Effect of glycemic control on periodontitis in type 2 diabetic patients with periodontal disease

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ABSTRACT

Aims/Introduction: Diabetes mellitus and periodontitis are closely related. A huge number of reports has addressed the effect of periodontal intervention therapy on glycemic control, but no reports have addressed the effect of glycemic intervention therapy on periodontal disease in type 2 diabetic patients. The aim of this study was to examine the effect of improved glycemic control by glycemic intervention therapy on periodontitis in type 2 diabetic patients.

Materials and Methods: A total of 35 patients underwent intervention therapy to improve glycemic control without periodontal treatment. Glycohemoglobin (HbA_{1c}), high-sensitivity C-reactive protein (hs-CRP), bleeding on probing (BOP), probing pocket depth (PPD) and intraoral community periodontal index (CPI) codes of the World health Organization (WHO) were examined at baseline, and 2 and 6 months after the intervention therapy to improve glycemic control.

Results: After the improvement of glycemic control, BOP lesions improved, but deep PPD lesions and WHO CPI codes did not improve. Subanalyses showed that effective glycemic control (average HbA_{1c} reduction 1.8%) improved BOP lesions, but did not affect deep PPD lesions and WHO CPI codes. In addition, high BOP lesions at baseline responded more effectively to glycemic intervention. Further analysis of CPI codes in all individual periodontal sites independent of WHO CPI codes in 35 patients showed that only gingival inflammation without a deep periodontal pocket improved after glycemic intervention.

Conclusions: Effective glycemic control improves BOP lesions in type 2 diabetic patients with periodontitis through ameliorating inflammation at the gingival sites of periodontal tissue. This trial was registered with the University Hospital Medical Information Network (no. UMIN000007670). (J Diabetes Invest doi: 10.1111/jdi.12026, 2013)

KEY WORDS: Bleeding on probing, Periodontitis, Type 2 diabetes intervention therapy

INTRODUCTION

Periodontitis is a chronic infectious disease caused by periodontal bacterial infection. Chronic periodontal inflammation causes loss of alveolar bone and periodontal supportive tissue, eventually leading to loss of teeth[1,2]. Type 2 diabetes mellitus is mainly characterized by hyperglycemia as a result of impaired insulin action[3]. Although the etiology of the two diseases is different, there is a huge number of reports that have shown a close relationship between periodontitis and diabetes mellitus[4].

Diabetes mellitus is considered one of the major risk factors for periodontitis, and, vice versa, periodontitis is considered to increase the risk of developing diabetes mellitus[5]. For many years, the effect of periodontal intervention therapy on glycemic control has been examined, and many intervention studies to validate these effects have been reported[6–10]. However, to the best of our knowledge, studies examining the effect of improved glycemic control by glycemic intervention therapy on periodontitis have never been reported. The aim of the present study was to examine whether improvement of glycemic control by glycemic intervention therapy affects periodontal disease in type 2 diabetic patients without treatment of periodontitis.

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METHODS

Participants

Type 2 diabetic patients were recruited from diabetic clinics at four institutions: Tokyo Medical University Hospital, Kyoto Prefecture Medical University Hospital, Aichi Gakuin University Hospital and Tokyo Teishin Hospital. At each institution, patients were selected based on the following inclusion criteria: age 40–75 years and glycohemoglobin (HbA_{1c}) $\geq$7.4%. The exclusion criteria were: severe diabetic complications, evidence of systemic disease other than diabetes as a risk factor for periodontitis, systemic antibiotics taken during the preceding 3 months, pregnancy or lactation and periodontal treatment during the preceding 6 months. A total of 42 participants fulfilled the criteria, but seven chose not to participate. The study protocol was approved by the Ethics Committee of each university hospital, and written informed consent was obtained from each participant.

Intervention and Measurements

Based on the physician's diagnosis, each participant underwent a 6-month treatment plan that ensured improvement in blood glucose levels, including dietary counseling, oral hypoglycemic agents and insulin administration. In each diabetic clinic, HbA_{1c} and high-sensitivity C-reactive protein (hs-CRP) measurements, and periodontal examinations were carried out at baseline and 2 and 6 months after the glycemic intervention therapy without receiving periodontal treatments. The white blood cell (WBC) count and serum creatinine were measured at baseline.

In each dental clinic, full-mouth measurements of bleeding on probing (BOP) and probing pocket depth (PPD) were recorded using a manual probe (PCP-UNC 15; Hu-Friedy Manufacturing, Chicago, IL, USA) at all six sites of each tooth, simultaneously, at baseline and 2 and 6 months after the glycemic intervention therapy. World Health Organization (WHO) community periodontal index (CPI) codes were also recorded as an estimate of periodontitis[11]. In this examination, the right central incisor in the maxilla and the left central incisor in the mandible were considered to be the representative teeth in the anterior teeth block, and the first and second molar teeth in the right and left maxilla and mandible were similarly considered to be representative teeth. CPI codes of 0–4 were given for healthy cases (0), and those with BOP (1), with calculus (2) and with a probing pocket depth of 4–5 mm (3) or $\geq$6 mm (4), respectively. In this WHO classification of periodontitis, it has been determined that the highest CPI code should be selectively applied for each patient by determining all codes in six individual blocks in each periodontal patient.

Blood samples were analyzed for HbA_{1c}, which was determined by high-performance liquid chromatography (Kyotokagaku, Kyoto, Japan). The value for HbA_{1c} (%) was described as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods, and referred to as HbA_{1c} (NGSP)[12]. The serum hs-CRP level was measured using a latex particle-enhanced immunonephelometric method.

Physicians collected the medical data, and dentists carried out oral examinations. Dentists did not know patients' glycemic control when they carried out oral examinations, so that the dentists were blinded to glycemic control.

Statistical Analysis

Statistical analysis was carried out using the JMP® software program (SAS Institute, Cary, NC, USA). Changes in all parameters from baseline to 2 and 6 months were compared using the Wilcoxon signed-rank test. For subanalyses, the Mann–Whitney *U*-test and Fisher's exact test were used to compare the parameters between the HbA_{1c}-decreased (HbA_{1c}-D) and HbA_{1c}-no decrease or increased (HbA_{1c}-ND) groups, and the baseline bleeding on probing high (BOP-H) and the baseline BOP low (BOP-L) groups. The correlations between any two parameters were examined by Spearman's rank correlation coefficient. Participants with WBC >8,000 were regarded as having severe inflammation and were excluded from the analysis of hs-CRP. $P < 0.05$ was regarded as significant.

RESULTS

The results of 35 patients (18 males, 17 females) were analyzed. As shown in Table 1, the mean age of the participants was 59.4 $\pm$ 9.3 years. The mean BMI was 25.9 $\pm$ 5.0 kg/m^2 at baseline. The mean number of present teeth was 23.1 $\pm$ 6.2. A total of 11 of the 35 patients were using insulin injections, 24 patients were using oral hypoglycemic drugs and none was being treated with diet alone. Creatinine in all participants was less than 1.0 mg/dL, meaning that no patients developed renal disfunction associated with diabetic nephropathy. The degree of BOP lesions was significantly reduced in parallel with the HbA_{1c} reduction, but no significant changes in the degree of PPD, WHO CPI code for each patient and hs-CRP were observed for 6 months.

To further explore the effect of improved glycemic control by glycemic intervention therapy on periodontitis, subanalyses were carried out. First, in order to examine whether the reduction of HbA_{1c} actually improved the BOP lesions, the patients were subdivided into two groups according to the change in HbA_{1c} (Table 2). Reduction of HbA_{1c} was observed in 25 patients at 6 months (HbA_{1c}-D group; average decrease 1.8%), and the HbA_{1c} level was not decreased or increased in 10 patients (HbA_{1c}-ND groups). There were no significant differences in types of glycemic treatment, HbA_{1c}, hs-CRP, degree of PPD, BOP lesions, and WHO CPI codes at baseline between the HbA_{1c}-D and HbA_{1c}-ND groups. In the HbA_{1c}-D group, the degree of BOP lesions was significantly less at 2 and 6 months, which indicated that reduced HbA_{1c} was actually related to the improvement of BOP lesions, but not related to the improvement of PPD, and WHO CPI codes did not change

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Table 1 | Diabetic and periodontal status at baseline and during follow up in all participants

All participants (n = 35)		Baseline	2 months	6 months
	Male/female	18/17	–	–
	Insulin/oral hypoglycemic	11/24	–	–
	HbA_{1c} (%)	9.5 ± 1.8	8.8 ± 1.3*	8.3 ± 1.4*
	hs-CRP (ng/mL)	725 ± 699	963 ± 1318	956 ± 1055
	PPD (mm)	2.8 ± 0.9	2.8 ± .9	2.8 ± 0.7
	BOP (%)	37.7 ± 23.2	25.9 ± 16.4*	24.7 ± 17.1*
	WHO classification of periodontitis CPI 1 or 2/CPI 3/CPI 4	3/10/22	2/12/21	2/14/19

Values are given as means ± SD. BOP, bleeding on probing; CPI, community periodontal index; HbA_{1c}, glycohemoglobin; hs-CRP, high-sensitivity C-reactive protein; PPD, probing pocket depth; WHO, World Health Organization.
Statistically significant decrease compared with baseline, *P < 0.01.

Table 2 | Diabetic and periodontal status at baseline and during follow up in glycohemoglobin decreased and glycohemoglobin no decrease or increased groups

HbA_{1c}-D and HbA_{1c}-ND groups		Baseline	2 months	6 months
HbA_{1c} decreased group (n = 25)	Male/female	13/12	–	–
	Insulin/oral hypoglycemic	8/17	–	–
	HbA_{1c} (%)	9.7 ± 2.0	8.7 ± 1.3*	7.9 ± 1.2*
	hs-CRP (ng/mL)	619 ± 447	649 ± 799	787 ± 843
	PPD (mm)	3.0 ± 0.9	2.9 ± 0.9	2.9 ± 0.8
	BOP (%)	42.6 ± 22.8	28.4 ± 17.3*	26.8 ± 17.3*
	WHO classification of periodontitis CPI 1 or 2/CPI3/CPI4	1/6/18	0/7/18	1/9/15
HbA_{1c} not decreased rather increased group (n = 10)	Male/female	5/5	–	–
	Insulin/oral hypoglycemic	3/7	–	–
	HbA_{1c} (%)	9.0 ± 1.4	8.9 ± 1.6	9.5 ± 1.4†
	hs-CRP (ng/mL)	950 ± 1049	1591 ± 1903	1333 ± 1405
	PPD (mm)	2.5 ± 0.6	2.5 ± 0.6	2.6 ± 0.6
	BOP (%)	25.6 ± 20.2	18.4 ± 11.4	19.6 ± 16.4
	WHO classification of periodontitis CPI 1 or 2/CPI 3/CPI 4	2/4/4	2/5/3	1/5/4

Values are given as means ± SD; CPI, community periodontal index; HbA_{1c}-D, glycohemoglobin decreased;HbA_{1c}-ND, glycohemoglobin no decrease or increased; hs-CRP, high-sensitivity C-reactive protein; PPD, probing pocket depth; BOP, bleeding on probing; WHO, World Health Organization.
Statistically significant decrease compared with baseline; *P < 0.01. Statistically significant increase compared with baseline and difference compared with glycohemoglobin (HbA_{1c}) decreased group. †P < 0.01.

significantly over 6 months. No significant improvements were observed in BOP lesions, degree of PPD and WHO CPI codes in the HbA_{1c}-ND group throughout the study period. Hs-CRP was not changed significantly during the study period in both groups.

Second, in order to examine whether high BOP responds well to the improved glycemic control by the intervention therapy, the patients were subdivided into two groups based on the baseline degree of BOP (Table 3). Of the 35 patients, the percentage of BOP lesions at baseline was higher than the median percentage of BOP lesions (38.7%) in 17 patients (BOP-H group), whereas the baseline percentage of BOP lesions was less than the median percentage of BOP lesions in the other 18 participants (BOP-L group). In the BOP-H group, BOP lesions were significantly reduced at 2 and 6 months with a significant reduction of HbA_{1c}, whereas in the BOP-L group, BOP lesions were not improved without a significant reduction in HbA_{1c} at 2 months, but BOP lesions were significantly improved with a significant reduction in HbA_{1c} at 6 months, which indicated that high BOP lesions responded more effectively to glycemic control by the intervention therapy, resulting in improvement of BOP lesions. However, no significant improvement was observed in the degree of PPD and WHO CPI codes throughout the study periods in the BOP-H and BOP-L groups. Hs-CRP was not changed significantly during the study period in both of the groups.

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Table 3 | Diabetic and periodontal status at baseline and during follow up in bleeding on probing high and bleeding on probing low groups

BOP-H and BOP-L groups		Baseline	2 months	6 months
Baseline BOP high group (n = 17)	Male/female	10/7	–	–
	Insulin/oral hypoglycemic	8/9	–	–
	HbA_{1c} (%)	9.7 ± 1.9	8.7 ± 1.3**	8.0 ± 1.5**
	hs-CRP (ng/mL)	831 ± 909	830 ± 1096	925 ± 1354
	PPD (mm)	3.0 ± 0.8	2.9 ± 0.7	3.0 ± 0.7
	BOP (%)	56.1 ± 16.9†	36.3 ± 16.0**†	36.5 ± 16.6**†
	WHO classification of periodontitis CPI 1 or 2/CPI3/CPI4	0/5/12	0/6/11	0/7/10
Baseline BOP low group (n = 18)	Male/female	8/10	–	–
	Insulin/oral hypoglycemic	3/15	–	–
	HbA_{1c} (%)	9.3 ± 1.8	8.8 ± 1.4	8.6 ± 1.4*
	hs-CRP (ng/mL)	613 ± 368	1087 ± 1526	989 ± 648
	PPD (mm)	2.7 ± 0.9	2.7 ± 1.0	2.6 ± 0.7
	BOP (%)	20.4 ± 12.1	15.6 ± 8.6	13.6 ± 7.5*
	WHO classification of periodontitis CPI 1 or 2/CPI 3/CPI 4	3/5/10	2/6/10	2/7/9

Values are given as means ± SD. BOP, bleeding on probing; BOP-H, bleeding on probing high; BOP-L, bleeding on probing low; CPI, community periodontal index; HbA1c-D, glycohemoglobin decreased; HbA1c-ND, glycohemoglobin no decrease or increased; hs-CRP, high-sensitivity C-reactive protein; PPD, probing pocket depth; WHO, World Health Organization. Statistically significant decrease compared with baseline, *P < 0.05. **P < 0.01. Statistically significant difference compared with baseline BOP low group, †P < 0.01.

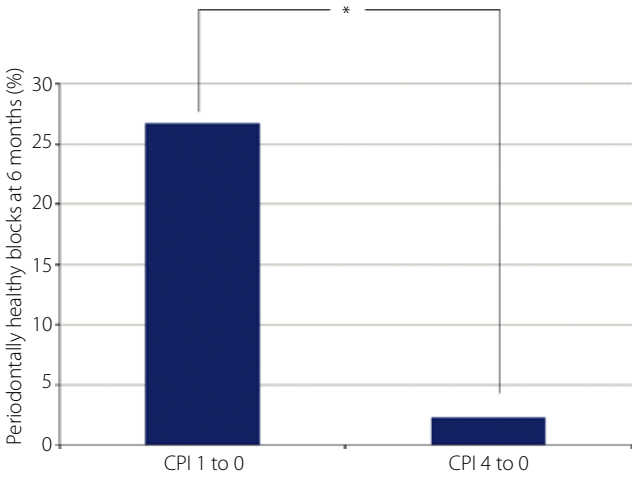

Figure 1 | Percentage of periodontally healthy blocks at 6 months, *P < 0.05.

Third, in order to examine whether improvement of glycemic control by the intervention therapy affected individual periodontal sites independent of WHO classification of periodontitis in each patient, because the WHO CPI code can only identify the highest degree of periodontitis, changes of all individual CPI codes in all individual blocks were examined in 35 patients from baseline to 6 months. There were 45 blocks that showed CPI code 1 at baseline, and in 12 of the 45 code 1 blocks (26.7%) CPI code 1 returned to CPI code 0 after 6 months' glycemic intervention therapy. In contrast, there were 43 blocks with CPI code 4 at baseline, and only in one of the 43 code 4 blocks (2.3%) did CPI code 4 return to CPI code 0 after 6 months (Figure 1), which indicated that lesions of inflammation responded more effectively to the glycemic improvement by the intervention therapy.

DISCUSSION

There have been many studies that have addressed the effect of improved periodontitis by periodontal intervention therapy on glycemic control, and recently, Teeuw *et al.*[13] carried out a meta-analysis by selecting five reliable studies among 639 intervention studies, and they found a significant decline of 0.4% in HbA_{1c} in type 2 diabetic patients after periodontal intervention therapy. Therefore, it is reasonable to consider that effective periodontal intervention therapy improves glycemic control in type 2 diabetic patients. However, to the best of our knowledge, no studies that addressed the effect of glycemic intervention therapy without periodontal treatment on periodontal status in type 2 diabetic patients have been reported.

In the present study, the effect of improved glycemic control by glycemic intervention therapy on periodontitis was investigated, and it was found for the first time that effective glycemic control with reduced HbA_{1c} by glycemic intervention therapy improved BOP lesions without periodontal treatment over the 6-month period. In addition, high BOP lesions at baseline responded more effectively to reduced HbA_{1c} by the glycemic intervention therapy in type 2 diabetic patients with periodontitis. The results of two subanalyses strongly indicated that effective glycemic improvement by intervention therapy is able to ameliorate BOP lesions in periodontitis without peri-

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odontal treatment in type 2 diabetic patients. However, it was also found that even effective glycemic control did not improve deep PPD lesions in these patients.

These results were confirmed by analysis of all CPI codes in all individual blocks independent of WHO classification. Although mean WHO CPI codes did not change significantly, 26.7% of the blocks with CPI code 1 (periodontal inflammation without a deep periodontal pocket) returned to blocks with CPI code 0 (healthy periodontal tissue) after the glycemic intervention, but just 2.3% of the blocks with CPI code 4 (severe periodontitis with a deep periodontal pocket) returned to CPI code 0. This suggests that effective glycemic control can improve BOP lesions, but cannot improve deep PPD lesions in type 2 diabetes patients.

The etiological agent for deteriorating BOP lesions and degree of PPD is plaque biofilm, but the susceptibility to plaque biofilm differs among patients. Host inflammatory responses are the key factors for deteriorating BOP lesions, and destruction of periodontal tissue is a key factor for deteriorating PPD. BOP lesions are easily changeable within a short period of time by the accumulation of plaque biofilm in gingival tissues; however, deterioration of PPD usually takes a long period of time by chronic periodontal bacterial infection and host tissue reaction, and it takes time to restore PPD. It is well recognized that the absence of BOP predicts the absence of deterioration of PPD, suggesting that the deterioration of BOP lesions precedes deterioration of PPD[14].

A large epidemiological study by Offenbacher *et al.*[15] showed that diabetes augmented the gingival inflammatory responses against plaque biofilm, and the prevalence of diabetes was significantly higher in the gingivitis patients with high BOP lesions than in those with low BOP lesions. Accordingly, the amelioration of diabetes might improve the gingival inflammatory responses. Recession of the affected gingival tissue is dependent on gingival biotype (thickness of the periodontal tissue) and resolution of the inflammation. In contrast, deep PPD lesions are the result of irreversible destruction of the attachment of the gingival tissue and/or periodontal ligament on the root surface. Restoration of PPD is the clinical result seen from the attachment gain of the gingival tissue on the root and/or the recession of the gingival tissue. The diseased root surface is contaminated with bacterial plaque, and debridement of the contamination is required for the gingival tissue to gain the attachment. Therefore, diabetic treatment alone might not be enough to restore deep PPD though the recession of gingival tissue.

It has been established that bacterial microflora at periodontal disease sites in diabetic patients are similar to the microflora at similar disease sites in non-diabetic subjects[16,17], and thus, the causes of susceptibility and severity of periodontitis in type 2 diabetic patients come from host problems. Diabetic complications originate from complex abnormalities on the host side through chronic hyperglycemia[18]. These abnormalities involve many factors, such as inflammation[19], advanced glycation end-products (AGEs)[20], oxidative stress[21], microangiopathy[22] and macroangiopathy[23]. We presume that the combination of these abnormalities makes diabetic patients susceptible to bacterial infection in the periodontal tissue.

Although BOP lesions in the HbA_{1c}-D group improved at 6 months, hs-CRP was not significantly changed in these patients. Several reasons might explain why BOP lesions improved without reduction of hs-CRP. First, improvement of BOP lesions in the HbA_{1c}-D group might not have had been strong enough to reduce circulatory hs-CRP levels. Second, periodontitis is one of the complications in diabetes[24], and gingival tissue might be susceptible to glycemic control compared with other parts of the human body. Chronic hyperglycemia might contribute to the simultaneous activation of many different pathological pathways, including oxidative stress and low-grade inflammation. Improvement of glycemic control might ameliorate oxidative stress through the reduction of AGEs and oxygen radicals. Takeda *et al.* reported that AGEs, not hs-CRP, were significantly related to the deterioration of periodontitis in type 2 diabetes patients[25], indicating that gingival inflammation in type 2 diabetic patients might not necessarily be associated with the fluctuation of systemic low grade inflammation (hs-CRP). Third, improvement of BOP was mainly observed in mild gingivitis lesions (CPI = 1), and severe periodontitis (CPI = 4) was not improved by glycemic control, implying that lack of improvement in the severe periodontal lesions might inhibit mean hs-CRP reduction after glycemic control. A larger scale intervention study might be required to show a significant correlation between improvement of BOP and hs-CRP levels.

Oral hygiene might also affect gingival conditions, such as BOP and PPD. The plaque control record of all patients was not available, and it is possible that improvement of oral hygiene might have affected BOP status even if the patients were not instructed in oral hygiene during the course of the study. In the present study, improvement of BOP lesions was observed only in the HbA_{1c}-D group; however, it is unlikely that HbA_{1c}-D group patients selectively improved their oral hygiene, resulting in the improvement of BOP lesions. The improvement of BOP lesions in the HbA_{1c}-D group strongly suggested that it was related to the improvement of HbA_{1c} in the present study, as improvement of BOP lesions was not observed in the HbA_{1c}-ND group.

Many studies have shown that effective periodontal treatment in type 2 diabetic patients improves glycemic control[6,13]. Periodontitis is a chronic, subclinical, inflammatory disease that increases the risk of onset and progression of diabetes mellitus and arteriosclerosis. Taken with the present and previous results, it is conceivable that glycemic treatment could be carried out simultaneously with periodontal treatments in the cases of type 2 diabetic patients with periodontitis; it might facilitate glycemic control and, furthermore, it might prevent and inhibit the development of arteriosclerosis.

In conclusion, the present study showed, for the first time, that effective glycemic control ameliorated periodontitis in type 2 diabetic patients without periodontal treatment

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through ameliorating inflammation at the gingival site of periodontal tissue. Further large-scale, multicenter studies are required to clarify the mechanisms by which improved glycemic control improves periodontitis in type 2 diabetic patients with periodontitis.

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