

A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control

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Abstract

Aim: The purpose of the present study was to assess the effect of non-surgical periodontal therapy on glycaemic control of type 2 diabetes patients with moderate-to-severe periodontitis.

Materials and methods: This was a randomized, controlled clinical trial of patients with type 2 diabetes. A total of 60 patients with moderate-to-severe periodontal disease were assigned to either a periodontal treatment arm, consisting of scaling and root planing (intervention group [IG]), or a delayed treatment arm that received periodontal care after 6 months (control group [CG]). Periodontal parameters and glycosylated haemoglobin (A1C) were evaluated at 1, 3 and 6 months.

Results: All periodontal parameters improved significantly in the IG. A1C levels decreased statistically significantly more in the IG *versus* the CG (0.72% *versus* 0.13%; p < 0.01) independently of other confounders.

Conclusions: This study provides evidence that periodontal treatment contributes to improved glycaemic control in type 2 diabetes mellitus patients. Larger controlled trials are needed to confirm if this finding is generalizable to other populations of patients with type 2 diabetes.

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A large body of evidence suggests that patients with diabetes, especially when

Conflict of interest and source of funding statement

The authors declare that there are no conflicts of interest in this study. The study was co-funded by the European National Fund and National Resources (EPEAEK 2 PYTHAGORAS). inadequately controlled, are at an increased risk of developing periodontal disease (Tsai et al. 2002, Mealey & Oates 2006), exhibit more severe and more extensive destruction of periodontal supporting tissues (deeper pocket depths and more clinical attachment loss) (Tsai et al. 2002, Mealey & Oates 2006), and show accelerated alveolar bone loss (Taylor et al. 1998). Periodontal disease is considered to be a significant complication of diabetes (Loe 1993, Khader et al. 2006).

On the other hand, the presence of periodontal disease itself in diabetic patients may influence their glycaemic control (Taylor et al. 1996). There is evidence that resolution of periodontal inflammation can improve metabolic control, thus establishing a two-way relationship between diabetes mellitus (DM) and periodontal disease/infection (Grossi & Genco 1998). Intervention studies examining the effects of periodontal treatment on glycaemic control in diabetic patients with periodontal disease have generally shown a beneficial effect, as expressed by reduced glycosylated haemoglobin (A1C) levels, although not all studies confirm this improvement. Meta-analyses of intervention studies suggest that additional trials are needed to clarify the effect of periodontal therapy on A1C levels (Janket et al. 2005, Darre et al. 2008, Teeuw et al. 2010).

The hypothesis of this study was that periodontal treatment in patients with DM improves glycaemic control by reducing local infection/inflammation. The specific aim was to prospectively assess the effect of non-surgical periodontal therapy on A1C levels in patients with type 2 diabetes patients and moderate-to-severe periodontitis.

Materials and Methods

Subjects - Periodontal Data

The study population consisted of 60 Greek patients (33 males) with type 2 DM, aged 40–75 years (mean \pm SD, 59.52 ± 8.88), with A1C levels ranging from 7% to 10% and having at least 16 teeth present, who at the screening periodontal examination had at least eight sites with probing pocket depth (PPD) $\geq 6 \text{ mm}$ and four sites with clinical attachment loss ≥ 5 mm, distributed in at least two different quadrants. Based on an expected mean difference in the reduction of A1C between the two groups of around 0.4% (Teeuw et al. 2010), we calculated that we would need at least 19 patients in each group to detect this difference with 90% power and a two-sided type 1 error of 5% estimating sample sizes for binary, ordered categorical, and continuous outcomes in two group comparisons (Campbell et al. 1995). Subjects were screened and recruited between January 2006 and December 2008 from the patient pool of an outpatient university hospital diabetes clinic (Laiko General Hospital, Athens, Greece), by a single examiner (P. M.). Patients were excluded if they had a history of systemic antibiotic usage over the previous 3 months; non-surgical periodontal treatment during the previous 6 months: surgical periodontal treatment over the previous 12 months; current medication usage of calcium channel blockers, phenytoin, or cyclosporine; history of stroke

or an acute cardiovascular event over

the previous 12 months; and renal (crea-

tinine > 1.5 mg/dl) or liver dysfunction

(AST/ALT levels > 2.5 times ULN).

Participants were randomized using a

computer program into two groups (30

patients each), the intervention group

(IG) and the control group (CG), and

were followed for 6 months, with inter-

mediate visits at 1 and 3 months. The

randomization sequence was generated

by one author (P. K.) before patient

recruitment. Numbers from 1 to 60

were assigned to patients according to

their recruitment date (first recruited

patient would be number 1 and last

would be number 60). Random assign-

ment into two groups of 30 patients each

was then accomplished with the use of a

computer program. Containers (num-

bered 1-60, four for each visit of each

patient) were designated to maintain

and physical examination before entry

into the study and data were collected at

baseline and at all three follow-up visits

(1, 3 and 6 months). A panoramic mouth

X-ray was taken at baseline. Patients

were examined dentally through the

course of the study by the same examiner

(X. D.) blinded to the allocated group.

The examiner (X. D.) was calibrated for

reproducibility of probing depth and

clinical attachment loss measurements.

Assessments were carried out using a

manual probe, measuring probing depth

and clinical attachment loss on six sur-

faces on all teeth (total 26 teeth) of the

same patient (not participating in the

study). Two assessments were carried out, the second 2h after the first, and

both sets of measurements were in excel-

lent agreement ($\kappa > 0.86$ both for prob-

ing depth and clinical attachment loss).

A periodontal chart, including PPD,

clinical attachment loss (CAL), bleeding

on probing (BOP), simplified gingival

index (GI) (Lindhe 2003) (percentage of

sites with presence of bleeding after light

mechanical stimulation by a periodontal

probe), and number of missing teeth, was

recorded at all four visits for all patients.

PPD, CAL, and BOP were recorded at six

sites/tooth and GI at four sites/tooth

[mesial (either buccal or lingual/palatal),

distal (either buccal or lingual/palatal),

mid-buccal and mid-lingual, palatal] for

all teeth present, third molars included.

Current smokers were defined as partici-

pants who smoked at least one cigarette

per day; never smokers as those who had

All patients had a complete history

examiner blinding.

never smoked in their life; and former smokers as those who had stopped smoking >1 year previously.

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All participants received oral hygiene instructions at baseline. The IG received non-surgical periodontal therapy in the form of full-mouth scaling and root planing (SRP), in two sessions, 1 week apart, with the use of an ultrasonic scaler (Minipiezon Electromedical Systems EMS, Nyon, Switzerland) and hand instruments, under local anaesthesia. Patients in the CG (minimal treatment group) received periodontal prophylaxis at baseline, in the form of supragingival removal of all deposits (plaque and calculus) with an ultrasonic scaler. SRP was performed in the CG after the completion of the study (after the 6-month visit). Teeth with hopeless teeth were extracted at SRP visits (two teeth were extracted in total, in two patients in the IG). Both of the extracted teeth had almost no remaining alveolar bone support and both had class III mobility. All subjects received oral hygiene instructions after each visit, while the IG received additional supportive SRP at each visit, if judged necessary (presence of sites with BOP and/or increased PPD). Periodontal treatment was administered by the same trained periodontist (P. K.).

All participants signed an informed consent according to the general recommendations of the Declaration of Helsinki and the study was approved by the University of Athens' Dental School and the participating hospital's ethical committees (Fig. 1).

Metabolic data

Blood was collected at each visit for A1C and biochemical analyses. A1C was measured immediately at the Biochemical laboratory of Laiko General Hospital (lab staff was blinded to the allocation group), using high-performance liquid chromatography, while the rest of the blood was centrifuged, deep frozen, and placed into the prelabelled containers until assayed. Total cholesterol, triglycerides, HDL- and LDL cholesterol were measured at baseline for both groups, using standard enzymatic assays.

Statistical analysis

All 60 patients were included in the statistical analysis performed. The seven patients that were lost to follow-up after the 1 month recall visit, were analysed

under the intention-to-treat principle, carrying their last observation forward (Lachin 2000). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Data not normally distributed were log-transformed for analysis. Data normally distributed are presented as mean \pm SD, while qualitative variables are presented as absolute and relative frequencies (%). Baseline comparisons between groups were performed using independent samples t-test for normally distributed data or the Wilcoxon-Mann-Whitney test for non-normally distributed data. Pearson's correlation coefficients were calculated where appropriate. Chi-squared test was used to analyse qualitative variables. Multiple logistic regression analysis was used to evaluate the association between the dependent variable (change in A1C after 6 months) and the independent variables of baseline A1C level, group, use of oral hypoglycaemic agents and insulin change. All reported p-values are from two-sided tests and compared with a significance level of 5%. Data were analysed using the Statistical Package SPSS (version 16.0).

Results

Tables 1 and 2 show baseline demographic, laboratory, and periodontal data of the participants. No significant differences were observed on any of these variables between the intervention and CGs. The majority of patients (80.0%) used oral hypoglycaemic medications for their diabetes treatment, while a similar proportion of intervention and CG participants used insulin (Table 1). Over the course of the study, no oral medication changes were performed. while a similar number of IG and CG participants increased their insulin dosages [four (13.3%) for the IG and three (10.0%) for the CG participants (p = 0.62)]. Out of the seven patients that increased their insulin dosages, five (three in the IG and two in the CG) were patients that were lost to follow-up.

Periodontal parameters

All periodontal parameters measured (BOP, GI, PPD, and CAL) showed improvement after 6 months of nonsurgical periodontal treatment in the IG compared with the CG (Table 3). Specifically, sites with BOP showed a mean reduction of $38.12 \pm 22.53\%$ (p < 0.01) for the IG, while for the CG the decrease was non-significant $(4.35 \pm 16.1\%)$. The GI decreased significantly for both groups, but more so for the IG $(48.01 \pm 27.33\%)$ in the IG and $13.90 \pm 18.03\%$ in the CG, p < 0.01). The percentage of shallow sites (pocket depth ≤ 3 mm) increased significantly in both groups (but more so in the IG), while the percentage of sites with PPD 4–6 mm and \geq 7 mm decreased significantly in the IG after 6 months of treatment. With the exception of the percentage of sites with CAL ranging



Fig. 1. CONSORT flow diagram of the participants.

Table 1	Baseline demograr	phic (% of sub	iects) and clinical	data of the pa	rticipants (+SD)
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Group (n)	Intervention (30)	Control (30)	Total (60)
Male/female (<i>n</i>)	17(56.7%)/13(43.3%)	16(53.3%)/14(46.7%)	33(55%)/27(45%)
Mean Age (years)	59.62 (± 7.95)	59.42 (± 9.8)	59.52 (± 8.88)
Mean BMI (kg/m ²)	27.76 (± 3.68)	$27.51 (\pm 3.83)$	27.63 (± 3.73)
Smoking (current/no/ex) (n)	4(13.3%)/13(43.3%)/13(43.3%)	7(23.3%)/1653.3%)/7(23.3%)	11(18.3%)/29(48.3%)/20(30%)
Mean remaining teeth (n)	23.52 (± 3.99)	24.23 (± 3.78)	23.88 (± 3.87)
Mean duration of diabetes (years)	$7.76 (\pm 4.33)$	$7.84 (\pm 6.8)$	7.80 (± 5.7)
OHA (no. of patients)	21 (70%)	27 (90%)	48 (80%)
Insulin (no. of patients)	12 (40%)	7 (23.3%)	19 (31.7)

All comparisons between the groups: non-significant.

BMI, body mass index; OHA, oral hypoglycaemic agents.

Table 2. La	aboratory a	and p	periodontal	data of	particip	oants at	baseline ($(mean \pm$	SD)
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	Intervention group	Control group
A1C (%) (minimum–maximum)	7.87 (0.74) (7.0-9.9)	7.59 (0.66) (7.0-10.2)
Total cholesterol (mmol/l)	4.37 (± 1.22)	4.30 (± 1.43)
Triglycerides (mmol/l)	$1.53 (\pm 1.65)$	$1.42 (\pm 0.95)$
HDL-C (mmol/l)	$1.18 (\pm 0.27)$	$1.11(\pm 0.25)$
LDL-C (mmol/l)	$2.51 (\pm 1.1)$	2.78 (± 1.22)
PPD≤3 mm (%)	33.22 (16.34)	36.41 (17.63)
PPD 4-6 mm (%)	56.44 (10.70)	55.01 (14.51)
$PPD \ge 7 \text{ mm} (\%)$	10.34 (10.45)	8.58 (7.46)
$CAL \leq 3 \text{ mm} (\%)$	24.32 (14.12)	30.21 (21.23)
CAL 4-6 mm (%)	58.60 (10.87)	55.02 (12.34)
$CAL \ge 7 \text{ mm} (\%)$	17.08 (17.11)	14.77 (18.33)
BOP (%)	71.55 (27.0)	69.27 (25.9)
GI (%)	65.78 (31.99)	61.09 (34.07)

All comparisons between the groups: non-significant.

A1C, glycosylated haemoglobin; A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPD, probing pocket depth (percentage of sites with ≤ 3 , 4–6, or ≥ 7 mm); CAL, clinical attachment level (percentage of sites with ≤ 3 , 4–6, or ≥ 7 mm); BOP, bleeding on probing (percentage of pockets with bleeding on probing); GI, gingival index (percentage of sites).

Table 3. A1c, and periodontal parameters changes (Δ) from baseline to 6 months for the intervention (IG) and control (CG) groups (mean \pm SD)

	Δ from baseline to 6 months (IG)	Δ from baseline to 6 months (CG)
A1C (%)	0.72 (0.93) ^{*†}	0.13 (0.46)
BOP (%)	38.12 (22.53)*†	4.35 (16.1)
GI (%)	48.01 (27.33)**	13.90 (18.03)*
PPD≤3 mm (%)	$-18.78(11.24)^{*\dagger}$	$-4.88(6.53)^{*}$
PPD 4–6 mm (%)	11.16 (15.34) ^{*‡}	2.61(7.90)
PPD≥7 mm (%)	7.60 (10.10)*†	$2.21(3.5)^{*}$
$CAL \leq 3 \text{ mm} (\%)$	$-18.33(12.53)^{*\dagger}$	$-4.92(8.56)^{*}$
CAL 4–6 mm (%)	6.23 (22.78)	0.91 (12.30)
CAL≥7 mm (%)	11.75 (13.01)*†	4.12 (8.74)\$

p < 0.01 for the comparison between baseline and 6 months for the same group.

 $^{\dagger}p < 0.01$ for the comparison between IG and CG.

p < 0.05 for the comparison between IG and CG.

 $p^{*} = 0.05$ for the comparison between baseline and 6 months for the same group.

IG, intervention group; CG, control group; A1C, glycosylated haemoglobin A1C; BOP, bleeding on probing (percentage of pockets with BOP); GI, gingival index (% of sites); PPD, probing pocket depth (percentage of sites with ≤ 3 , 4–6, or ≥ 7 mm); CAL, clinical attachment level (percentage of sites with ≤ 3 , 4–6, or ≥ 7 mm).

from 4 to 6 mm, which did not reach statistical significance, all other CAL indices showed a statistically significant improvement in favour of the IG after 6 months of treatment (Table 3).

Metabolic control

After 6 months of follow-up, participants in the IG showed a significant reduction in A1C levels ($0.72 \pm 0.93\%$, p < 0.001),

whereas in the CG there was no significant change (Table 3) (the treatment group improved 0.59 percentage points more than the minimally treated controls). This difference was already present after the first 4 weeks of treatment and persisted through 3 and 6 months of followup (Fig. 2). Univariate analyses, in the whole group of participants, showed that the reduction of A1C after 6 months was significantly correlated with the IG $(r = 0.445 \ p < 0.001)$, the baseline A1C level (r = 0.426, p < 0.001), the use of oral hypoglycaemic agents (no versus yes, r = 0.270, p = 0.037), and the number of subjects changing their insulin doses (r = 0.365, p = 0.004). A multivariate linear regression analysis model, with the A1C change from baseline to the 6month follow-up visit as the dependent variable, and the independent variables of baseline A1C level, group, use of oral hypoglycaemic agents, and insulin change, showed that only being in the IG (b = -0.409, p = 0.013) and baseline A1C level (b = -0.330, p = 0.021) significantly and independently predicted the variance of A1C decline over 6 months. The addition of age, gender, body mass index, and smoking status in the model did not significantly alter the results.

Discussion

The results of the present study show that non-surgical periodontal treatment of type 2 diabetic patients with moderate-to-severe periodontal disease is associated with significant improvement in their glycaemic control after 6 months. All periodontal clinical parameters (BOP, GI, PPD, CAL) were significantly improved in the IG compared with the CG (Table 3), and this decrease of periodontal inflammation was independently associated with the glycaemic improvement in the multi-



Fig. 2. A1C levels of participants at baseline and follow-up visits (4 weeks, 3 and 6 months) in the intervention (IG) and control (CG) groups. Mean value (SD).

variate analysis. The independent effect of baseline A1C also noted, was expected, because it is well known that the higher the baseline A1C, the higher its decrease, with any anti-diabetic treatment modality (Nathan et al. 2009).

Results in the literature regarding the influence of periodontal therapy on glycaemic control in diabetes are generally contradictory (Janket et al. 2005, Darre et al. 2008, Teeuw et al. 2010). The effectiveness of periodontal therapy on glycaemic control and systemic inflammation is not proven beyond doubt (Salvi et al. 2008) and studies should be interpreted with caution because they may differ in design, severity, and extent of periodontal disease, use of local and systemic antibiotic treatment in addition to SRP and periodontal treatment efficacy.

Outcome of an initial meta-analysis of 10 studies, including 456 patients with diabetes of both types, showed that following mechanical periodontal debridement, HbA1c levels decreased on average by 0.38% for all studies, by 0.66% when restricted to subjects with type 2 diabetes and by 0.71% if antibiotics were administered. The magnitude of such improvement was not statistically significant (Janket et al. 2005). Another meta-analysis (Darre et al. 2008), however, incorporating a more extensive search of the literature and finally including 485 patients with both types of diabetes, only from studies with a CG (nine studies) concluded that periodontal treatment could lead to a significant 0.79% (95% CI: 0.19-1.40) reduction in A1C levels, very similar to the findings of the present study. Results from the most recent meta-analysis (Teeuw et al. 2010), which included

only RCTs of type 2 DM (five studies, 371 patients) suggest that periodontal treatment can lead to an improvement in glycaemic control in type 2 diabetic patients [Δ A1C before and after therapy of -0.40% (-0.77 to -0.04%), 95% CI] for at least 3 months.

In the present study, antibiotics were not used as an adjunctive to non-surgical periodontal disease treatment. Administration of antibiotics, especially systemic, can lead to controversial results regarding A1C, because they may affect other systemic sources of infection/inflammation and potential reduction in A1C levels cannot be solely attributed to the local reduction in the infectious/inflammatory periodontal burden. Furthermore, it is well accepted that A1C is affected by systemic inflammation (Moutsopoulos & Madianos, 2006, Shoelson et al. 2006). Most studies (Janket et al. 2005, Darre et al. 2008, Teeuw et al. 2010) examining the effect of periodontal disease treatment in patients with diabetes have incorporated antibiotic administration (topical or systemic). The results of the present study, concerning the glycaemic effect of non-surgical periodontal therapy (without any local or systemic antibiotic administration) in diabetes, are in accordance with those of Kiran et al. (2005), who on 44 Turkish patients with type 2 diabetes and moderate periodontal disease, showed such treatment provided a statistically significant reduction in periodontal parameters and A1C levels (by 0.86%) after 3 months.

The definition and extent of periodontal disease and the effectiveness of periodontal disease treatment is another questionable issue in some of the studies (Jones et al. 2007, Darre et al. 2008, O'Connell et al. 2008, Teeuw et al.

2010) regarding the effect of periodontal disease treatment on patients with diabetes. Because the resolution of inflammation from the periodontal tissues, as a result of periodontal disease treatment is a prerequisite for A1C improvement, studies of patients with mild or no periodontal disease cannot be expected to exhibit a significant decrease in A1C after periodontal disease treatment. Taking this into account, only patients with moderate-to-severe periodontal disease were included in the present study. The clinical effectiveness of non-surgical periodontal disease treatment is shown in the current study through the significant improvement of all periodontal parameters, being consistent with the A1C improvement throughout the observation period of 6 months.

The biologic rationale and the mechanisms underlying the effect that periodontal treatment has on glycaemic control and chronic inflammation are not clarified completely, but there is evidence to support the hypothesis that resolution of inflammation from the periodontal tissues has a favourable effect on A1C levels. In a pilot study of 10 patients with both types of diabetes, a significant reduction of hsCRP was observed (-37%, p < 0.05) 1 month after periodontal treatment (Lalla et al. 2007). The present study was not designed to investigate the underlying mechanisms through which periodontal treatment results in improvement of glycaemic control. It is clear that more studies are needed to clarify these mechanisms.

Among the strengths of the present study are its observation period of 6 months, and the effectiveness of periodontal treatment (statistically significant improvement of all periodontal parameters) of the participants in the IG, which in the multivariate analysis was found to contribute to the observed glycaemic improvement. The CG received minimal treatment in the form of prophylaxis and oral hygiene instructions. It was considered unethical not to provide any form of treatment to the CG for 6 months, even though this may be the reason why glycaemic control improvement (not statistically significant) was observed even in this group. An issue in question regarding this trial is its generalizability (due to the trials' sample size) to the overall population of patients with DM and periodontal disease. Our sample size is admittedly small and may be subject to selection

In conclusion, this study has demonstrated that non-surgical periodontal treatment can improve the periodontal status of patients with type 2 diabetes and have a favourable effect on glycaemic control of these patients.

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Clinical Relevance

Scientific rationale: There is evidence that the resolution of periodontal inflammation can help patients with DM maintain better glycaemic control. The benefit of non-surgical periodontal therapy on

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A1C levels of patients with type 2 DM has not been clearly established. *Principal findings*: A statistically significant reduction (0.72% p < 0.05) in A1C levels and a significant improvement in all periodontal parameters was observed.

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Practical implications: Non-surgical treatment of periodontal disease in patients with type 2 DM has a favourable effect on their glycaemic and periodontal status.

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