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ORIGINAL ARTICLE

The effect of periodontal treatment on metabolic control of type 1 diabetes mellitus

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Abstract The objective of this investigation was to study the effect of nonsurgical periodontal treatment, with or without systemic administration of doxycycline, on the metabolic control of patients with type 1 diabetes. Sixty type 1 diabetic subjects with moderate to severe periodontitis were recruited. Periodontal parameters were measured, and blood samples were obtained to evaluate glycosylated hemoglobin (HbA1c). Group 1 (30 patients) was treated with scaling, root planning, and chlorhexidine rinses for 3 months in conjunction with systemic administration of doxycycline (100 mg once a day for 15 days). Group 2 (30 patients) received the same periodontal treatment but without the use of doxycycline. The paired Student *t*-test was used to detect differences between glycosylated hemoglobin means before and 3 months after periodontal treatment in group 1 and group 2 separately. Changes in mean HbA1c after treatment were 0.07% in group 1 and –0.06% in group 2, which were not statistically significant after 3 months. Significant changes were not found even in patients with the best response to periodontal treatment. Periodontal treatment in type 1 diabetic patients after 3 months follow-up did not improve metabolic control of diabetes as measured by glycosylated hemoglobin.

Keywords Type 1 diabetes mellitus · Periodontal treatment · Doxycyline · Glycosylated hemoglobin · Diabetes metabolic control

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Introduction

Type 1 diabetes mellitus is a type of diabetes caused by cell-mediated autoimmune destruction of the insulin-producing β cells in the pancreas. The rate of β-cell destruction is variable, but the process ends up with an absolute insulin deficiency [18]. Treatment of this disease is based on subcutaneous administration of insulin, regular physical exercise, diet, and weight control. Pancreas or β-cell transplantation could also be performed in certain cases [15].

A relationship between diabetes mellitus and periodontal disease is supported by numerous publications. It is well established that diabetes increases the prevalence, severity, and progression of periodontal disease [7, 21, 33, 35]. Certain factors such as the vascular endothelial growth factor are augmented in the periodontium of diabetic subjects [25]. Taylor found that 44 out of 48 publications showed that diabetes had an influence over periodontal disease. The articles that showed no relationship were

isolated cases [34]. However, the influence of periodontal disease on diabetes mellitus is not so well established because there is not much literature available, and the contradictory results are shown by some studies.

Severe periodontal disease seems to increase the risk of poorly controlled diabetes mellitus [8, 32]. Some publications have shown that nonsurgical periodontal treatment improved glycemic control in diabetes [10, 11, 13, 19, 20, 23, 31]; in these studies, doxycycline was frequently included as part of the therapy. Chronic Gram-negative infections, such as periodontal disease, could induce insulin resistance and worsen metabolic control in diabetes similar to that demonstrated for acute infections [26, 38]. Consequently, periodontal treatment might improve glycemic control in diabetes by reducing periodontal infection and improving the effect of insulin.

Literature has also shown, however, that periodontal treatment had no effect on metabolic control in diabetes [1, 6, 27, 30, 36, 37]. Reasons to explain these results are not clear, factors such as type of diabetes, periodontal disease severity, effectiveness of periodontal treatment, or control of diabetes medication, diet, or exercise may be involved. Taylor GW, in one of its reviews, stated that more clinical and controlled studies are needed to clarify the influence of periodontal disease and its treatment on the metabolic control in diabetes [34].

To clarify this issue, type 1 and 2 diabetic subjects must not be included in the same study because type 1 diabetic patients may respond differently than type 2. It would also be interesting to evaluate whether the effect of periodontal treatment on diabetes is greater in those patients that show the best periodontal response and whether periodontal treatment has a greater impact on diabetic patients with poorer metabolic control of their disease. Accordingly, the purpose of this investigation was to study the effect of nonsurgical periodontal treatment, with or without systemic administration of doxycycline on the metabolic control of patients with type I diabetes mellitus, analyzing also the effects in patients with the best periodontal response to treatment and in patients with the poorer diabetic metabolic control at baseline. Periodontal response of these patients to nonsurgical periodontal treatment has already been reported [17]. Now, all the laboratory data has been gathered to study the influence of nonsurgical periodontal treatment on type 1 diabetes control.

Material and methods

Study population

This randomized clinical study was conducted at a single center (Dr. Peset University Hospital in Valencia, Spain) from September 2003 to March 2004. Study protocol was approved by Dr. Peset Hospital Research Committee, and participants signed an approved consent form to participate in the study. Sixty type 1 diabetic subjects with moderate to severe periodontitis (30 females and 30 males) ranging in age from 19 to 61 (mean 35.3 ± 9 years) were recruited from the endocrinology division for this single-blind study. Type 1 diabetic patients were diagnosed according to the criteria published by the American Diabetes Association in 1997 [3], and they were treated by insulin, diet, and physical exercise recommendations.

Participants were selected for this study according to specific inclusion criteria. They had diabetes for more than 1 year, and none of them had other major illnesses or severe diabetic complications. Patients had not taken antibiotics for at least 3 months prior to baseline and did not have any active infection. A panoramic radiograph was taken to assure that neither extensive caries nor periapical lesions were present. Eligible subjects had 14 or more natural teeth, of which at least five had a site with probing pocket depth (PPD) ≥ 5 mm and clinical attachment level (CAL) ≥ 3 mm. From this point, subjects with moderate to severe periodontal disease were included. They had not had periodontal treatment or professional cleaning of the teeth for at least 1 year prior to the study. Pregnant and breastfeeding women were excluded. Diabetic control was measured by glycosylated hemoglobin A1c (HbA1c) in blood samples and was variable within the groups. Individuals were classified in good, moderate, and poor metabolic control according to the American Diabetes Association criteria [4]. Twenty-two patients (37%) had good diabetic control (HbA1c < 7%), 15 individuals (25%) had moderate control (HbA1c between 7% and 8%), and 38% of the sample (23 diabetic individuals) had poor metabolic control (HbA1c > 8%). Most of the patients selected were nonsmokers (38 patients), some smoked less than 15 cigarettes per day (11 patients), and the rest were heavy smokers consuming more than 15 cigarettes per day (11 patients). This sample was the same as the one used by Llambés et al. in 2005 to study the periodontal response on type 1 diabetic patients [17].

Laboratory and periodontal examination

Fasting blood samples were obtained early in the morning, and A1c glycosylated hemoglobin (HbA1c) was measured. HbA1c values were determined by high-pressure liquid chromatography[1] and expressed in percentages. HbA1c values between 6% and 7% were considered as a sign of good control of the diabetes, HbA1c values between 7.1% and 8% indicated moderate control, and HbA1c values >8% were designated as poor control of the diabetes. Fructos-

[1] Adams TM, HA-8160, Menarini Diagnostics

amine was measured by using the enzymatic method,[2] and normal values for fructosamine according to this method range from 0 to 285 μmol/L. They received an oral soft tissue examination including periodontal measurements of plaque index (PI), bleeding on probing (BOP), PPD, and CAL for all teeth present. O'Leary PI was measured in four areas per tooth [22] (mesiobuccal, midbuccal, distobuccal, and midlingual), and the other periodontal parameters were registered on six sites by tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual).

Study design

One hundred thirty-six type 1 diabetic patients from Dr. Peset Hospital were screened, and 72 were found to match the selection criteria. They were told not to change their diet, exercise, or insulin dose unless absolutely necessary and to inform investigators if any change occurred. HbA1c values at the screening time, 3 month previous to the beginning of the study, were obtained from the medical records of the patients to evaluate changes in this parameter before the initiation of the investigation. These HbA1c values from the medical records were obtained in the same center and were made by the same laboratory that was used for this clinical protocol. The sample was randomized, allowing the subjects to self-select a coded number contained in an envelope; this number identified the group to which the patient was assigned (group 1 or 2). Baseline examination was performed 3 months after screening and within the 30 days prior to the beginning of the periodontal treatment. All periodontal measurements were taken by only one trained periodontist. This clinician was blinded to the treatment applied in each patient and care was taken that subjects did not disclose their group category.

Group 1 had baseline HbA1c measured just before the beginning of the periodontal treatment. Subjects were instructed on the modified Bass brushing technique and interproximal cleaning. After that, scaling and root planing (SRP) under local anesthesia was performed by two trained dental hygienists using ultrasonic devices[3] and manual Gracey curets.[4] SRP was scheduled in one or two sessions 1 week apart according to the periodontal disease severity and the number of teeth present. No less than 30 min were assigned to each quadrant. Chlorhexidine rinses[5] were prescribed after SRP (20 ml during 30 s, twice daily) and maintained for 12 weeks to the end of the clinical protocol. No other rinses or toothpaste was used during the study. Individuals were placed on doxycycline 100 mg (b.i.d. for the first day and then one capsule per day thereafter) for 15 days.

Group 2 had the same treatment as group 1 with the exception of the doxycycline which was not used in this group.

Twelve weeks after treatment, blood samples were taken again, and HbA1c was analyzed. At the same time, periodontal parameters were measured again. Compliance with use of oral hygiene devices, chlorhexidine, and doxycycline was assessed with a personal oral interview with the participants. It was classified as good (instructions were followed), fair or poor (prescriptions were not followed).

At the end of the study, 12 subjects were dropped out because they did not follow appropriately the study protocol or due to active acute infections during posttreatment period. Finally, 30 patients remained in group 1 and 30 patients in group 2.

Data analysis

Sample size in groups 1 and 2 has enough statistical power to detect HbA1c changes ≥0.3% with α risk of 0.05. However, sample size on each group was not enough to detect changes in HbA1c below 0.3%. The statistical test performed to analyze the results was the paired Student *t*-test to compare laboratory changes within the same patient. All samples had a normal distribution as showed by the Shapiro–Wilk test. Means and standard deviations were given to describe values. Linear regression analysis was also calculated to study the influence of certain factors on HbA1c changes after periodontal treatment. Factors such as age, sex, diabetes duration and complications, smoking habits, plaque and bleeding index, percentage of pockets ≥6 mm and mean PPD, mean CAL, and percentage of sites with CAL ≥ 3 mm were included in this regression analysis.

Results

Differences between groups for sex, age, diabetes control, and smoking were minimal (Table 1). In groups 1 and 2, 19 patients were nonsmokers, five from group 1 and six from group 2 smoked less than 15 cigarettes per day, and finally, six diabetic patients from group 1 and five from group 2 smoked 15 or more cigarettes per day. The analysis of baseline data across all clinical periodontal parameters was almost within the same range, and statistical analysis did not show any significant difference between the two groups at baseline visit ($p < 0.05$).

HbA1c was expressed in percentages and was obtained at the screening time, from the subjects medical records.

[2] Itachi 747, Roche

[3] Cavitron, Dentsply Company, Madrid, Spain

[4] Gracey, HuFriedy Instruments, Chicago, IL, USA

[5] PerioAid 0.2%, Dentaid Company, Barcelona, Spain

Table 1 Sample description

	Group 1	Group 2
Number of type 1 diabetics	30	30
Mean age (years; mean ± SD)	36.8±9.5	33.8±9
Female	13 (43%)	17 (57%)
Male	17 (57%)	13 (43%)
Diabetes duration (years; mean ± SD)	14±7.5	15±10
HbA1c (%) number of diabetics and %		
<7%	13 (43%)	9 (30%)
7–7.9%	5 (17%)	10 (33%)
≥8%	12 (40%)	11 (37%)
Smoking habits		
Nonsmokers	19	19
<15 cig/day	5	6
≥15 cig/day	6	5
Baseline periodontal parameters		
PI (%)	64	59
BOP (%)	65	66
Sites with PPD 1–3 mm (%)	58	58
Sites with PPD 4–5 mm (%)	35	37
Sites with PPD≥6 mm (%)	7	5
Mean PPD (mm)	3.43	3.35
Sites with CAL≥3 mm (%)	54	46
Mean CAL (mm)	2.94	2.65

Twenty-eight subjects who participated in the study had this data available. HbA1c value at the screening time was compared with HbA1c at baseline, just before periodontal treatment that was performed 3 months after screening. The goal of this analysis was to observe how HbA1c changed in 3 months in the absence of dental treatment. Mean HbA1c and standard deviation 3 months previous to the study was 7.9 ± 1.1% and at baseline was 7.7 ± 1.2%. This 0.2% reduction was not statistically significant. However, if absolute values were considered, we were able to detect that HbA1c had a mean oscillation of 0.48% during this time frame. The minimum change experienced was 0%, and the maximum change was 1.8%.

All patients from group 1 followed doxycycline prescriptions, 18 patients from group 1 and 18 from group 2 had good compliance and 12 patients from each group had a fair compliance with oral hygiene instructions and chlorhexidine rinses.

At baseline, mean PI was 64% for group 1 and 59% for group 2. Mean BOP was 65% in group 1 and 66% on group 2. PPD and CAL distribution can be observed in Table 1. Baseline data across all clinical periodontal parameters was almost within the same range and statistical analysis did not show any significant difference between the two groups at baseline visit ($p > 0.05$).

Both groups showed very good periodontal response to treatment; PI, BOP, PPD, and CAL showed a very significant improvement as was published in a previous paper [25]. However, after this successful nonsurgical periodontal treatment, HbA1c levels did not change significantly.

HbA1c changes after periodontal treatment were analyzed in group 1 (30 patients) and in group 2 (30 patients). Mean baseline HbA1c was 7.64 ± 1.81% in group 1 (doxycycline group) and 7.51 ± 1.36% in group 2, and 3 months after treatment, mean HbA1c was 7.71 ± 1.74% and 7.45 ± 1.29%, respectively. Mean HbA1c variations were 0.07 in group 1 and –0.06 in group 2, and these differences were not statistically significant (Table 2). Two subjects in group 1 and five in group 2 (12% of the population) had HbA1c reduction of ≥0.5%. In contrast, six subjects in group 1 and five in group 2 (18% of total population) increased their HbA1c ≥ 0.5%. A total of 17 patients (28% of the total population) had HbA1c below 6.5% after treatment, but only three of these patients had an initial HbA1c ≥ 6.5%. Linear regression analysis did not show any correlation of the factors studied on HbA1c changes after treatment (dependent variable). This model included as independent variables factors such as age, sex, diabetes duration and complications, smoking habits, plaque and bleeding index, percentage of pockets ≥6 mm and mean PPD, mean CAL, and percentage of sites with CAL ≥ 3 mm.

Fructosamine was also measured in groups 1 and 2 before and after treatment. This parameter has been used in other studies [21] and gives information about the glycemic control during the last 3–4 weeks [2, 5]. Group 1 had 354 ± 87 μmol/L at baseline and 358 ± 103 μmol/L after treatment; group 2 registered 342 ± 68 μmol/L at baseline and 342 ± 90 μmol/L at the end of the study, which showed

Table 2 HbA1c values (%) at baseline and 3 months after treatment

Group	Initial HbA1c (baseline)		Final HbA1c (3 months posttreatment)		Difference	*P* value
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)	
Group 1 (n=30)	7.64 (1.81)	7.5 (5.1–13.1)	7.71 (1.74)	7.6 (5.2–12.2)	+0.07 (0.47)	0.44*
Group 2 (n=30)	7.51 (1.36)	7.4 (3.8–10)	7.45 (1.29)	7.4 (3.7–10)	-0.06 (0.5)	0.52*

The mean changes from baseline to the 3 month examination are also presented
*No statistical difference

Table 3 Fructosamine values (μmol/L) at baseline and 3 months after treatment

Group	Initial fructosamine (baseline)		Final fructosamine (3 months posttreatment)		Difference	*P* value
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)	
Group 1 (n=30)	354 (87)	333 (200–517)	358 (103)	338 (228–665)	+4 (71)	0.74*
Group 2 (n=30)	342 (68)	338 (187–526)	342 (90)	340 (235–504)	0 (89)	0.99*

The mean changes from baseline to the 3 month examination are also presented
*No statistical difference

that no significant mean difference from baseline occurred after treatment (Table 3).

Insulin doses were quite stable in both groups. Eighteen patients from group 1 and 20 patients from group 2 did not change their insulin dose during the clinical investigation. Twelve patients changed insulin doses in group 1, but half of them had a variation of less than three units a day. In group 2, ten patients modified insulin doses during the study, and eight of them had changes of less than three units a day.

HbA1c changes were also studied in the patients with the best periodontal response to treatment. To achieve this goal, patients with the highest BOP and PPD reduction after periodontal treatment were selected from group 1 and 2. A total of 21 patients with BOP reduction above 60% was obtained; ten of these patients came from group 1, and 11 patients came from group 2. In this group of patients with the best BOP reduction, HbA1c was 7.16 ± 1.27% initially and 7.16 ± 1.25% at the reevaluation. As it can be seen, data showed minimal changes in HbA1c values after periodontal treatment. Another group was made with patients with the most significant PPD reduction after therapy. For this purpose, 30 patients were selected, and these patients had reduced the mean baseline PPD to 18% or more. Sixteen of these patients were from group 1 and 14 were from group 2. Mean HbA1c was 7.21 ± 1.31% at baseline and 7.21 ± 1.27% after treatment, which again showed no changes in diabetes metabolic control (Table 4).

Patients with the worst metabolic diabetes control at baseline were selected from groups 1 and 2, and HbA1c oscillations were analyzed. Thirty patients with initial HbA1c ranging from 7.5% to 13% were included, 16 from group 1 and 14 from group 2. Mean HbA1c was 8.8 ± 1.2% initially and 8.7 ± 1.1% 3 months after periodontal treatment, and these minimal changes were not significant. These results suggest that HbA1c might not change after periodontal treatment in type 1 diabetic patients, even in the cases with the worst diabetic metabolic control (Table 4). Ten patients from groups 1 and 2 had initial HbA1c ≥ 9%, mean HbA1c was 10% in this group at baseline, and after periodontal treatment, mean HbA1c had a 0.1% reduction. Other 33 patients from the total sample had HbA1c from 6.5% to 8.9% before treatment, mean HbA1c was 7.7%. This parameter did not change during the study in this group.

Differences between smokers and nonsmokers regarding HbA1c at baseline and after periodontal treatment were not analyzed in this study because the smokers group was very small. Only six patients in group 1 and five patients in group 2 smoked ≥15 cigarettes a day. Thus, statistical analysis of this comparison was not possible.

Discussion

It is accepted that HbA1c is a good parameter to evaluate diabetes metabolic variations over 2 to 3 months [12]. This analytic value is widely used in the periodontal literature to evaluate the influence of periodontal treatment on the control of diabetes. Most of the studies compare HbA1c baseline values with the results obtained 3 months after periodontal treatment [11, 13, 19]; however, it is not very common to evaluate the HbA1c changes during the 2–

Table 4 Mean HbA1c changes (%) in the subgroups with the best periodontal response to treatment and with the worst diabetes control at baseline

	Initial HbA1c (baseline)		Final HbA1c (3 months posttreatment)		Difference	P value
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)	Mean (SD)	
Patients with ≥60% BOP reduction (n=21)	7.157 (1.27)	8.9 (5.1–9.7)	7.162 (1.25)	8.6 (5.2–9.9)	0.005 (0.48)	0.98*
Patients with ≥18% mean PPD reduction (n=30)	7.21 (1.31)	7.5 (3.8–9.7)	7.21 (1.27)	7.7 (3.7–9.3)	0 (0.47)	1.00*
Patients with ≥7.5% HbA1c at baseline (n=30)	8.8 (1.2)	8.6 (7.5–13.1)	8.7 (1.1)	8.5 (7.1–12.2)	-0.1 (0.6)	0.65*

*No statistical difference

3 months previous to periodontal treatment. The present investigation reports that HbA1c had a mean oscillation of 0.2% over 2–3 months where no periodontal treatment was performed. These data might show that HbA1c can change in type 1 diabetic patients, in the absence of dental treatment. Other authors have shown a 1% oscillation of this parameter over 1 year without performing any dental treatment [31]. Maybe, even when insulin doses, diet, and exercise are under control, diabetes metabolic control is difficult to achieve, and consequently, some minor changes in HbA1c have to be expected in type 1 diabetic patients in a 3-month interval.

The present study has found that periodontal treatment with or without doxycycline did not have any beneficial influence on type 1 diabetes glycemic control after 3 months follow-up, as seen by mean HbA1c and fructosamine values before and after treatment. Our data are consistent with those reported by other authors in the literature [1, 6, 27, 30, 36, 37]. Patients included in this study had moderate to severe periodontal disease, and their response to nonsurgical periodontal treatment could be considered successful, as shown in a previous publication [22]. Consequently, it could be hypothesized that periodontal disease is a chronic infection, and maybe its influence on type 1 diabetes metabolism is not as evident as other acute infections [26, 38]. Factors such as insulin dose, diet, and exercise could play a greater role, and benefits from periodontal infection control may not be detected. In this clinical protocol, the patients with the best periodontal response (the highest reductions in BOP and mean PPD) were investigated separately. No changes in HbA1c were detected even in these cases, which showed again that as far as type 1 diabetes control is concerned, there may be other factors more important than treatment of the periodontal infection and inflammation, even when systemic doxycycline was used. One study published by Skaleric et al. showed HbA1c reduction after scaling and root planning combined with local minocycline on the periodontal pockets, but this reduction was not statistically significant. [29].

The clinical studies reviewed above have treated type 1 diabetic patients mainly, but other studies have found positive effects of periodontal treatment on diabetes metabolic control [10, 11, 13, 19, 20, 23, 31]. Most of these authors have worked with type 2 diabetic patients. Maybe effects of periodontal treatment can be easily detected in type 2 diabetic subjects because the influence of the main factors (diabetes medication, diet, and exercise) may not be as strong as in type 1 diabetic patients. Type 1 diabetic individuals cannot produce insulin by themselves at all; consequently, minor changes in diabetes medication, diet, and physical exercise produce important changes in diabetes metabolic control, making difficult to detect any influence of periodontal treatment on diabetes. Type 2 diabetic patients usually can produce some insulin by themselves, so changes on their diet and physical activity do not affect HbA1c as significantly as type 1 diabetic subjects, and benefits of treatment of a chronic infection such as periodontal disease might be detected easily on these patients. It also must be considered that these authors reported a better improvement in diabetes metabolic control when doxycycline was associated [10, 11, 13, 19]. These data might suggest that doxycycline by itself may help to improve diabetes control. Tetracyclines have shown their capacity to inhibit protein glycosilation in rats [24] and their ability to diminish monocyte production of tumor necrosis factor α and interleukin 1β [28], which are factors that produce an insulin antagonism [9, 16]. A recent meta-analysis published by Janket et al. on 2005 showed that HbA1c was reduced more efficiently on type 2 diabetic patients treated with scaling and root planning, specially when antibiotics were associated; however, even in those cases, reduction was not statistically significant [14].

Thirty-seven percent of the samples were at the ADA treatment goal of HbA1c $\leq$ 7%; they had good diabetes metabolic control and on those patients, it might be difficult to reduce HbA1c after periodontal treatment even more. To avoid this problem, patients with the worst control of diabetes at baseline were selected and studied; however, they did not experience any HbA1c improvement after successful periodontal treatment. Maybe these patients did not have good control of insulin, diet, and exercise, and this would make more difficult to detect any effect of periodontal treatment.

To study patients with the best periodontal response and with the worst diabetes metabolic control at baseline, an attempt was made to establish subgroups as close as possible to 30 individuals each so the *t*-test could have some statistical significance. This was impossible to achieve for every subgroup. This analysis could have been more powerful if sample size in these subgroups would have been increased, but that was not possible in this study.

Within the limitations of the present study, our data indicate that periodontal treatment in type 1 diabetic patients after 3 months follow-up did not improve the metabolic control of diabetes as measured by glycosylated hemoglobin. Even in those patients with the best periodontal response or in those with the worst diabetic metabolic control at baseline, no differences after treatment could be found. However, more clinical prospective and randomized studies are needed to establish definitive conclusions. In these studies, type 1 diabetic patients must not be mixed with type 2 diabetic individuals because their metabolic behavior after periodontal treatment may be different.

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