seen in the lower BOP group.

The reason for the reduction in body weight among participants with a lower BOP in the present study is not clear. One potential reason is that obesity may be linked to oral bacteria [22]. Dental treatment in the present study was associated with weight loss, and was anticipated to have favorable effects on oral bacteria, both of which could have activated adipocytokines [23,24].

Several trials showed that periodontal treatment was associated with improvement of adipocytokines [9,10]. Another potential reason is related to lifestyle changes. As participants in this study were unblended, and dental health instruction was provided by a dentist and a dental hygienist, the intervention could have increased motivation for lifestyle change among the study participants, especially in those with lower BOP (%) that may have exhibited higher health consciousness.

Several systematic reviews have suggested that obesity is a risk factor for the development of periodontitis [25–27], and another review article has suggested a bidirectional relationship between the metabolic syndrome (including obesity) and periodontitis, mediated by circulating cytokines and oxidative stress [28]. In addition, in another study which demonstrated no effects of periodontal intervention on glycemic control, other risk factors were more frequent, i.e., smoking, poor oral hygiene, hormonal changes in women, medication, and stress [29]. Likewise, individuals with a higher BOP (%) appear to have had more risk factors in the present study.

The strength of this study was that we performed full-mouth dental examinations and evaluated BOP levels using scores of 0–4 per tooth for all teeth. Since two examiners carried out the dental examinations with probes designed to apply pressure at a weight of 20 g, variations of measurements between examiners were minimized (kappa value; 0.88). In addition, a 75 g OGTT was performed to assess the pre- and postload serum glucose and insulin levels, which enabled us to assess insulin sensitivity and resistance by calculating Matsuda Index and HOMA-IR, respectively.

The present study has several limitations. First, we did not assess the counts of bacteria, including *P. gingivalis,* which needs heme iron to live in the human body and is strongly related to bacterial pathogenicity in the mouth [30]; and we did not measure cytokines such as TNF-α and IL-6 during the intervention. These factors may affect how periodontal treatment changes glucose metabolism [31,32]. Second, our subjects were more health-conscious compared with general individuals. In fact, the percentage of current smokers was lower than that in the National Health and Nutrition Survey in Japan in 2011 (8.1% in the early intervention group and 2.9% in the later intervention group versus 32.4% in the Survey) [33]. A healthy lifestyle, even during the non-intervention periods, could have reduced differences in oral conditions between the intervention and control periods. Third, although a single dentist treated participants to avoid any bias in treatment planning among dentists, the dental therapy was not standardized; therefore, planning varied by periodontal conditions and related disease levels. Accordingly, generalization of dental therapy was limited.

5. Conclusion

Periodontal therapy had no significant effect on markers related to insulin and glucose metabolism among individuals with borderline diabetes. However, participants with a lower BOP (%) showed significant improvements in BMI, fasting serum insulin, HOMA-IR, HOMA-β and Matsuda Index. Although the effect is limited to those who had relatively better oral conditions, the dental therapy, in accordance with dental health guidance, could contribute to improved glucose metabolism.

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References

[1] G.G. Nascimento, F.R.M. Leite, P. Vestergaard, F. Scheutz, R. López, Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies, Acta Diabetol. 55 (2018) 653–667, https://doi.org/10.1007/s00592-018-1120-4.
[2] N.G. Chavarry, M.V. Vettore, C. Sansone, A. Sheiham, The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis, Oral Health Prev. Dent. 7 (2009) 107–127.
[3] Q. Li, S. Hao, J. Fang, J. Xie, X.H. Kong, J.X. Yang, Effect of non-surgical periodontal treatment on glycemic control of patients with diabetes: a meta-analysis of randomized controlled trials, Trials 16 (2015) 1–8, https://doi.org/10.1186/s13063-015-0810-2.
[4] F. Sgolastra, M. Severino, D. Pietropaoli, R. Gatto, A. Monaco, Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials, J Periodontol 84 (2013) 958–973, https://doi.org/10.1902/jop.2012.120377.
[5] W.-L. Sun, L.-L. Chen, S.-Z. Zhang, Y.-M. Wu, Y.-Z. Ren, G.-M. Qin, Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis, Intern. Med. 50 (2011) 1569–1574, https://doi.org/10.2169/internalmedicine.50.5166.
[6] S. Srirangarajan, R. Setty, A. Satyanarayan, S. Shetty, Effect of full-mouth disinfection on insulin sensitivity in type 2 diabetes patients with and without chronic periodontitis, Quintessence Int. (Berl) 47 (2016) 103–112, https://doi.org/10.3290/j.qi.a34811.
[7] S.P. Engebretson, L.G. Hyman, B.S. Michalowicz, E.R. Schoenfeld, M.C. Gelato, W. Hou, et al., The effect of Non-surgical periodontal therapy on hemoglobin a 1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial, JAMA 18 (December) (2013) 2523–2532, https://doi.org/10.1001/jama.2013.282431.
[8] T.-F. Wang, I.-A. Jen, C. Chou, Y.-P. Lei, Effects of periodontal therapy on metabolic control in patients with type 2 diabetes mellitus and periodontal disease, Medicine (Baltimore) 93 (2014) e292, https://doi.org/10.1097/MD.0000000000000292.
[9] H. Ogawa, T. Damrongrungruang, S. Hori, K. Nouno, K. Minagawa, M. Sato, et al., Effect of periodontal treatment on adipokines in type 2 diabetes, World J. Diabetes 5 (2014) 924–931, https://doi.org/10.4239/wjd.v5.i6.924.
[10] G.G. Nascimento, F.R.M. Leite, M.B. Correa, M.A. Peres, F.F. Demarco, Does periodontal treatment have an effect on clinical and immunological parameters of periodontal disease in obese subjects? A systematic review and meta-analysis, Clin. Oral Investig. 20 (2015) 639–647, https://doi.org/10.1007/s00784-015-1678-y.
[11] S.N. Papageorgiou, C. Reichert, A. Jäger, J. Deschner, Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis, J. Clin. Periodontol. 42 (2015) 247–261, https://doi.org/10.1111/jcpe.12365.
[12] N. Miyoshi, T. Tanigawa, S. Nishioka, K. Maruyama, E. Eguchi, K. Tanaka, et al., Association of salivary lactate dehydrogenase level with systemic inflammation in a Japanese population, J. Periodontal Res. (2018) 1–8, https://doi.org/10.1111/jre.12537.
[13] I. Saito, K. Maruyama, E. Eguchi, T. Kato, R. Kawamura, Y. Takata, et al., Low heart rate variability and sympathetic dominance modifies the association between insulin resistance and metabolic syndrome-the Toon health study, Circ. J. 81 (2017) 1447–1453, https://doi.org/10.1253/circj.CJ-17-0192.
[14] M.L. Barnett, The rationale for the daily use of an antimicrobial mouthrinse, J. Am Dent Assoc. (137 Suppl) (2006) 16S–21S.
[15] S. Jenkins, M. Addy, R.G. Newcombe, Dose response of chlorhexidine against plaque and comparison with triclosan, J. Clin. Periodontol. 21 (1994) 250–255.
[16] T. Saito, Y. Shimazaki, Y. Kiyohara, I. Kato, M. Kubo, M. Iida, et al., Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the hisayama study, J. Periodontal Res. 40 (2005) 346–353, https://doi.org/10.1111/j.1600-0765.2005.00813.x.
[17] H. Zhang, C. Li, S. Shang, Z. Luo, Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: a randomized controlled clinical trial, J. Dent. Sci. 8 (2013) 272–280, https://doi.org/10.1016/j.jds.2012.10.009.
[18] M. Kiran, N. Arpak, E. Unsal, M.F. Erdogan, The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus, J. Clin. Periodontol 32 (2005) 266–272, https://doi.org/10.1111/j.1600-051X.2005.00658.x.
[19] S. Singh, V. Kumar, S. Kumar, A. Subbappa, The effect of periodontal therapy on the improvement of glycemic control in patients with type 2 diabetes mellitus: a

randomized controlled clinical trial, Int. J. Diabetes Dev. Ctries 28 (2008) 38–44.
[20] C. Bodet, F. Chandad, D. Grenier, Hemoglobin and LPS act in synergy to amplify the inflammatory response, J. Dent. Res. 86 (2007) 878–882, https://doi.org/10.1177/154405910708600914.
[21] A. Bascones-Martínez, J. González-Febles, J. Sanz-Esporrín, Diabetes and periodontal disease. Review of the literature, Am J. Dent. 27 (2014) 63–67.
[22] J.M. Goodson, D. Groppo, S. Halem, E. Carpino, Is obesity an oral bacterial disease? J. Dent. Res. 88 (2009) 519–523, https://doi.org/10.1177/0022034509338353.
[23] V. Andrade-Oliveira, N.O.S. Câmara, P.M. Moraes-Vieira, Adipokines as drug targets in diabetes and underlying disturbances, J. Diabetes Res. 2015 (2015), https://doi.org/10.1155/2015/681612.
[24] H.S. Mattu, H.S. Randeva, Role of adipokines in cardiovascular disease, J. Endocrinol. 216 (2013) T17–T36, https://doi.org/10.1530/joe-12-0232.
[25] B.W. Chaffee, S.J. Weston, Association between chronic periodontal disease and obesity: a systematic review and meta-analysis, J. Periodontol. 81 (2010) 1708–1724, https://doi.org/10.1902/jop.2010.100321.
[26] G.G. Nascimento, F.R.M. Leite, Peres K.G. Do LG, M.B. Correa, F.F. Demarco, et al., Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis, J. Clin. Periodontol. 42 (2015) 495–505, https://doi.org/10.1111/jcpe.12417.
[27] A. Keller, J.F. Rohde, K. Raymond, B.L. Heitmann, Association between periodontal disease and overweight and obesity: a systematic review, J. Periodontol. 86 (2015) 766–776, https://doi.org/10.1902/jop.2015.140589.
[28] P. Bullon, J.M. Morillo, M.C. Ramirez-Tortosa, J.L. Quiles, H.N. Newman, M. Battino, Metabolic syndrome and periodontitis: Is oxidative stress a Common link? J. Dent. Res. 88 (2009) 503–518, https://doi.org/10.1177/0022034509337479.
[29] M.A. Nazir, Prevalence of periodontal disease, its association with systemic diseases and prevention, Int. J. Health Sci. (Qassim) 11 (2017) 72–80.
[30] J.P. Lewis, Metal uptake in host-pathogen interactions: role of iron in porphyromonas gingivalis interactions with host organisms, Periodontology 2010 (52) (2000) 94–116, https://doi.org/10.1111/j.1600-0757.2009.00329.x.
[31] J.J. Taylor, P.M. Preshaw, E. Lalla, A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes, J. Periodontol. 84 (2013) S113–34, https://doi.org/10.1902/jop.2013.134005.
[32] L. Marigo, R. Cerreto, M. Giuliani, F. Somma, C. Lajolo, M. Cordaro, Diabetes mellitus: biochemical, histological and microbiological aspects in periodontal disease, Eur. Rev. Med. Pharmacol. Sci. 15 (2011) 751–758.
[33] Ministry of Health, Labour and Welfare, The National Health and Nutrition Survey Japan, (2011) Accessed 7 March, 2018 http://www.mhlw.go.jp/bunya/kenkou/eiyou/h23-houkoku.html.