

# Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis

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Navarro-Sanchez AB, Faria-Almeida R, Bascones-Martinez A. Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis. J Clin Periodontol 2007; 34: 835–843. doi: 10.1111/j.1600-051X.2007.01127.x.

## Abstract

**Objectives:** The purpose of this study was to compare the local efficacy of nonsurgical periodontal therapy between type 2 diabetic and non-diabetic patients and the effect of periodontal therapy on glycaemic control.

**Background:** A complex two-way relationship exists between diabetes mellitus and periodontitis.

**Material and Methods:** After selection, 20 subjects (10 diabetic and 10 non-diabetic) underwent baseline examination, periodontal clinical study and biochemical analysis of gingival crevicular fluid (GCF). After the pre-treatment phase, subgingival scaling and root planing were performed. Subsequently, all subjects continued the maintenance programme and were re-examined at 3 and 6 months.

**Results:** Diabetic and non-diabetic subjects responded well after therapy, showing a very similar progression during the follow-up period. Both groups showed clinically and immunologically significant improvements. Significant reductions were also found in the total volume of GCF and levels of interleukin-1 $\beta$  and tumour necrosis factor- $\alpha$ . Diabetic subjects showed an improvement in their metabolic control. The change in glycosylated haemoglobin (HbA<sub>1c</sub>) was statistically significant at 3 and 6 months.

**Conclusions:** The clinical and immunological improvements obtained were accompanied by a significant reduction in HbA<sub>1c</sub> values in type 2 diabetic subjects. Larger studies are needed to confirm this finding and establish whether periodontal therapy has a significant effect on glycaemic control.

Key words: cytokines; diabetes mellitus; metabolic control; periodontitis

Accepted for publication 9 July 2007

## Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.  
This research was supported by a public grant from the Autonomous Community of Madrid (4165/98 BOCM).

Our understanding of the aetiopathogenesis of periodontitis has considerably improved over the past decade (Page & Kornman 1997a, Page et al. 1997b, Page 1998). The risk of developing periodontitis, which is largely determined by the presence of risk factors, varies among individuals (Genco 1996, Albandar & Rams 2002). Thus, certain

systemic diseases, such as diabetes mellitus (DM), are known to increase this risk (Grossi et al. 1994, Page & Beck 1997c). Less research attention has been paid to the role that chronic oral disease may play in systemic diseases, despite the possibility that the morbidity and mortality rates of some diseases might be reduced by an improvement in periodontal health.

However, interest in the association between periodontitis and different systemic diseases has grown over recent years (Beck et al. 1996, Offenbacher et al. 1996, Grossi & Genco 1998, Scannapieco & Genco 1999).

Periodontitis was traditionally considered to be a localized oral infection with adverse effects limited to the periodontium. It is currently regarded as a chronic localized oral infection that triggers a systemic as well as local host immune-inflammatory response and that can be a source of bacteraemia, because of the large epithelial surface with ulcerated periodontal pockets (Ebersole & Cappelli 2000). Periodontitis, especially in its severe clinical form, is currently considered to influence the pathogenesis or increase the risk of some systemic diseases (García et al. 2001).

The biological relationship between DM and periodontal disease is well documented (Mattson & Cerutis 2001, Soslone & Klinger 2001). Periodontal disease and DM are closely associated and are highly prevalent chronic diseases with many similarities in pathobiology. Inflammation is a critical player in the association, and its importance is just now coming to light (Mealey & Oates 2006). DM, the most common human endocrinal disease, is characterized as a metabolic disorder associated with a chronic hyperglycaemic state. By the mid-1990s, after more than 30 years of exhaustive research and around 90 published epidemiological studies, there was already overwhelming scientific support for the association between DM and periodontitis, which became designated the sixth complication of DM (Löe 1993). It was first demonstrated that DM was a risk factor for periodontitis and subsequently the inverse relationship was proposed, i.e. that periodontitis may be a risk factor for diabetic decompensation, and this hypothesis has been supported by various studies (Grossi 2001, Iacopino 2001, Lalla et al. 2001, Taylor 2001, Katz et al. 2005, Takeda et al. 2006, Lim et al. 2007). The concept is therefore becoming established of a complex two-way relationship between DM and periodontitis, creating a vicious circle that exacerbates both diseases when present in the same individual (Mealey 2000).

Several recent experimental studies have addressed the mechanisms underlying the interaction between DM and periodontitis. All reported a strong inflammatory response characterized by

a large secretion of inflammation mediators, mainly pro-inflammatory cytokines, which can have both local (periodontal destruction) and systemic (impaired glycaemic control) effects (Grossi 2001, Iacopino 2001, Lalla et al. 2001, Nishimura et al. 2003, Genco et al. 2005).

Various studies have been published on the effect of periodontal treatment on DM control. Although some authors found (Miller et al. 1992, Grossi et al. 1996, 1997, Iwamoto et al. 2001, Rodrigues et al. 2003, Kiran et al. 2005) that periodontal therapy may have a beneficial effect on glycaemic control, not all reported this improvement (Seppälä et al. 1993, Seppälä & Ainamo 1994, Aldridge et al. 1995, Smith et al. 1996, Westfelt et al. 1996, Christgau et al. 1998, Hagiwara et al. 2002, Jones et al. 2007). Even now, at the beginning of the 21st century, the scientific evidence remains inadequate and inconclusive. With this background, a clinical study was designed to determine whether an improvement in the periodontal status of type 2 diabetic subjects is accompanied by an improvement in their metabolic control. This study had three main objectives: (1) to explore differences in clinical response variables between diabetic and non-diabetic subjects, (2) to compare gingival crevicular fluid (GCF) levels of interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) between diabetic and non-diabetic subjects and (3) to evaluate the effect of periodontal treatment on the metabolic control of type 2 diabetic subjects.

## Material and Methods

### Patients

A total of 20 patients took part in this study. After applying the inclusion and exclusion criteria, two groups of 10 patients were consecutively selected: an experimental group of patients diagnosed with type 2 DM (American Diabetes Association 1997) and no modification of diabetes treatment for in the past 2 months (diabetic group,  $N=10$ ); and a group of non-diabetic patients (control group,  $N=10$ ).

All consecutive patients referred to the Masters Periodontal Clinical of our School of Dentistry were recruited for the study if they signed informed consent to study participation and met the following enrolment criteria. Inclusion criteria were age 35–70 years; a clinical diagnosis of moderate generalized chronic periodontitis (Armitage 1999);

presence of  $\geq 16$  teeth in the mouth, excluding third molars; and no previous periodontal treatment. Additional exclusion criteria were applied: the presence of systemic diseases that influence the course of periodontal disease (other than DM); intake of antibiotics or anti-inflammatories for the previous 4 weeks; smoker (current or former smoker for  $<5$  years); pregnancy or intention to become pregnant during the study period; and refusal of informed consent.

### Study design

Both study groups underwent an initial examination consisting of: signing of an informed consent, blood and urine analysis, complete periapical radiographic series, clinical history, clinical periodontal study, instruction on oral hygiene techniques with a gift of a toothbrushing manual, inter-proximal brushes, plaque revealer and dental floss (Laboratorios Dentaïd<sup>®</sup>, Cerdanyola, Spain) and supragingival prophylaxis. The diabetic group was instructed to continue with their medical treatment of DM (oral hypoglycaemic agents), diet and lifestyle without modifications during the study period.

All subjects then underwent non-surgical periodontal treatment, consisting of four 1-h sessions of scaling and root planing over a maximum 4-week period using standard rigid Gracey curettes (Hu-Friedy<sup>®</sup> Manufacturing Inc., Chicago, IL, USA) and ultrasonic instrumentation (Cavitron<sup>®</sup> Ultrasonics Inc., Long Island City, NY, USA).

Subjects were followed up at 3 and 6 months. At each visit, blood and urine samples were taken, clinical periodontal and immunologic studies were performed, oral hygiene instructions were reinforced, another oral hygiene kit was given and supragingival prophylaxis was carried out.

### Clinical periodontal examination

A North Carolina manual probe (Hu-Friedy<sup>®</sup> Manufacturing Inc.) was used for the periodontal examination. A single previously calibrated examiner recorded the following clinical variables for all teeth, except third molars at six sites per tooth: supragingival plaque index, bleeding on probing index, probing depth, gingival recession and clinical attachment level. The examiner had not been involved in the periodontal

treatment of the study patients, avoiding any bias in the evaluations.

#### Biochemical-immunological study

After the initial examination, three sites were selected in different quadrants of the mouth of the patient, choosing those with greater probing depth and bleeding. GCF samples were taken using one Periopaper<sup>®</sup> absorbent paper strip (Pro-Flow Corp., Amityville, NY, USA) per site by the superficial intra-crevicular method (Löe & Holm-Pedersen 1965). Samples were always taken from the same sites at the three visits. The volume of GCF was determined by means of a previously calibrated electronic Periotron<sup>®</sup> 6000 device (Ide-interstate, New York, NY, USA). All strips were immediately and individually stored in a Micro-Spin Eppendorf tube with a filter (Lida Manufacturing Corp., New York, NY, USA) and maintained at  $-20^{\circ}\text{C}$  in our Research Laboratory until their use within a maximum of 6 months.

For their analysis, samples were eluted and concentrations of IL-1 $\beta$  and TNF- $\alpha$  were measured by an enzyme-linked immunosorbent assay using a specific commercial test for each cytokine under study (Cytoscreen<sup>™</sup>, Biosource International, California, CA, USA). In each test, samples were processed in duplicate to rule out methodological errors. Assessments of IL-1 $\beta$  and TNF- $\alpha$  were performed in GCF by means of the double antibody method, following the manufacturers' instructions.

#### Metabolic study

Complete analyses were carried out, measuring multiple biochemical parameters in blood and urine. Only the glycosylated haemoglobin (HbA<sub>1C</sub>) value was considered for the statistical analysis of the metabolic response to periodontal treatment.

All follow-up analyses were performed at the Laboratory of the Institute of Cardiology in Madrid, where the normal ranges were 4.8–6% for HbA<sub>1C</sub>. HbA<sub>1C</sub> was measured by high-resolution liquid chromatography using an L-9100 glycosylated haemoglobin analyser (Hitachi, Merck, Japan).

#### Statistical analysis

In the statistical analysis, the patient (not the number of sites) was considered

as the evaluation unit.  $p \leq 0.05$  was considered to be statistically significant. The analyses were carried out considering the two groups as unmatched samples. The homogeneity of the study groups was studied by Fisher's exact test for sex and tobacco use (categorical variables) and by Student's  $t$  test for the age variable.

Application of the Shapiro–Wilk normality test showed that biochemical (GCF volume and IL-1 $\beta$  and TNF- $\alpha$  levels) and analytical (HbA<sub>1C</sub> value) variables were normally distributed. A two-way analysis of variance (ANOVA) (group factor: control diabetic; time factor: initial visit, 3, 6 months) with repeated measures on the time factor was used to analyse biochemical variables. Because no significant interaction was found between groups and time (treatment progression of groups was similar), group and time effects were jointly studied. When the time effect was significant in the two-way ANOVA of repeated measures, a multiple comparison test was applied a posteriori to identify the time or times responsible for the difference. In this procedure, the level of significance was divided by three (i.e., the number of paired comparisons) and  $p \leq 0.016$  was considered to be statistically significant. Analytical variables in the diabetic group were analysed by one-way ANOVA with repeated measures on the time factor. When the time effect was significant, a contrast of the means was performed between the initial and final time points.

The periodontal clinical variables probing depth, gingival recession, clinical attachment level, and percentage of sites  $\leq 3$  mm showed a normal distribution (Shapiro–Wilk test). The percentage of sites 4–6 mm variable was log transformed (percentage of sites  $4-6+0.1$  mm) to enable use of a parametric statistical method. A two-way ANOVA (group factor: control diabetic; time factor: initial visit, 3, 6 months) with repeated measures on the time factor was used to analyse these clinical variables. Because no significant interaction was found between groups and time (treatment progression of groups was similar), group and time effects were jointly studied. When the time effect was significant in the two-way ANOVA of repeated measures, a multiple comparison test was applied a posteriori to identify the time or times responsible for the difference. In this procedure, the level of significance was divided

by three (i.e., the number of paired comparisons) and  $p \leq 0.016$  was considered to be statistically significant.

Plaque index and bleeding on probing index variables could not be normalized at time 0 for the diabetic group; therefore, the study groups were separately analysed for these variables (or their log-transformed values). A single-factor ANOVA with repeated measures on the time factor was used for the control group and the non-parametric Friedman test for the diabetic group. Both analyses were followed by a posteriori multiple comparisons to identify the time or times responsible for the difference. It was also not possible to normalize the variable percentage of sites  $\geq 7$  mm, which was analysed in each group by means of the Friedman non-parametric test, followed by multiple comparisons. Differences between the groups in these three variables at each time point were studied with Student's  $t$  test and Wilcoxon's rank sum test.

Two of the diabetic patients enrolled were excluded from the statistical analysis due to missing data (one female missed the 3-month follow-up and one male was lost to the study after 3 months). In the Tables below, the periodontal clinical, biochemical and analytical variables for the diabetic group only correspond to the eight patients with complete data. All subjects in the control group completed the study.

## Results

### Study population

The participants in this study formed a homogeneous group. There were no significant differences between study groups in age or the proportion of males or former smokers between the two study groups ( $p > 0.05$ ) (Table 1). Differences found between groups in sex and tobacco use did not reach statistical significance, likely because of the small sample size.

In the diabetic group, one woman missed her 3-month follow-up due to the death of her husband but attended her 6-month follow-up, while one man left the study for personal reasons after the 3-month follow-up session. All patients in the control group completed the study.

### Clinical periodontal response

The groups did not significantly differ in plaque index, bleeding on probing

index, gingival recession or clinical attachment level at any examination time ( $p > 0.05$ ). The only significant differences in the periodontal variables studied were in the distribution of periodontal pockets and probing depth ( $p < 0.05$ ). The mean percentage of sites with depth  $\leq 3$  mm was significantly lower in the diabetic group than in the control group throughout the study ( $p = 0.019$ ). The mean percentage of sites with a depth of 4–6 mm was significantly higher in the diabetic group versus controls at the first visit and at 3 and 6 months ( $p < 0.016$ ). The per-

tage of sites  $\geq 7$  mm was higher in the diabetic group at the first visit and at 3 months ( $p = 0.038$ ). The mean probing depth was significantly greater in the diabetic group than in controls at all time points ( $p = 0.02$ ).

There was a significant ( $p < 0.016$ ) improvement in all periodontal variables in both study groups at 3 and 6 months after periodontal treatment with respect to the initial visit (Table 2).

At 3 months, the plaque index had significantly ( $p < 0.0001$ ) reduced from  $85 \pm 26\%$  to  $13 \pm 13\%$  in diabetic subjects and from  $84 \pm 17\%$  to  $10 \pm 9\%$  in

controls, and the bleeding on probing index had significantly ( $p < 0.0001$ ) reduced from  $91 \pm 15\%$  to  $19 \pm 14\%$  in diabetic subjects and from  $84 \pm 17\%$  to  $15 \pm 6\%$  in controls. At 6 months, both indexes remained below 15% in both groups.

At 3 months, the percentage of sites with probing depth  $\leq 3$  mm had significantly ( $p < 0.016$ ) increased from  $31 \pm 20\%$  to  $76 \pm 16\%$  in diabetic subjects and from  $46 \pm 22\%$  to  $90 \pm 6\%$  in controls, and the percentage of sites with probing depths of 4–6 mm and  $\geq 7$  mm was also significantly reduced in both groups. At 6 months, a reduction in the percentage of sites with periodontal pockets was again observed, although the difference with the findings at 3 months was not significant ( $p > 0.016$ ).

At 3 months, the mean probing depth of the whole mouth was reduced by 1 mm in both groups: a significant ( $p < 0.0001$ ) reduction from  $4.1 \pm 0.3$  to  $3.1 \pm 0.4$  mm in diabetic subjects and from  $3.8 \pm 0.5$  to  $2.8 \pm 0.2$  mm in controls. At 6 months, the mean probing depth of the whole mouth was significantly ( $p < 0.016$ ) reduced in comparison with the 3-month findings.

Table 1. Characteristics of the study population at the first visit

	Control group (N = 10)	Diabetic group (N = 10)
Age: mean (years)	56.4	57.4
Sex (female/male)	7/3	2/8
Tobacco (non-smoker/former smoker*)	7/3	2/8
Diabetic therapy		
Diet and exercise	–	2
Oral drugs	–	5
Insulin	–	1
Oral drugs + insulin	–	2
Duration of DM: mean (years)	–	12

\*Former smoker for >5 years.

DM, diabetes mellitus.

Table 2. Mean values and mean changes (SD) in periodontal clinical variables during the study period (diabetic group  $n = 8$ , control group  $n = 10$  patients)

	Time 1	Time 2	Time 3	$\Delta(2-1)$	$\Delta(3-1)$	$\Delta(3-2)$
Plaque (%)						
Diabetic group	$84.7 \pm 25.8$	$13.3 \pm 12.8$	$11.1 \pm 12.2$	$-71.4 \pm 23.9^*$	$-73.6 \pm 23.1^*$	$-2.2 \pm 3.4$
Control group	$83.9 \pm 16.6$	$10.4 \pm 9.4$	$7.9 \pm 9.7$	$-73.6 \pm 15.8^*$	$-76.0 \pm 14.0^*$	$-2.5 \pm 6.5$
Bleeding on probing (%)						
Diabetic group	$91.0 \pm 14.8$	$18.6 \pm 13.9$	$11.4 \pm 9.7$	$-72.4 \pm 21.7^*$	$-79.6 \pm 16.7^*$	$-7.2 \pm 10.9$
Control group	$83.9 \pm 17.2$	$15.1 \pm 6.0$	$12.1 \pm 5.9$	$-68.8 \pm 18.1^*$	$-71.8 \pm 16.4^*$	$-3.0 \pm 4.4$
Sites $\leq 3$ mm (%) <sup>#</sup>						
Diabetic group	$31.0 \pm 20.2$	$75.7 \pm 16.3$	$80.6 \pm 12.2$	$44.6 \pm 22.0^*$	$49.6 \pm 20.3^*$	$5.0 \pm 13.6$
Control group	$45.7 \pm 21.7$	$89.9 \pm 5.9$	$92.6 \pm 5.3$	$44.2 \pm 19.3^*$	$46.9 \pm 18.5^*$	$2.7 \pm 3.5$
Sites 4–6 mm (%) <sup>#</sup>						
Diabetic group	$64.9 \pm 22.6$	$22.2 \pm 15.9$	$17.7 \pm 11.0$	$-42.6 \pm 22.2^*$	$-47.2 \pm 22.0^*$	$-4.6 \pm 13.7$
Control group	$53.1 \pm 20.9$	$9.9 \pm 5.9$	$7.1 \pm 5.0$	$-43.2 \pm 1.3^*$	$-46.0 \pm 18.1^*$	$-2.8 \pm 3.3$
Sites $\geq 7$ mm (%) <sup>#</sup>						
Diabetic group	$4.1 \pm 3.5$	$2.1 \pm 2.7$	$1.7 \pm 2.5$	$-2.0 \pm 2.8^*$	$-2.4 \pm 3.1^*$	$-0.4 \pm 0.4$
Control group	$1.2 \pm 1.5$	$0.2 \pm 0.6$	$0.3 \pm 0.6$	$-1.0 \pm 0.43^*$	$-0.9 \pm 1.2^*$	$0.1 \pm 0.2$
Probing depth (mm) <sup>#</sup>						
Diabetic group	$4.1 \pm 0.3$	$3.1 \pm 0.4$	$3.0 \pm 0.4$	$-1.0 \pm 0.3^*$	$-1.1 \pm 0.2^*$	$-0.1 \pm 0.2$
Control group	$3.7 \pm 0.5$	$2.8 \pm 0.2$	$2.6 \pm 0.2$	$-1.0 \pm 0.3^*$	$-1.1 \pm 0.3^*$	$-0.1 \pm 0.1$
Recession (mm)						
Diabetic group	$1.6 \pm 1.7$	$2.1 \pm 1.7$	$2.2 \pm 1.7$	$0.6 \pm 0.3^*$	$0.6 \pm 0.3^*$	$0.1 \pm 0.0^*$
Control group	$1.2 \pm 0.7$	$1.8 \pm 0.7$	$1.9 \pm 0.7$	$0.6 \pm 0.2^*$	$0.7 \pm 0.3^*$	$0.1 \pm 0.1^*$
Attachment level (mm)						
Diabetic group	$5.7 \pm 1.9$	$5.3 \pm 2.0$	$5.2 \pm 2.0$	$-0.4 \pm 0.2^*$	$-0.5 \pm 0.2^*$	$-0.1 \pm 0.2^*$
Control group	$4.9 \pm 0.8$	$4.6 \pm 0.8$	$4.5 \pm 0.8$	$-0.3 \pm 0.2^*$	$-0.4 \pm 0.2^*$	$-0.1 \pm 0.1^*$

\*Statistically significant changes between times ( $p < 0.016$ ).

<sup>#</sup>Statistically significant difference at baseline between groups ( $p < 0.05$ ).

Time 1, baseline; Time 2, 3 months after non-surgical periodontal therapy; Time 3, 6 months after non-surgical periodontal therapy;  $\Delta(2-1)$ , changes from baseline to 3 months;  $\Delta(3-1)$ , changes from baseline to 6 months;  $\Delta(3-2)$ , changes from 3 to 6 months.

Gingival recession was significantly ( $p < 0.0001$ ) increased by a mean of  $>0.5$  mm in each group at 3 and 6 months with respect to the initial visit. The mean recession of the whole mouth significantly ( $p < 0.0001$ ) increased from  $1.6 \pm 1.7$  to  $2.1 \pm 1.7$  mm in diabetic subjects and from  $1.2 \pm 0.7$  to  $1.8 \pm 0.7$  mm in controls over the 6-month follow-up period.

At 3 months, a significant ( $p < 0.0001$ ) gain in clinical attachment level was observed in both groups, which remained stable at 6 months. Between the initial and 3-month visit, the mean clinical attachment level for the whole mouth improved from  $5.7 \pm 1.9$  to  $5.3 \pm 1.9$  mm in diabetic subjects and from  $4.9 \pm 0.8$  to  $4.6 \pm 0.8$  mm in controls.

#### Immunological response

There were no significant differences between diabetic subjects and controls in GCF volume or GCF concentrations of the two cytokines under study at any examination time ( $p > 0.05$ ).

After treatment, both diabetic subjects and non-diabetic subjects responded with significant reductions in the biochemical variables under study (Table 3). At 3 months, the GCF volume had significantly ( $p < 0.0001$ ) reduced from  $1.0 \pm 0.2$  to  $0.7 \pm 0.3$   $\mu$ l in diabetic subjects and from  $0.9 \pm 0.2$  to  $0.6 \pm 0.1$   $\mu$ l in controls. At 6 months, GCF volume was again significantly ( $p < 0.016$ ) reduced in both groups with respect to findings at 3 months.

At 3 months, the concentration of IL-1 $\beta$  in GCF had significantly ( $p < 0.016$ ) reduced from  $28.9 \pm 15.8$  to  $16.2 \pm 8.2$  pg/ $\mu$ l in diabetic subjects and from  $17.3 \pm 8.0$  pg to  $14.8 \pm 7.1$  pg/ $\mu$ l in controls. At 6 months, a continued reduction was observed but significance was not reached with respect to findings at 3 months ( $p > 0.016$ ).

The same behaviour was observed for TNF- $\alpha$ , with a significant ( $p < 0.016$ ) reduction from  $16.0 \pm 4.2$  to  $10.2 \pm 5.8$  pg/ $\mu$ l in diabetic subjects and from  $13.9 \pm 9.2$  to  $12.5 \pm 6.8$  pg/ $\mu$ l in controls, and a continued but not significantly greater ( $p > 0.016$ ) reduction at 6 months.

#### Metabolic response

The results obtained showed a positive metabolic response to the periodontal treatment, with a lowering of HbA<sub>1C</sub> values at each follow-up (Table 3). After the non-surgical periodontal treatment, there was a significant decrease in the mean HbA<sub>1C</sub> level in the diabetic group from  $7.2 \pm 1.3\%$  at the initial visit to  $6.5 \pm 1.1\%$  at 3 months and  $5.9 \pm 0.6\%$  at 6 months. The diabetic subjects showed a significant difference in this variable between baseline and 3 months and between baseline and 6 months ( $p < 0.05$ ).

#### Discussion

The patient sample was relatively small in this study due to the very strict inclusion and exclusion criteria applied

(to minimize confounding factors, despite the consequent reduction in the sample size) and the limitations of a study of this nature. Type 2 diabetic subjects were selected for this study because type 2 DM and chronic periodontitis are present in adults and highly prevalent among the general population, and type 2 DM has shown a spectacular increase in the past few decades (King et al. 1993, Mealey 1998).

Our study was not a randomized-controlled clinical trial and did not include a group of diabetic subjects not under periodontal treatment. Although this would have been desirable, it was considered unethical to withhold periodontal treatment from these patients. The absence of a placebo group is a study limitation, because it is not known how diabetic patients not under periodontal treatment would progress and many parameters can improve in the placebo group in clinical trials because patients are under more intense observation and become more health aware.

The groups did not significantly differ in plaque index, bleeding on probing index, gingival recession or clinical attachment level at any examination time ( $p > 0.05$ ). The only significant differences in the periodontal variables studied were in the distribution of periodontal pockets ( $p < 0.05$ ) and probing depth ( $p < 0.05$ ).

Both study groups showed a significant improvement in their periodontal status by the end of the study, confirming the widely documented clinical improvement in periodontal patients after non-surgical treatment (Badersten

Table 3. Mean values and mean changes (SD) in biochemical variables and in the HbA<sub>1C</sub> value during the study period (diabetic group  $n = 8$ , control group  $n = 10$  patients)

	Time 1	Time 2	Time 3	$\Delta(2-1)$	$\Delta(3-1)$	$\Delta(3-2)$
Volume of GCF ( $\mu$ l) <sup>NS</sup>						
Diabetic group	$1.0 \pm 0.2$	$0.7 \pm 0.3$	$0.6 \pm 0.2$	$-0.3 \pm 0.2^*$	$-0.4 \pm 0.2^*$	$-0.1 \pm 0.1^*$
Control group	$0.9 \pm 0.2$	$0.6 \pm 0.1$	$0.5 \pm 0.2$	$-0.3 \pm 0.1^*$	$-0.4 \pm 0.2^*$	$-0.1 \pm 0.2^*$
IL-1 $\beta$ in GCF (pg/ $\mu$ l) <sup>NS</sup>						
Diabetic group	$28.9 \pm 15.8$	$16.2 \pm 8.2$	$13.6 \pm 8.6$	$-12.6 \pm 8.0^*$	$-15.3 \pm 8.0^*$	$-2.7 \pm 1.8$
Control group	$17.3 \pm 8.0$	$14.8 \pm 7.1$	$11.0 \pm 7.3$	$-2.6 \pm 6.0^*$	$-6.4 \pm 12.0^*$	$-3.8 \pm 11.0$
TNF- $\alpha$ in GCF (pg/ $\mu$ l) <sup>NS</sup>						
Diabetic group	$16.0 \pm 4.2$	$10.2 \pm 5.8$	$9.6 \pm 4.7$	$-5.8 \pm 3.1^*$	$-6.4 \pm 5.6^*$	$-0.6 \pm 5.5$
Control group	$13.9 \pm 9.2$	$12.5 \pm 6.8$	$7.5 \pm 3.4$	$-1.4 \pm 5.4^*$	$-6.4 \pm 7.0^*$	$-5.0 \pm 3.8$
HbA <sub>1C</sub> (%)						
Diabetic group	$7.2 \pm 1.3$	$6.5 \pm 1.1$	$5.9 \pm 0.6$	$-0.7 \pm 1.1^*$	$-1.3 \pm 1.4^*$	$-0.6 \pm 1.5$

\*Statistically significant changes between times ( $p < 0.016$ ).

<sup>NS</sup>Not statistically significant difference at baseline between groups ( $p > 0.05$ ).

Time 1, baseline; Time 2, 3 months after non-surgical periodontal therapy; Time 3, 6 months after non-surgical periodontal therapy;  $\Delta(2-1)$ , changes from baseline to 3 months;  $\Delta(3-1)$ , changes from baseline to 6 months;  $\Delta(3-2)$ , changes from 3 to 6 months; GCF, gingival crevicular fluid; IL-1 $\beta$ , interleukin-1 $\beta$ ; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; HbA<sub>1C</sub>, glycosylated haemoglobin.

et al. 1981, 1984a, b, Lindhe et al. 1982, Kaldahl et al. 1996).

An improvement in the clinical response was observed in both study groups at 3 and 6 months, with a reduction in the percentage of sites with plaque and bleeding, reduction in the percentage of periodontal pockets  $\geq 4$  mm, reduction in probing depth and gain in clinical attachment level. These findings confirm previously published reports that diabetic and non-diabetic subjects do not differ in periodontal healing over the short term after non-surgical periodontal treatment (Tervonen et al. 1991, Christgau et al. 1998). In the present study design, any potential difference in periodontal healing between the groups could be attributable to baseline differences in levels of disease, because the periodontal examination at the first visit showed a significantly higher percentage of periodontal pockets and deeper probing depth in the diabetic patients than in the non-diabetic controls.

In periodontitis, proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  are potent mediators of tissue destruction that induce degradation of connective tissue and resorption of alveolar bone (Graves & Cochran 2003). The volume of GCF in which gingival sulci and periodontal pockets are bathed is known to be proportionally related to the degree of tissue inflammation and to be reduced after periodontal treatment (Uitto 2003). Several authors have demonstrated high GCF concentrations of IL-1 $\beta$  and TNF- $\alpha$  at sites with active periodontal destruction (Masada et al. 1990, Stashenko et al. 1991) and reduced concentrations after periodontal treatment (Heasman et al. 1993, Gamonal et al. 2000). The present findings confirm these observations, with significant post-treatment reductions in all three biochemical variables studied.

It has also been reported that the presence of periodontitis-induced asymptomatic bacteraemia/endotoxaemia produces increased plasma concentrations of pro-inflammatory cytokines, with detection by Haraszthy et al. (2000) of periodontopathogens in blood. Some authors have suggested that GCF levels of IL-1 $\beta$  and TNF- $\alpha$  are sufficiently high in advanced periodontitis to pass into the blood stream by a phenomenon designated "systemic dumping" by Prabhu et al. (1996), with a resulting elevation of their plasma levels. Persistently high levels of IL-1 $\beta$ , IL-6 and

TNF- $\alpha$  are known to have numerous metabolic effects, including the release of acute-phase proteins (e.g., C-reactive protein) in the liver, alteration of fat metabolism (giving rise to hyperlipidaemia) and even effects on pancreatic  $\beta$ -cells. Moreover, because TNF- $\alpha$  is a potent inhibitor of the tyrosine kinase activity of the insulin receptor, it has been implicated as an aetiological factor in the development of a state of tissue resistance to the action of insulin (Hotamisligil et al. 1993, 1999).

Although the GCF analyses revealed no significant difference between diabetic subjects and controls at the initial visit, higher concentrations of IL-1 $\beta$  and TNF- $\alpha$  were observed in the GCF of the diabetic group, who showed an almost twofold higher mean level of IL-1 $\beta$  ( $28.9 \pm 15.8$  versus  $17.3 \pm 8.0$  pg/ $\mu$ l). The failure to reach significance can probably be attributed to the small sample size. Several reports have shown significantly higher GCF levels of IL-1 $\beta$  in the diabetic group versus the control group and suggested that the inflammatory response to bacterial aggression was more marked in diabetic subjects than in individuals without systemic disease (Salvi et al. 1997, 1998, Engebretson et al. 2004).

In the present study, periodontal treatment was accompanied by a significant reduction in HbA<sub>1C</sub> levels in the type 2 diabetic subjects at 3 and 6 months. The determination of glucose in plasma or urine shows the level at the specific time of the sampling but this value can change within a few minutes due to various factors, including diet, physical activity and/or medication. For this reason, unlike HbA<sub>1C</sub> measurements (Rees 1994), this parameter is not an appropriate indicator of long-term metabolic control. The HbA<sub>1C</sub> test provides an estimate of the average glucose level over the 30–90 days preceding the test. It does not account for short-term fluctuations in plasma glucose levels (Rohlfing et al. 2002).

The main finding of this study was the improved periodontal status of type 2 diabetic subjects accompanied by a significant improvement in their metabolic control. No changes in the life style or medical treatment of their DM were recorded that could have influenced these results. By the end of the study, some patients experienced little change in glycaemic control, whereas others experienced a major improvement. Thus, the variability in the

HbA<sub>1C</sub> values observed at the end of the study, from little change to major improvement, may be attributable to differences in baseline HbA<sub>1C</sub> values. In fact, a tendency was observed for diabetic patients with higher baseline HbA<sub>1C</sub> values to show a more marked reduction in this variable in comparison with patients with lower baseline values.

This finding confirms previous reports of significant improvements in glycaemic control in DM patients after non-surgical periodontal treatment. Thus, Miller et al. (1992) studied nine type 1 diabetic subjects with moderate-severe periodontitis and found a marked reduction after periodontal treatment in the bleeding on probing index and a significant reduction in the mean HbA<sub>1C</sub> of five of these patients. In a controlled clinical trial, Grossi et al. (1996, 1997) treated type 2 diabetic subjects with severe periodontitis with root scaling and planing and subgingival irrigation (H<sub>2</sub>O, chlorhexidine, or povidone iodine) plus placebo or doxycycline (100 mg/day orally for 15 days). They found a significant reduction in HbA<sub>1C</sub> levels in the group receiving doxycycline, whereas the reduction in the placebo-treated group did not reach significance. Iwamoto et al. (2001) performed a controlled clinical trial of 13 Japanese patients with type 2 DM and found a significant reduction in the plasma HbA<sub>1C</sub> levels (mean reduction of 0.8%). Rodrigues et al. (2003) studied the response to periodontal treatment of an experimental group of 15 type 2 diabetic patients with chronic periodontitis receiving mechanical debridement plus amoxicillin/clavulanic acid for 2 months, with a similar group receiving only mechanical debridement. Although both groups showed a marked improvement in all periodontal variables, a significant reduction in HbA<sub>1C</sub> was only significant ( $p < 0.05$ ) in the latter group, indicating a less-favourable response in the group receiving adjunctive treatment with systemic antibiotic. Kiran et al. (2005) recently conducted a study of patients with type 2 diabetes. They examined the effect of prophylaxis and localized scaling and root planing without systemic antibiotic therapy on periodontal health and glycaemic control. A control group of subjects with diabetes whose periodontal status was similar received no treatment. The treated subjects experienced a 50% reduction in the prevalence of gingival bleeding 3 months after treatment. This

was accompanied by a statistically significant improvement in glycaemic control, with a reduction in the mean HbA<sub>1C</sub> value of 0.8% (baseline, 7.3%; follow-up, 6.5%). The untreated control group experienced no change in gingival bleeding or glycaemic control.

Our results differ from those showing no improvement in metabolic control after periodontal treatment (Seppälä et al. 1993, Seppälä & Ainamo 1994, Aldridge et al. 1995, Smith et al. 1996, Westfelt et al. 1996, Christgau et al. 1998, Hagiwara et al. 2002, Jones et al. 2007), perhaps because of the initial metabolic control of the latter (low levels of HbA<sub>1C</sub> indicate a good metabolic control) or because of an inadequate time interval before evaluation of the differences (the value of HbA<sub>1C</sub> must be determined between 90 and 120 days).

Janket et al. (2005) published a recent meta-analysis of 10 intervention trials in order to quantify the effects of periodontal treatment on HbA<sub>1C</sub> level among diabetic patients, explore possible causes for the discrepant reports and make recommendations for future studies. More than 450 patients were included in this analysis, with periodontal treatment as the predictor and the actual change in HbA<sub>1C</sub> level as the outcome. The weighted average decrease in actual HbA<sub>1C</sub> level was 0.38% for all studies, and 0.66% when restricted to type 2 diabetic patients. The addition of adjunctive antibiotic therapy to the scaling and root planing regimen resulted in a mean absolute reduction of 0.71% in post-treatment HbA<sub>1C</sub> values. However, none of these differences were statistically significant.

A review of the literature does not yield a definitive conclusion about an improvement in glycaemic control produced by periodontal treatment of patients with DM, due to the wide variety in the methodology used by these studies. Because the present results were based on a small sample of patients, further studies in larger samples of type 2 diabetic subjects are required to establish whether effective periodontal therapy confers a significant clinical benefit on their glycaemic control.

## Conclusions

Short-term periodontal healing after non-surgical periodontal treatment is similar between type 2 diabetic and non-diabetic periodontal patients. After

treatment, both groups showed a significant improvement in clinical periodontal status, and the presence of DM does not appear to have a major effect on the success of periodontal therapy.

Analysis of the GCF revealed no significant difference between diabetic and non-diabetic subjects at the initial visit. Both groups responded to treatment with significant reductions in the total volume of GCF and in the concentrations of the two cytokines studied.

In the group with type 2 diabetes, there was a significant improvement in metabolic control concurrent with periodontal intervention that may or may not have been causally related. Because the results of this study were based on a very small sample of patients, larger studies are required to confirm this finding and determine whether periodontal therapy confers a significant benefit on glycaemic control.

## Acknowledgements

The authors gratefully acknowledge Dra. Itziar González Benítez and Ana O'Connor de la Oliva (of the Laboratory of Oral Microbiology, Faculty of Dentistry, Complutense University), Dra. Carmen Bravo Llatas (of the Teaching and Research Support Computational Service of the Complutense University), Dra. Pilar Manzano Arroyo (of the Endocrinology Department of Puerta de Hierro Hospital) and Dr. Jesús Escribano San Germán (of the Laboratory Department at the Madrid Institute of Cardiology), for their invaluable contributions to this study. The authors also thank Richard Davies for assistance with the English version.

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### Clinical Relevance

*Scientific rationale for the study:* Patients with diabetes who have periodontal disease have two chronic conditions, and each one may affect the other. Treatment of periodontal disease and reduction of oral inflammation may have a positive effect on the diabetic condition. Intervention studies during the past 15 years have resulted in varied metabolic responses in patients with diabetes. *Principal findings:* Short-term periodontal healing after non-surgical

periodontal treatment is similar in type 2 diabetic and non-diabetic periodontal patients. After treatment, both groups showed a significant improvement in clinical periodontal status, and the presence of DM does not appear to have a major effect on the success of periodontal therapy. The clinical and immunological improvements obtained were accompanied by a significant reduction in HbA<sub>1C</sub> values in type 2 diabetic subjects.

*Practical implications:* In the group with type 2 diabetes, there was a significant improvement in metabolic control concurrent with periodontal intervention that may or may not have been causally related. Because the results of this study were based on a very small sample of patients, larger studies are required to confirm this finding and determine whether periodontal therapy confers a significant benefit on glycaemic control.

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