J Clin Periodontol 2005; 32: 915–920 doi: 10.1111/j.1600-051X.2005.00736.x

Journal of Clinical Periodontology

Effect of non-surgical periodontal treatment with or without doxycycline on the periodontium of type 1 diabetic patients

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Llambés F, Silvestre F-J, Hernández-Mijares A, Guiha R, Caffesse R. Effect of non-surgical periodontal treatment with or without doxycycline on the periodontium of type 1 diabetic patients. J Clin Peridontol 2005; 32: 915–920. doi: 10.1111/j.1600-051X.2005.00736.x. © Blackwell Munksgaard, 2005.

Abstract

Aim: The present investigation was performed to study how type 1 diabetics responded to non-surgical periodontal treatment with and without adjunctive doxycycline.

Method: Sixty diabetic type 1 patients (mean age 35.3 ± 9 years) with moderate-to-severe periodontal disease were selected and divided into two groups of 30 patients each. Both groups were sex and age matched and had similar amounts of periodontal destruction. Plaque index (PI), bleeding on probing (BOP), probing depth (PD) and clinical attachment levels (CAL) were recorded. Group 1 (30 patients) was treated with oral hygiene instruction, scaling and root planing, chlorhexidine rinses twice a day and doxycycline (100 mg/day for 15 days). Group 2 (30 patients) had the same treatment but without doxycycline. After 12 weeks their periodontal condition was reevaluated.

Results: After treatment, both groups had a significant improvement in all periodontal parameters, since PI, BOP, probing pocket depth (PPD) and CAL were significantly reduced. However, the reduction in PD in pockets $\geqslant$6 mm and in BOP were more evident when doxycycline was used (group 1). Differences between groups for these parameters were statistically significant ($p = 0.03$).

Conclusion: Although both periodontal treatment regimens are effective in type 1 diabetics, the use of doxycycline as an adjunct, provided more significant results when good plaque control was achieved.

Key words: diabetes; doxycycline; periodontal disease; periodontal therapy; root planing

Accepted for publication 29 October 2004

Diabetes mellitus is an endocrine–metabolic disease produced by non-well-controlled blood glucose levels because of deficiencies in insulin production or activity (Owen & Shuman 1992). Type 1 diabetes is produced by an autoinmune destruction of β pancreatic cells and type 2 diabetes appears when tissues increase their resistance to insulin or when pancreatic insulin production diminishes. The American Diabetes Association published in 1997 the last criteria for the diagnosis of diabetes mellitus. According to this criteria, a patient will be diabetic if: (1) classic symptoms of diabetes appear plus plasma glucose $\geqslant$200 mg/dl; (2) fasting plasma glucose $\geqslant$126 mg/dl or (3) 2-h post-prandial glucose $\geqslant$200 mg/dl during an oral glucose tolerance test. Whatever method is used, it must be confirmed on a subsequent day by using any one of the three methods previously described (American Diabetes Association, 1997).

Clinical and epidemiological studies have shown that patients with a long history of diabetes seem to have more periodontal tissue breakdown than age-matched, non-diabetic controls (Belting et al. 1964, Cohen et al. 1970, Thorstensson & Hugoson 1993). Prevalence, severity and progression of the periodontitis is higher in diabetic patients (Cianciola et al. 1982, Nelson et al. 1990, Shlossman et al. 1990, Papapanou 1996, Taylor et al. 1998). In an extensive literature review, Taylor (2001) reported that 44 out of 48 reviewed articles showed an increased severity of periodontal destruction in diabetic patients.

On the other hand, diabetic subjects have a good response to appropriate periodontal treatment. The short- and

long-term periodontal response is equal to non-diabetic patient (Bay et al. 1974, Westfelt et al. 1996, Christgau et al. 1998). However if diabetes is not well controlled, periodontal recurrences will be more frequent and periodontal disease more difficult to control (Seppälä et al. 1993, Tervonen & Karjalainen 1997).

The influence of diabetes over periodontal disease is well established, but the effect of periodontal disease and its treatment over the diabetes control is not so clear. Some authors found no influence of periodontal disease and its treatment on diabetes (Wolf 1977, Seppälä et al. 1993, Aldridge et al. 1995, Westfelt et al. 1996, Smith et al. 1996, Christgau et al. 1998). Others have shown that non-surgical periodontal treatment could improve diabetes metabolic control, especially when doxycycline was used as an adjunct (Miller et al. 1992, Grossi et al. 1996, 1997, Iwamoto et al. 2001).

Doxycycline is a tetracycline derivative which has been widely used to treat localized aggressive forms of periodontal disease (Genco et al. 1981, Slots & Rosling 1983). The properties of doxycycline seem to be useful in periodontics, not only because of its antibacterial effect, but also because of the inhibition of the inflammatory periodontal response (Webster et al. 1994, Shapira et al. 1997) and its anti-colagenolitic effect (Lauhio et al. 1992, Sorsa et al. 1993). Nevertheless, in placebo-controlled trials of chronic periodontitis, only slight differences were noted in the change of mean probing depths (PDs) and attachment levels between patients receiving tetracycline or placebo as an adjunct to periodontal mechanical therapy (Listgarten et al. 1978, Slots et al. 1979, Lindhe et al. 1983). Grossi et al. studied periodontal response to treatment on type 2 diabetic patients, and saw that when doxycycline was associated to non-surgical periodontal therapy, there was a trend to find more pocket depth reduction and more gain in clinical attachment levels (CAL), however, these differences were not clear and were not statistically significant (Grossi et al. 1996, 1997).

According to the review of the literature, doxycycline seems to be beneficial for the control of diabetes, but its effect on periodontal tissues of diabetic patients is not well established. The aim of the present trial was to study how type 1 diabetic patients responded to non-surgical periodontal treatment with or without adjunctive doxycycline.

Materials and Methods

This randomized clinical study was conducted at a single centre (Dr. Peset University Hospital in Valencia, Spain). Sixty type 1 diabetic subjects with moderate-to-severe periodontitis (30 females and 30 males) ranging in age from 19 and 61 years (mean 35.3 ± 9 years) were recruited from the Endocrinology Division for this single-blinded study.

The subjects controlled their diabetes by insulin, diet and physical exercise recommendations. They had been diabetic for more than 1 year with no other major illness or severe diabetic complications. Patients had not taken antibiotics for at least 3 months prior to baseline and did not have any active infection. Pregnant and breast-feeding women were excluded. Diabetic control was measured by glycosylated haemoglobin A1c (HbA1c) in blood samples and was variable within the group: 22 patients (37%) had good diabetic control (HbA1c $<7\%$), 15 individuals (25%) had moderate control (HbA1c between 7% and 8%) and 23 subjects (38%) had poor metabolic control (HbA1c $>8\%$). Most of the patients selected were non-smokers (38 patients), some smoked less than 15 cigarettes/day (11 patients) and the rest were heavy smokers consuming more than 15 cigarettes/day (11 patients). A panoramic radiograph was taken to assure that neither extensive caries nor periapical lesions were present. The subjects had a minimum of 14 natural teeth with at least five areas with probing pocket depth (PPD) $\geqslant 5$ mm and CAL $\geqslant 3$ mm. They did not have periodontal treatment or professional cleaning of the teeth for at least 1 year prior to the study (Table 1).

All subjects signed a consent form approved by the institutional review board. 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 (O'Leary et al. 1972) was measured in four areas per tooth (mesiobuccal, midbuccal, distobuccal and midlingual) and the other periodontal parameters were registered on six sites by tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual). All periodontal measurements were taken by only one trained periodontist. The study was randomized by allowing the subjects to self-select a coded number contained in an envelope which identified the group that the patient was going to be assigned to (group 1 or 2). Clinicians conducting the study were blinded to the treatment applied in each patient and care was taken that subjects did not disclose their group categories to the clinicians performing the study. When a patient dropped out of the study, a new patient that matched the selection criteria was included in order to maintain the sample size which consisted of 30 patients in each group. In the present study, 12 patients dropped out and were replaced by 12 new patients. Description of both groups can be seen in Table 1.

Group 1 (test group) had 30 type 1 diabetic subjects (17 females and 13 males) ranging in age from 21 to 60 years (mean 36.8 ± 9.5 years). Subjects were instructed to use the modified Bass brushing technique and dental floss or interproximal toothbrushes depending on the size of the interproximal spaces. After that, scaling and root planing

Table 1. Sample description

	Total	Group 1	Group 2
Number of type 1 diabetics	60	30	30
Mean age (years) (mean ± SD)	35.3 ± 9	36.8 ± 9.5	33.8 ± 9
Female	30	13 (43%)	17 (57%)
Male	30	17 (57%)	13 (43%)
Diabetes duration (years) (mean ± SD)	15 ± 9	14 ± 7.5	15 ± 10
HbA1c (%)			
<7	22	13	9
7–7.9	15	5	10
⩾8	23	12	11
Smoking habits			
Non-smokers	38	19	19
<15 cigarettes/day	11	5	6
⩾15 cigarettes/day	11	6	5

HbA1c, haemoglobin A1c.

(SRP) under local anaesthesia was performed by two-trained dental hygienists using ultrasonic devices (Cavitron, Dentsply Company, Madrid, Spain) and manual Gracey curets (Gracey, HuFriedy Instruments, Chicago, IL, USA). SRP was scheduled in one or two sessions according to the periodontal disease severity and the number of teeth present. No less than 30 min. were assigned to each quadrant. Chlorhexidine rinses (PerioAid 0.2%, Dentaid Company, Barcelona, Spain) were prescribed after SRP (20 ml during 30 s, 2 × 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 fist day and then 1 capsule/day thereafter) for 15 days.

Group 2 (control group) consisted of 30 type 1 diabetic subjects (13 females and 17 males) ranging in age from 19–61 years (mean 33.8 ± 9 years). These patients had the same treatment as the test group with the exception of the doxycycline, which was not used in this group.

Periodontal reevaluation which included the same indices measured during baseline was performed 12 weeks after the SRP by the same periodontist, who was not aware of the group the patients belonged to. All teeth were recorded with the exception of the third molars. A questionnaire was given to the participants to evaluate how well they did follow the oral hygiene instructions and their cooperation was assessed as good, fair or poor. Patients with controlled periodontal disease were referred to their general dentist for maintenance, but if further periodontal treatment was required, patients were advised to be referred to a periodontist in the city.

The statistical test performed to analyse the results was Student's *t*-test since all samples had a normal distribution as showed by the Shapiro–Wilk test. Student's *t*-test for paired variables was used to study changes within the groups and Student's *t*-test for independent variables was applied to compare group 1 with group 2. Three levels of statistical significance were established ($^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$). Means and standard deviations were given to describe values. χ^2 test was used to compare groups when pocket changes were studied considering pocket variations expressed in millimetres.

Results

Differences between groups for sex, age, diabetes control and smoking were minimal (Table 1). PI and BOP was evaluated in percentages. PD was divided in 1–3 mm pockets, 4–5 mm pockets, ⩾6 mm pockets and mean PD. Mean CAL and sites with CAL ⩾3 mm were also calculated. At baseline, mean PI was 64% for group 1 and 59% for group 2. Mean BOP was 65% in group 1 and 66% in group 2. In group 1 ($n=30$), 19 patients had 1/3 of its PPD⩾4 mm and five of them had 1/10 of its PPD⩾6 mm, In group 2 ($n=30$), 18 subjects had 1/3 of its PPD⩾4 mm and three of them had 1/10 of its PPD⩾6 mm. Regarding CAL, 54% of the explored sites had CAL⩾3 mm in group 1 and group 2 had 46% of these sites. 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 ($p>0.05$).

Both groups showed very good periodontal response to treatment. Group 1 (SRP+doxycycline) reduced its PI from 64 ± 19% to 21 ± 17% and BOP from 65 ± 17% to 27 ± 14%. Mean PD change from 3.43 ± 0.64 to 2.69 ± 0.32 mm. Significant changes in all three pockets categories were also seen, pockets ⩾6 mm diminished from 7% to 1%, 4–5 mm pockets changed from 35% to 13% and 1–3 mm pockets increased from 58% to 86% because of the reduction of PD in the moderate and severe groups. Mean CAL went from 2.94 ± 1.31 to 2.49 ± 0.86 mm and sites with CAL⩾3 mm were also reduced, changing from 54% to 41%. Group 2 (SRP) had also a marked improvement of the periodontal parameters. PI changed from 59 ± 20% to 21 ± 23% and BOP from 66 ± 17% to 36 ± 20% (Table 2). PD also had significant variations, mean PD varied from 3.35 ± 0.66 to

Table 2. Percentage of sites with plaque (PI) and bleeding on probing (BOP) at baseline (BL) and 3 months after treatment

Index	Group 1 (test)			Group 2 (control)		
	baseline	3 months	difference	baseline	3 months	difference
PI	64 (19)	21 (17)	-43^{***}(24)	59 (20)	21 (13)	-38^{***}(22)
BOP	65 (17)	27 (14)	-38^{***}(16)	66 (17)	36 (20)	-30^{***}(18)

Mean differences from baseline to 3 months are also presented. Standard deviations in parentheses.
$^{***}p<0.001$. *t*-test analysis.

Table 3. Percentage of sites with pockets of different categories (1–3, 4–5 and ⩾6 mm) and mean probing pocket depth (PPD)

Index	Group 1 (test)			Group 2 (control)		
	baseline	3 months	difference	baseline	3 months	difference
Pockets (mm)						
1–3	58 (17)	86 (9)	28 (13)	58 (19)	83 (13)	25 (13)
4–5	35 (11)	13 (8)	− 22 (11)	37 (14)	16 (11)	− 21 (11)
⩾6	7 (11)	1 (2)	-6^{**}(11)	5 (11)	1 (3)	-4^{*}(9)
Mean PPD (mm)	3.43 (0.64)	2.69 (0.32)	-0.74^{***}(0.46)	3.35 (0.66)	2.70 (0.41)	-0.65^{***}(0.33)

Baseline, 3 months and mean differences. Standard deviations in parentheses.
$^{*}p<0{,}05$, $^{**}p<0{,}01$, $^{***}p<0{,}001$. *t*-test analysis.

Table 4. Percentage of sites with loss of attachment ⩾3 mm and mean clinical attachment level (CAL)

Index	Group 1 (test)			Group 2 (control)		
	baseline	3 months	difference	baseline	3 months	difference
CAL ⩾3 mm	54 (27)	41 (25)	−13***(11)	46 (28)	35 (29)	−11***(10)
Mean CAL (mm)	2.94 (1.31)	2.49 (0.86)	−0.45***(0.55)	2.65 (1.25)	2.23 (1.19)	−0.42 mm***(0.37)

Baseline, 3 months and mean differences. Standard deviations in parentheses.
*$p<0{,}05$, **$p<0{,}01$, ***$p<0{,}001$. *t*-test analysis.

Table 5. Percentage of periodontal index improvement after treatment

Index	Group 1 (test)	Group 2 (control)	Differences between groups
PI	65 (30)	62 (29)	3
BOP	59 (18)	46 (27)	13*
PPD⩾6 mm	88 (22)	65 (43)	23*
Mean PPD	20 (9)	19 (6)	1
CAL⩾3 mm	25 (23)	33 (29)	−8
Mean CAL	12 (13)	17 (17)	−5

Differences between groups are also shown. Standard deviations in parentheses.
*$p<0{,}05$. *t*-test analysis.
PI, plaque index; BOP, bleeding on probing; PPD, probing pocket depth; CAL, clinical attachment level.

2.70 ± 0.41 mm, pockets ⩾6 mm from 5% to 1%, 4–5 mm pockets from 37% to 16%, 1–3 mm pockets from 58% to 83% (Table 3). Mean CAL dropped from 2.65 ± 1.25 to 2.23 ± 1.19 mm and sites with CAL⩾3 mm from 46% to 35% (Table 4).

Reductions in PI, BOP, mean PD, mean CAL and CAL⩾3 mm were statistically significant for both groups ($p<0.001$). Groups 1 and 2 also had statistically significant improvements of pockets ⩾6 mm ($p<0.01$).

Oral hygiene instructions were followed by most of the patients (18 patients in each group), the rest of the patients followed the instructions in a fair way. There was not any individual who ignored the given instructions.

To compare results between groups the percentage of improvement of the baseline values after treatment was calculated, and comparisons were established for PI, BOP, mean PD, pockets ⩾6 mm, mean CAL and CAL⩾3 mm (Table 5). PI had a 65 ± 30% reduction for group 1 (SRP+doxycycline) and 62 ± 29% for group 2 (SRP) and no difference between groups was found. BOP was reduced 59 ± 18% in group 1 and 46 ± 27% in group 2, changes in group 1 were more apparent than in group 2 and these differences resulted to be statistically significant when the *t*-test for independent variables was applied ($p = 0.03$).

After treatment, pockets ⩾6 mm had an 88 ± 22% reduction for group 1 and 65 ± 43% reduction for group 2. This means that in group 1, 88% of the ⩾6 mm pockets have changed after treatment to another category of shallower pockets. In group 2, reduction in PD occurred in 65% of the pockets ⩾6 mm pockets. Changes in group 1 were more accentuated than in group 2 and these differences were statistically significant for the *t*-test ($p = 0.03$).

Pockets variations after treatment were expressed in millimetres and analysed for each pocket category. Comparison between groups were established. One to three millimetre pockets had a similar response in groups 1 and 2 (Fig. 1). Four to five millimetre pockets had a better response in group 1 because 34% of them had a reduction of 2 mm or more after treatment, however, in group 2, only 28.5% of these pockets had this amount of reduction (Fig. 2). Difference between groups were more evident in ⩾6 mm pockets, 77.5% of these pockets had a reduction ⩾2 mm in group 1 against 66% in group 2 (Fig. 3). These differences were statistically significant ($p<0.01$).

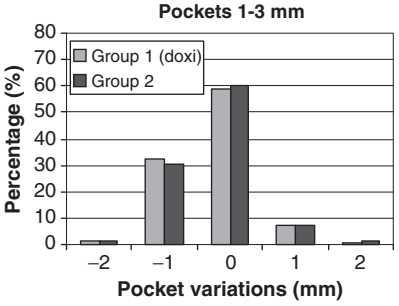

Fig. 1. Variations of 1–3 mm pockets after periodontal treatment.

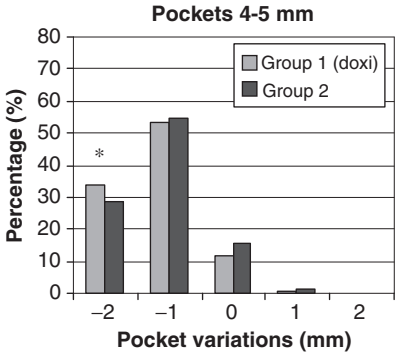

Fig. 2. Variations of 4–5 mm pockets after periodontal treatment.

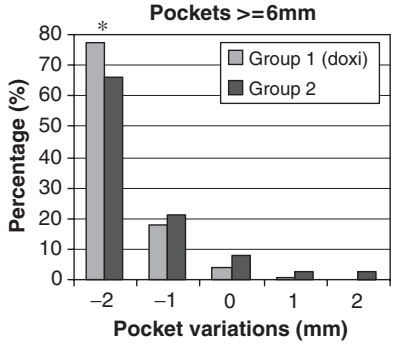

Fig. 3. Variations of ⩾6 mm pockets after periodontal treatment.

Mean PD was reduced by 20% in group 1 and 19% in group 2, mean CAL diminished 12% in group 1 and 17% in group 2, and sites with CAL⩾3 mm were reduced to 25% in group 1 and 33% in group 2. No statistical differences between both groups were found.

Periodontal response in smokers and non-smokers within each group were not studied because of the reduced size of the sample available. For the same reason, periodontal response to treat-

ment according to diabetes control status was not analysed.

Discussion

In this clinical trial, the response of diabetic patients with moderate-to-severe periodontal disease to non-surgical periodontal therapy with or without the use of doxycycline was investigated. When analysing group 1 (SRP+doxycycline) and group 2 (SRP alone) separately, it can be noticed that the short-term periodontal response to treatment has been very apparent in both groups, since all periodontal measurements (PI, BOP, PPD and CAL) have been largely reduced after non-surgical treatment. These results have been superior to most of those published in the literature where mechanical periodontal therapy was performed in diabetic patients, However, it must be noted, that some of the published studies were performed on diabetics with worse metabolic control than the patients in this trial (Grossi et al. 1996, 1997, Smith et al. 1996, Tervonen & Karjalainen 1997, Christgau et al. 1998, Al-Mubarak et al. 2002). It is worth noting that SRP was performed meticulously. PI experienced an important reduction even though the questionnaires showed that some patients did not strictly follow the oral hygiene instructions provided. However, the use of chlorhexidine rinses twice daily was performed during the length of the study in both groups. The efficacy of chlorhexidine to control supragingival plaque is well documented (Löe & Schiott 1970, Addy 1986). BOP, PPD and CAL have responded positively to treatment. The oral hygiene, the use of chlorohexidine and the thoroughness of SRP could have been the decisive factors.

When comparing both groups, the short-term reductions in BOP and $\geqslant$6 mm PD were more pronounced when doxycycline was given (group 1), and these differences were statistically significant ($p = 0.03$). The percentage of pockets that improve 2 mm or more was higher also in group 1 when 4–5 mm pockets and $\geqslant$6 mm pockets were studied. No difference between both groups were found for the PI as expected, because of the limited effect of the doxycyline on supragingival plaque. However, inside the crevicular sulcus, the effects of doxycycline are noticeable and may be responsible for the differences observed between both groups. There are only few studies comparing the efficacy of non-surgical periodontal treatment with or without doxycycline in diabetic patients (Grossi et al. 1996, 1997). In these studies conducted in type 2 diabetics, differences between groups were not found, but the authors expressed that there was a trend for the group with the use of doxycycline to have a higher reduction of mean PD and an increase in mean CAL. In this study, the same doxycycline doses were used and for the same period of time as other authors suggested. However, the present design included chlorhexidine rinses during the whole study, which could have avoided pocket repopulation allowing the doxycycline to express more clearly its periodontal effect. The literature supports the importance of supragingival plaque control on periodontal healing (Nyman et al. 1977, Magnusson et al. 1984, Sbordone et al. 1990). On the other hand, other authors were not able to detect any additive effect of the doxycycline on mean PPD and mean CAL changes. Mean values of PD and CAL are not good parameters to study the benefits of doxycycline: Shallow pockets or sites with incipient attachment loss are included to calculate the mean values. These sites are unlikely to change following periodontal treatment and they will also be included to calculate the mean values post-operatively. The effects of antibiotics in deep pockets will be ''diluted'', resulting in an inability to detect ''changes'' in these sites statistically. For that reason, analysing deep pockets separately is the best way to determine if doxycycline is beneficial in the short term. Deep periodontal pockets change the most after periodontal treatment (Ramfjord et al. 1987, Kaldahl et al. 1996) so PD changes in these pockets are the easiest to detect. Changes in CAL are not so apparent, even in deep pockets. In the present study, doxycycline improved the reduction of deep pockets ($\geqslant$6 mm), but no additive effect was detected in mean PD and mean CAL.

The data from the present trial, seem to indicate that type 1 diabetics had a good periodontal short-term response to non-surgical periodontal therapy, and this response may have been enhanced by the use of doxycycline. However, the long-term effects are not known, and the stability of the periodontal condition will depend on oral hygiene, periodontal maintenance and diabetes control. More studies with larger number of patients are encouraged. If the sample size is increased in future studies, differences in mean PD and mean CAL may be detected.

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