International Journal of Diabetes Mellitus 2 (2010) 158–164

Contents lists available at ScienceDirect

International Journal of Diabetes Mellitus

journal homepage: www.elsevier.com/locate/ijdm

Original Article

A new paradigm between mechanical scaling and root planing combined with adjunctive chemotherapy for glycated hemoglobin improvement in diabetics

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ARTICLE INFO

Article history:
Received 29 May 2010
Accepted 31 August 2010

Keywords:
Diabetics
Gingival health
Periodontal disease

ABSTRACT

Aim: The objective of the study was to evaluate the effectiveness of scaling and root planing (SRP) and adjunctive chemotherapy (doxycycline hyclate, 20 mg) on gingival health, specific cytokines and glycemic control in diabetic subjects.

Methods: Three hundred and forty-six type 1 and 2 diabetic subjects were randomized into four test groups: (1) one session of SRP at the baseline visit and placebo tablets twice/day, started at the baseline visit, for 3 months, (2) one session of SRP at the baseline visit, and doxycycline hyclate (20 mg, twice/day) started at the baseline visit for 3 months, (3) two sessions of SRP, first at the baseline visit and second at the 6 months, with placebo tablets twice/day started at the baseline visit and 6-month visit, for 3 months at each visit, and (4) two sessions of SRP, first at the baseline visit and the second at the 6-month visit, and doxycycline hyclate 20 mg twice/day, started at the baseline visit and the 6-month visit, for 3 months at each visit. Venous blood samples were obtained to evaluate TNF-α, IL-1α and glycated hemoglobin (HbA1c); dental measurements were also included.

Results: HbA1c showed significant improvement ($P < 0.05$) only for subjects with glycated hemoglobin ⩽8.8% within each group, as well as when subjects were combined together. All groups achieved statistically significant improvements for most of the dental parameters at follow-up visits ($P < 0.05$) compared to the baseline.

Conclusions: Eliminating periodontal inflammation may significantly reduce glycated hemoglobin levels for subjects with HbA1c ⩽8.8%; furthermore, SRP and adjunctive therapy improved periodontal inflammation in diabetics.

1. Introduction

The World Health Organization (WHO) and International Diabetes Federation (IDF) have predicted that the number of diabetics will increase significantly by the year 2030 to approximately 366 million, an increase of 214% compared to the percentage in 2006 [1]. Diabetes is associated with several complications, and some types have been linked to a chronic hyperglycemic state. Diabetes is also frequently associated with pathological changes in the blood vessel walls [2]. The IDF and American College of Endocrinology (ACE) recommend HbA1c values of below 6.5%, while the American Diabetes Association (ADA) recommends that the HbA1c be below 7.0% for most patients [3]. Loe [4] reported that diabetes is a risk factor for periodontitis, and periodontal disease is the sixth-leading complication of diabetes [4]. Hyperglycemia appears to trigger a series of events leading to a higher risk of infection. The association between diabetes and an increased susceptibility to oral infection, including periodontal disease, is significant [5]. Chronic periodontitis is a slowly progressing disease that is primarily the result of an inflammatory response to plaque and calculus accumulation [6]. A more rapidly progressing clinical presentation of chronic periodontitis has been described in diabetic subjects [3,5]. Periodontal disease may also be an independent predictor of incident type 2

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doi:10.1016/j.ijdm.2010.08.006

diabetes, according to a study published in the July issue of Diabetes Care [7]. Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycemic control over time, when compared to diabetic subjects without periodontitis [8]. The level of specific inflammatory markers (TNF-alpha) in the gingival crevice fluid has also been related to the level of glycemic control in diabetic patients [9]. The diabetic state has also been shown to have an upregulated monocytic TNF-alpha secretion phenotype which, in the presence of Gram-negative bacterial challenge, is associated with the expression of more severe periodontal disease [9].

Several studies addressed the effect of periodontal treatment on the glycemic control of diabetic subjects [9–14]. However, the role of periodontal treatment on metabolic control within diabetics is still controversial [11,12,14–16]. Some studies show that periodontal treatment improves periodontal status in diabetic subjects [16]. However, other studies report that a further improvement in metabolic control is achieved when mechanical periodontal treatments and systemic antibiotics are used together [10,17]. Studies have also demonstrated that the subgingival delivery of doxycycline improves dental parameters, i.e., PPD, CAL, BOP, GI and PI in subjects with chronic periodontitis, when used in conjunction with supragingival scaling and dental prophylaxis. Mechanical therapy is the standard treatment in arresting disease progression and inflammation, and non-surgical care with adjunctive pharmacotherapies (such as antimicrobials and/or antibiotics aimed at modifying the destructive host response) has proved to be of additional benefit [11,16,18,19].

The aim of this study is to evaluate the effectiveness of scaling and root planing (SRP) therapy with or without chemotherapy (doxycycline hyclate, 20 mg) on gingival health, specific cytokines, and glycemic control in diabetic subjects.

2. Subject and methods

2.1. Study design

This study is a double-blinded, randomized, placebo-controlled, 12-month multi-center trial. Subject selection was conducted using eligibility screening following an assessment of periodontal status during baseline visits, and eligible subjects were given individual patient numbers; this was to validate the blinding and randomization analysis. The subjects at each hospital were allocated numbers which were used to randomize the different groups. This was achieved by distributing the subject number among the four test groups by sequentially allocating them to one of four alphabetical codes relating to a test group (i.e., A for group 1, B for group 2, C for group 3, and D for group 4). The four test groups were: (1) one session of SRP at the baseline visit only and placebo tablets twice/day, starting at baseline visit and continuing for 3 months only; (2) one session of SRP at the baseline visit only and doxycycline hyclate (20 mg, twice/day) starting at the baseline visit and continuing for 3 months only; (3) two sessions of SRP, the first at the baseline visit and the second at the 6-month visit and placebo tablets twice/day starting at the baseline visit and the 6-month visit, continuing for 3 months after each visit; and (4) two sessions of SRP, first at the baseline visit and the second at the 6-month visit, with doxycycline hyclate 20 mg, twice/day starting at the baseline visit and 6-month visit, continuing for 3 months after each visit (Table 1). Clinical measurements included the following periodontal parameters: probing pocket depth (PPD), clinical attachment level (CAL), gingival index (GI), plaque index (PI) and bleeding on probing (BOP). Fasting venous blood samples (20 mL) were obtained from the antecubital vein by venipuncture using a 27-G butterfly needle in the morning between 8:00 a.m. to 10:30 a.m. for the laboratory analysis of cytokines [Tumor Necrosis Factor alpha (TNF-α), Interleukin-1 alpha (IL-1α)] and to evaluate glycated hemoglobin (HbA1c) in all subjects. It should be mentioned here that the examiners as well as the dental hygienist in the different hospital were all blinded to the assigned treatment. Subjects were also blinded to the prescribed medication (doxycycline hyclate, 20 mg or placebo).

2.2. Study population

This study was conducted on 369 diabetic subjects registered at Riyadh Armed Forces Hospital, King Faisal Specialist Hospital and Research Center, King Abdul Aziz Medical City, Naval Base Hospital and Sultan Bin Adulaziz Humanitarian City, Riyadh, Saudi Arabia. The subjects were recruited from the above hospitals during their routine dental follow-up appointments. All subjects who were willing to participate in this research were asked to sign an informed consent agreement to participate in this study. The study was approved by the Research and Ethics Committee of the five involved hospitals and the study registered with International Standard Randomized Controlled Trial Number (ISRCTN-11742127). Twenty-three subjects did not continue at several intervals during the 12 months of the study, for reasons that violated the inclusion criteria – i.e., taking an antibiotic during the study period, extraction of tooth/teeth, minor or major surgical intervention during the study period, or due to loss of contact information. It should be mentioned here that those who failed to show up at any time point after the baseline visit or failed to show at the last visit (12 months) were also completely excluded from the study. A total of 346 subjects continued until the end of the study. Inclusion criteria were as follows: age range between 18 and 65 years old; diabetes identified as type 1 or 2; diabetes diagnosed $\geqslant$1 year; diabetes under control by oral hypoglycemic agent or insulin or both; constant type and dose of diabetic medication administered for the previous 6 months; and good physical condition with no serious medical conditions or transmittable diseases – i.e., malignant disease; active hepatitis; freedom from any cardiac condition that would require antibiotic prophylaxis prior to SRP; a minimum of 18 remaining natural and non-capped teeth; a minimum of six sites in a minimum of two different quadrants with PPD $\geqslant$5 mm but $\leqslant$8 mm; no treatment with SRP in the 6 months prior to the baseline visit; visible supragingival calculus in a minimum of four teeth in two different quadrants; the absence of orthodontic bands and brackets and/or dental appliances that would compromise the scored index; no use of antibiotics within the 3 months prior to the

Table 1
Distribution of different groups based on the treatment.

Months	Baseline	3 months	6 months	9 months	12 months
Groups					
Group-1	SRP + placebo (for 3 months)	–	–	–	–
Group-2	SRP + doxycycline hyclate (for 3 months)	–	–	–	–
Group-3	SRP + placebo (for 3 months)	–	SRP + placebo (for 3 months)	–	–
Group-4	SRP + doxycycline hyclate (for 3 months)	–	SRP + doxycycline hyclate (for 3 months)	–	–

SRP: scaling and root planing.

baseline appointment; and female subjects not pregnant or nursing.

2.3. Assessment procedures

Three trained, precalibrated examiners (periodontists) were allocated among the four centers. They were assigned to perform clinical assessments for all subjects throughout the study. Inter- and intra-examiner variability in the dental examination criteria were tested by performing duplicate examinations on 16 randomly selected subjects among the four centers at the baseline visit. The percentages of agreement were 93% for PPD, 87% for CAL, 94% for BOP, 91% for PI, and 88% for GI. An assessment for the each subject was conducted at baseline and at 3, 6, 9 and 12 months. Clinical dental measurements included PPD, CAL, BOP, GI, and PI; they were collected at the baseline, and at 3, 6, 9 and 12 months.

Each subject received full mouth supragingival and subgingival debridement using ultrasonic and hand instrumentation. This treatment was undertaken at one or two different visits, with a maximum of seven days between the first and second visits, by four trained dental hygienists, who were recruited solely for this purpose, at the four centers. Dental hygiene aids were provided for the subjects – i.e., toothbrush and toothpaste at the baseline visit. Written oral hygiene instructions were given to all subjects within the different treatment groups at each session, including appropriate teeth brushing technique (Bass method) [20] and demonstration of the proper use of inter dental brushes and dental floss. The Bass method calls for up and down strokes on the sides of the teeth with back and forth strokes on the tops of teeth. PPD, CAL, and BOP were measured on all existing teeth based on the above inclusion criteria at the six sites (mesio-buccal, med-buccal, disto-buccal, mesio-lingual, med-lingual and disto-lingual) using pressure-sensitive periodontal probes (® Florida Probe Corporation, 3700 NW 91st Street, C-100, Gainesville, FL 32606, USA). Four teeth within a minimum of two quadrants were selected, based on the criteria mentioned earlier for the follow-up examination at the 3-, 6-, 9- and 12-month visits. CAL was measured for teeth using the cemento-enamel junction (CEJ) as a reference point. GI [21], PI [22] were measured for all teeth on the facial, lingual, mesial and distal surfaces excluding the third molars. GI scores were as follows: 0 = normal gingiva, no inflammation, discoloration or bleeding; 1 = mild inflammation, slight color change, mild alteration of gingival surface, no bleeding; 2 = moderate inflammation, erythema and swelling, bleeding on probing or when pressure was applied; and 3 = severe inflammation, erythema and swelling, tendency to spontaneous bleeding, perhaps ulceration. The PI scores were as follows: 0 = no plaque; 1 = thin film of plaque at the gingival margin, visible only when scraped with an explorer; 2 = moderate amount of plaque along the gingival margin, which can be seen by the naked eye; 3 = heavy plaque accumulation at the gingival margin; interdental space filled with plaque. BOP was measured for all teeth at the six sites for each tooth, and rated as follows: 0 = no bleeding within 15 s after probing, or 1 = bleeding within 15 s after probing. The HbA1c test was performed at baseline and during the 3-, 6-, 9- and 12-month visits.

2.4. Cytokines analysis

A commercially available human interleukin enzyme-linked immunosorbent assay kit (Duo Set, ELISA Development System, UK) was used to determine the effect of the periodontal treatment on TNF-alpha, IL-1 alpha. The standards and samples were incubated in a 96-well polystyrene microplate coated with Capture Antibodies TNF-alpha, and IL-1 alpha, respectively. The interleukins in the samples were bound to the wells, and the other components of the samples were removed by washing and aspiration. The interleukins were detected by biotinylated goat anti-human antibodies. The amount of peroxidase bound to each well was measured by adding a tetramethylbenzidine (TMB) substrate. The reaction was quenched by the addition of 2 N sulphuric acid. The plate was read at 450 nm. The concentration of the interleukins in the serum samples was calculated by interpolation from a standard curve.

2.5. Statistical analysis

Statistical analyzes were performed on the data obtained from all subjects who completed the study and had no substantial protocol violations. All the available data from these subjects were analyzed, and no imputations were carried out for missing data. The results of dental parameters (PPD, CAL, GI, PI, and BOP), cytokines (TNF-α and IL-1α) and HbA1c measurements were analyzed using one-way analysis of variance (ANOVA). The Tukey–Kramer multiple comparisons test was used for comparisons among test groups. *P*-values <0.05 were assumed to be statistically significant.

3. Results

The age, gender and distribution of patients to the different study groups are illustrated in Table 2. A total of 346 subjects continued until the end of the study. 33 subjects were defined as type 1 diabetics out of the total sample; the remaining were defined as type 2 diabetics.

3.1. HbA1c (%)

Group 1 showed a marked but insignificant reduction at 3 and 6 months (8.89 ± 0.34% and 8.97 ± 0.48%, respectively). However, it rebound to a higher (but statistically insignificant) level than that recorded at the baseline visit (9.87 ± 0.33% and 9.90 ± 0.52%, respectively). Group 2 showed the same trend as group 1, and the changes were not significant. Group 3 did not show significant changes at the 3-, 6-, 9-, and 12-month visit (9.05 ± 0.39%, 8.58 ± 0.54%, 8.82 ± 0.42%, and 8.90 ± 0.53%, respectively) as compared to the baseline value (8.87 ± 0.29%), with no statistical difference between the different follow-up visits. Compared to the baseline value the group 4 showed a slight increase, with no

Table 2
Distribution of subjects in respective study groups.

Group	Subjects distribution	Gender		Mean age (years)	Types of diabetes	
		Male	Female		Type-1	Type-2
1	98	41	57	51 ± 6	9	89
2	93	44	49	48 ± 5	9	84
3	75	34	41	47 ± 4	7	68
4	80	42	38	43 ± 6	8	72
Total	346	161	185	47 ± 6	33	313

significant differences at the 3-, 6- and 12-month visits (9.14 ± 0.30%, 9.20 ± 0.28%, and 9.78 ± 0.38%, respectively) except 9-month visit (9.03 ± 0.35%). However, no significant differences were observed between the different groups (Fig. 1a).

A scaled-down statistical analysis of HbA1c for those subjects with baseline readings ⩽8.8% within each individual treatment group showed a steady but continuous (and significant) numeric reduction associated with an improvement in periodontal health (Fig. 1b). Interestingly, this significant reduction was observed when those subjects with HbA1c ⩽8.8% (n = 132) within the four groups combined together (Fig. 1c).

3.2. TNF-α (pg/ml)

The results showing the effect of different treatments on TNF-alpha are described in Table 3. There were no significant changes at the different time points within the four examination groups (1, 2, 3, and 4) or between the different groups (Table 3) except group 3 at 6-month and group 4 at 9-month visit compared to the baseline readings.

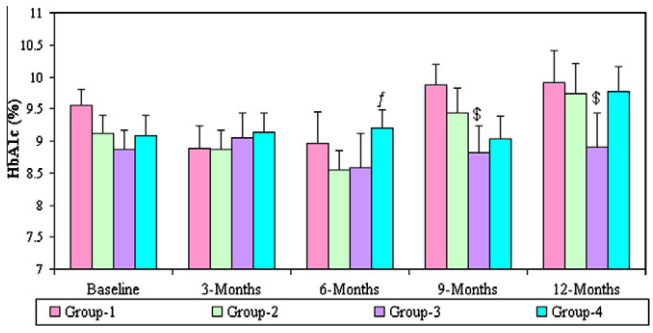

Fig. 1a. HbAlc (%) level within different treatment groups. Values are mean ± SEM, *P-values versus base line, Tukey–Kramer multiple comparisons test. Groups compared by Tukey–Kramer multiple comparisons test: $ 1 vs. 3 (P < 0.05), ^{f} 2 vs. 4 (P < 0.05).

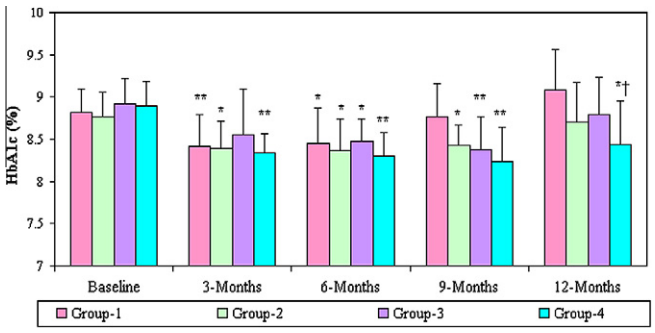

Fig. 1b. Periodontal treatment on HbAlc (%) (=<8.8). Values are mean ± SEM, *P-values versus base line, Tukey–Kramer multiple comparisons test, *P < 0.05, **P < 0.01. Groups compared by Tukey–Kramer multiple comparisons test: † 1 vs. 4 (P < 0.05).

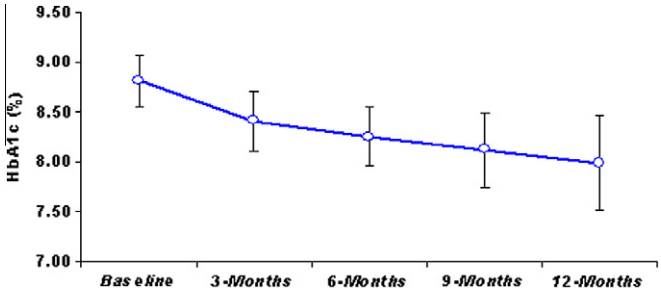

Fig. 1c. Periodontal treatment on HbA1c (%) (=<8.8). For all groups.

3.3. IL-1α (pg/ml)

The results showing the effect of different treatments on TNF-alpha are described in Table 3. There were no significant changes at the different time points within the four examination groups (1, 2, 3, and 4) or between the different groups (Table 3) except group 3 at 12-month and group 4 at 12-month visit compared to the baseline readings.

3.4. Clinical periodontal parameters

3.4.1. Dental indices

Changes within the periodontal parameters are illustrated in Table 4. It should be noted here that there were significant changes in PPD, PI, GI, and BOP for all groups, as compared to the baseline in the follow-up visits; such changes were not observed for CAL (Table 4).

4. Discussion

Adult periodontitis is a chronic inflammatory condition, characterized by acute episodes of periodontal destruction occurring in a susceptible host. The successful long-term management of periodontitis may require an integrated and tailored treatment that ensures that mechanical debridement will help in protecting the susceptible host and eliminating the causes of periodontitis. Previous studies have demonstrated that the subgingival delivery of doxycycline improves dental parameters, i.e., PPD, CAL, BOP, GI and PI in subjects with chronic periodontitis, when used in conjunction with supragingival scaling and dental prophylaxis [14,19,23]. Extending the longevity of teeth and reducing pathological, microbial anaerobic bacteria are the important reasons for performing periodontal therapy, to stabilize periodontal health within susceptible individuals and to prevent further loss of periodontal support [24].

Many studies have addressed the effect of periodontal treatment on the glycemic control of diabetic subjects [10–14,16]. The outcome of these studies is controversial. Some studies have shown that periodontal treatment has made little – if any-clinical improvement to glycemic control within diabetic subjects [10,16]. However, other studies show that periodontal treatment improves glycemic control in diabetic subjects [16], and report that there are further significant numeric as well as clinical improvements achieved in metabolic control when mechanical periodontal treatments and systemic antibiotics were combined together [10,17]. A reduction in glycated hemoglobin was noted in type 1 diabetes subjects following periodontal therapy, combined with systemic antibiotic treatment [17]. Similar results were found in type 2 diabetes subjects using systemic doxycycline [10]. It should be mentioned that in the present study, there were no significant changes to be observed in HbA1c; in addition, such changes were not equal for all groups within the study population or for subjects within each group. This is in agreement with previous studies, which show that mechanical periodontal treatment demonstrates an improvement in periodontal status without changes in glycemic control [10,14,19,25]. However, other studies have reported improvements in periodontal status and glycemic control when mechanical treatment and systemic antibiotics are included [10,19]. Williams and Mahan [17] also demonstrate that periodontal therapy improves metabolic control, as indicated by reduced insulin requirements and reductions in the blood glucose level.

Table 3
Effect of different treatments on IL-1 alpha (pg/ml) and TNF-alpha (pg/ml).

Periodontal parameter	Group	Baseline	3 months	6 months	9 months	12 months
IL-1 alpha (pg/ml)	1	3.16 ± 0.43	3.42 ± 0.42	2.85 ± 0.39	2.74 ± 0.37	2.83 ± 0.41
	2	3.02 ± 0.37	3.16 ± 0.37	2.97 ± 0.37	2.73 ± 0.32	2.72 ± 0.42
	3	3.08 ± 0.27	3.1 ± 0.43	2.63 ± 0.39	3.05 ± 0.37	2.46 ± 0.36*
	4	3.04 ± 0.43	3.16 ± 0.38	2.57 ± 0.41	2.89 ± 0.38	2.35 ± 0.36*†
TNF-alpha (pg/ml)	1	12.06 ± 2.43	12.86 ± 2.54	10.28 ± 2.16	12.1 ± 2.14	11.02 ± 2.34
	2	11.87 ± 2.12	12.42 ± 2.67	11.96 ± 2.42	10.73 ± 2.22	9.87 ± 2.72
	3	11.06 ± 1.73	12.96 ± 2.12	9.07 ± 2.02*‡	11.06 ± 2.87	11 ± 2.65
	4	11.4 ± 2.45	12.06 ± 2.03	10.13 ± 2.97	8.26 ± 2.83*†	10.24 ± 2.24

Values are mean ± SEM.
* *P*-values versus base line, Tukey–Kramer multiple comparisons test, $^{*}P < 0.05$. Groups compared by Tukey–Kramer multiple comparisons test: † 1 vs. 4 ($P < 0.05$), ‡ 2 vs. 3 ($P < 0.05$).

Table 4
Effect of different treatments on periodontal parameter.

Periodontal parameter	Group	Baseline	3 months	6 months	9 months	12 Months
PI (mean) all teeth	1	2.51 ± 0.08	1.71 ± 0.14***	1.87 ± 0.13***	1.95 ± 0.15***	1.46 ± 0.21***
	2	2.3 ± 0.1	1.53 ± 0.13***	1.82 ± 0.12**	1.46 ± 0.16***	1.69 ± 0.16**
	3	2.15 ± 0.1	1.5 ± 0.13***	1.59 ± 0.16**	1.4 ± 0.18***$	1.51 ± 0.22*
	4	2.11 ± 0.1	1.66 ± 0.13**	1.55 ± 0.13**†	1.8 ± 0.13	1.64 ± 0.18*
GI (mean) all teeth	1	2.38 ± 0.07	1.49 ± 0.12***	1.5 ± 0.12***	1.78 ± 0.13***	1.64 ± 0.2***
	2	2.15 ± 0.11	1.23 ± 0.12***	1.55 ± 0.1***	1.34 ± 0.16***#	1.35 ± 0.21***
	3	2.06 ± 0.11	1.27 ± 0.12***	1.39 ± 0.13***	1.4 ± 0.17***$	1.34 ± 0.25***
	4	2.06 ± 0.1	1.47 ± 0.13***	1.53 ± 0.12***	1.64 ± 0.13***	1.27 ± 0.23***†
PPD (mm) experimental teeth only	1	4.06 ± 0.13	3.2 ± 0.13***	2.94 ± 0.16***	3.16 ± 0.26***	2.69 ± 0.25***
	2	3.9 ± 0.14	2.88 ± 0.15***	3.05 ± 0.17***	2.82 ± 0.22***	2.4 ± 0.2***
	3	3.86 ± 0.18	2.7 ± 0.14***$	2.74 ± 0.16***	2.63 ± 0.22***	2.46 ± 0.35***
	4	3.92 ± 0.13	2.86 ± 0.15***	2.94 ± 0.15***	2.99 ± 0.16***	2.29 ± 0.27***
CAL (mm) experimental teeth only	1	5.58 ± 0.23	4.92 ± 0.22	4.87 ± 0.25	4.8 ± 0.31	5.25 ± 0.29
	2	5.01 ± 0.2	4.43 ± 0.23	4.6 ± 0.25	4.47 ± 0.3	4.37 ± 0.25
	3	5.32 ± 0.27	4.42 ± 0.24*	4.53 ± 0.25	4.48 ± 4.41	4.89 ± 0.29
	4	4.96 ± 0.18	4.45 ± 0.19	4.64 ± 0.2	4.65 ± 0.17	3.83 ± 0.18 †
BOP (%) all teeth	1	75.8 ± 3.3	35.2 ± 4.5***	31.2 ± 5.3***	34.8 ± 5.8***	5.25 ± 6***
	2	75.01 ± 3.4	24.1 ± 4.2***	31.2 ± 4.5***	28 ± 5.4***	15.9 ± 6.4***
	3	61.7 ± 4.8	21.9 ± 3.9***	21.4 ± 4.2***	24.3 ± 6.4***	20.9 ± 8.4***
	4	65.2 ± 4.7	32.5 ± 5.3***	24.6 ± 4.2***	28.4 ± 5.9***	15.1 ± 6.1***

PPD – probing pocket depth, CAL – clinical attachment level, GI – gingival index, PI – plaque index, BOP – bleeding on probing.
Values are mean ± SEM, *P-values versus base line, Tukey–Kramer multiple comparisons test, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Groups compared by Tukey–Kramer multiple comparisons test: # 1 vs. 2 ($P < 0.05$), $ 1 vs. 3 ($P < 0.05$), † 1 vs. 4 ($P < 0.05$).

A scaled-down statistical analysis of HbA1c for those subjects with baseline readings ⩽8.8% within each individual treatment group showed a steady but continuous (and significant) numeric reduction associated with an improvement in periodontal health (Fig. 1b). Interestingly, this significant reduction was observed when those subjects with HbA1c ⩽8.8% ($n = 132$) within the four groups are combined together (Fig. 1c).

In addition, there was a statistically significant improvement at each time point when compared to the baseline reading; also, when the HbA1c value became higher within that range (⩽8.8%), the reduction was more noticeable. This observation may be explained by the impact of the local oral infection and periodontal inflammation, i.e., swelling, bleeding and calculus accumulation on the underlying systemic conditions may be systemically effective, and add numerical impact and value, which could further provoke an underlying inflammatory response when HbA1c is higher within that range (⩽8.8%) [4,15] and enhance the glycemic disturbance. In addition, when combined with high HbA1c levels within the range ⩽8.8%, this may synergistically raise the HbA1c level within this group of diabetic patients. Therefore, the improvement may be numerically noticeable, due to the improvement in previously mentioned local factors, which may contribute to the systemic improvement maintained by hypoglycemic medications. On the other hand, when the glycemic level is uncontrolled (i.e., >9%), which may occur because of several major systemic factors (i.e., inappropriate dose of hypoglycemic medications, uncontrolled diabetes), the influence of periodontal therapy is defined hereby as local factors, i.e., improvement in periodontal infection will be diminished, and may not enhance improvement compared to the underlying compromised systemic condition (poor glycemic control). Also, it was noticeable that when the HbA1c level approached near to the normal range (≈6.5%), such associations became weak or/and insignificant. This complex phenomenon may be explained hypothetically by the fact that when the glycated hemoglobin level is relatively controlled (≈6.5%), any improvement within the local oral environment (measured by periodontal indices) may have minimal impact, if any, on the systemic improvement measured by HbA1c. Thus, periodontal therapy may enhance improvement near the normal range of glycated hemoglobin for those subjects under good diabetic control. The evidence and reasoning described herein may improve the understanding of the significant conflict and controversy that resulted from previous studies, as most of those studies did not establish a clear and appropriate link to the trends and levels of glycated hemoglobin. Further studies may be needed to test these findings.

Studies have shown that TNF has a broad range of biological effects, including the stimulation of bone resorption [26]. The present study shows that there is a general trend toward a slight

mean reduction among the four groups when compared to the baseline measurements. However, this change is not significant when comparing different groups, or when comparing any of the follow-up time points to the baseline reading (Table 3). This may be explained by the fact that the improvement of certain inflammatory mediators (i.e., TNF-α) is sensitive to the given treatment and that this effect may not last long as such levels will rebound within 24 h [27]. Therefore, because periodontal inflammation is a chronic disease that recurs in most of the affected subjects at different levels after the given treatment, the level of TNF-α may have reduced further after the prescribed treatment but rebound before the next evaluation visit.

The potential role of IL-1 in periodontal tissue destruction involves negative effects on periodontal ligament cells [28]. IL-1 has been shown to have strong stimulatory effects on increased bone resorption and inhibitory effects on bone formation [28]. Other studies have clearly demonstrated that interleukin-1 is a potent stimulator of bone resorption and that this effect is mediated via prostaglandin E2 (PGE2) [29]. The present study shows that all groups achieved a mean improvement in IL-1α by the end of the study, compared to baseline levels (Table 3). However, none of the groups achieved any clinical or statistical significance or added advantage when compared to each other. In comparing the results of this study to those of previous studies [30,31], it is suggested that SRP reduces TNF-α and IL-1α levels in the studied population. However, the reductions found were not statistically significant.

In the present study, the severity of periodontal disease measured by dental indices (PPD, CAL, GI, PI, and BOP) was approximately within the same range at baseline, with no significant difference among the four groups (Table 4). Clinical improvement was statistically significant in most of the clinical periodontal parameters (PPD, GI, PI, and BOP) within the four treatment groups at the 3-, 6-, 9-, and 12-month visits (Table 4). This is in accordance with the results of several previous studies [32,33]. The findings indicate that (1) periodontal maintenance therapy, including scaling and root planing and tooth debridement, when given periodically to diabetics, and (2) oral hygiene instruction, which was given at each recall visit, resulted in markedly improved oral hygiene conditions for all treatment groups (Table 4), a result that supports the findings of earlier studies [32,33].

Therefore, it is confirmed that scaling and root planing (SRP) has a significant and beneficial effect on periodontal health in these diabetic subjects, and reduced tissue breakdown. However, adjunctive therapy (groups 2 and 4) had numeric but not statistically significant clinical advantages. The present study shows that although there is a general trend toward improvement (as measured by dental indices at each follow-up visit), group 4 subjects had a statistically significant improvement at the 12-month visit, compared to the baseline level. This is in agreement with existing research [34] and may be due to the efficacy of the repeated sessions of SRP, as well as the repeated adjunctive chemotherapy treatment (doxycycline hyclate, 20 mg) that might help in reducing gingival inflammation. It is consistent with earlier reports describing the efficacy of regular and low-dose tetracyclines, such as minocycline and low-dose doxycyline [35]. The beneficial effects of adjunctive chemotherapy (doxycycline hyclate, 20 mg), along with SRP (group 2), may help in reducing gingival inflammation. Accordingly, our observation needs further validation to provide better evidence in this regard. Whether there is a cut-off point in the HbA1c level that can be improved by treating local factors, i.e., periodontal disease is an interesting point to discuss in future studies. Further studies are needed to enhance our understanding of the role of periodontal treatment in diabetes mellitus. In conclusion to this study, the present results suggest that the improvement in periodontal inflammation measured by periodontal indices may lead to a significant improvement in the glycated hemoglobin level for subjects with HbA1c $\leqslant$8.8%.

Contribution

All authors contributed equally to the conception, design, and interpretation of data and the final manuscript.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Acknowledgements

This project was funded by King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia (Research Grant #3/21/T1).

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