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ORIGINAL ARTICLE

Non-surgical periodontal therapy with and without subgingival minocycline administration in patients with poorly controlled type II diabetes: a randomized controlled clinical trial

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Abstract The aim of this study was to evaluate changes in clinical parameters and levels of inflammatory biomarkers in plasma in periodontal patients with poorly controlled type 2 diabetes mellitus (T2DM) after non-surgical periodontal therapy. Twenty-eight poorly controlled T2DM patients were randomly assigned to treatment with scaling and root planning (SRP) and SRP + subgingival minocycline administration. Clinical parameters, including the probing depth (PD), bleeding on probing (BOP), plaque score (PS), clinical attachment level (CAL), and plasma interleukin (IL)-6, soluble receptor of advanced glycation end products (sRAGE), chronic reactive protein (CRP), and hemoglobin A1c (HbA1c) were measured before and after a 6-month treatment period. Significant changes in PD, BOP, PS, and CAL were found in both groups. The latent growth curve model showed an overall reduction in the log HbA1c level in the SRP group (−0.082, p=0.033). Small changes in the log sRAGE level and log CRP level in plasma were found in both groups. IL-6 in the plasma increased in the SRP group, but slightly decreased in the SRP+minocycline group (0.469 pg/ml, p=0.172). Non-surgical periodontal therapy with or without subgingival minocycline application may achieve significant periodontal improvement and moderate improvement in HbA1c, but had no significant effect on plasma levels of IL-6, CRP, or sRAGE in patients with poorly controlled T2DM. For patients with both periodontal diseases and diabetes, non-surgical periodontal treatments may be helpful in their diabetic control.

Keywords Root planning · Type II diabetes · Minocycline · HbA1c · sRAGE · CRP

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Introduction

Many studies show that periodontal infection and inflammation are associated with the development and progression of systemic conditions [1, 2]. Epidemiological studies demonstrated associations between periodontal disease and diabetes, and diabetic patients with poor glycemic control are at an increased risk for periodontitis [3–9]. Diabetics with severe periodontal disease are six times more likely to have poor glycemic control [10, 11].

Strong evidence indicates that elevated cytokine and chemokine expression levels by cells within gingival connective tissue in chronic periodontitis lesions are related to increased levels of these inflammatory mediators in the blood circulation where they can induce or perpetuate systemic effects. The elevated serum levels of these mediators may have deleterious effects on glucose and

lipid metabolism [12–15]. Several pro-inflammatory cytokines can induce periodontal tissue destruction and are considered indicators or diagnostic markers of periodontitis. Our previous investigation showed that interleukin (IL)-6 and oncostatin may play a role in modulating the inflammatory cascade of chronic periodontitis [16]. Hyperglycemia progressively glycates body proteins and forms advanced glycation end products (AGEs) [17]. Accumulation of AGEs in tissues may result in a significant alteration of the normal cellular composition and accelerated destruction of non-mineralized connective tissue and bone in diabetes [18]. Since advanced AGEs upregulate receptor of AGE (RAGE) expression and endogenous soluble RAGE (sRAGE) can be generated from the cleavage of cell surface RAGEs, it is conceivable that sRAGEs are positively associated with circulating AGE levels in diabetes [19, 20]. sRAGE levels may possibly become a novel biomarker of vascular inflammation in type 2 diabetes mellitus (T2DM) patients.

Intervention trials have assessed the potential effects of periodontal therapy in glycemic control in subjects with diabetes [21]. However, evidence to support the beneficial effects of periodontal therapy on improving glycemic control remains inconsistent [22–25].

Our previous study indicated that treating periodontal disease by incorporating local minocycline administration might yield a significant reduction in periodontal infection and inflammation [26]. Non-surgical periodontal treatment can improve cytokine levels and was proven to be an effective way to control periodontitis progression [24]. However, the use of systemically delivered antibiotic therapy in conjunction with non-surgical periodontal therapy may therefore be of great value in treating diabetic patients with periodontitis [21, 27], but very few studies have addressed the effects of conventional periodontal treatment with and without adjunctive local antibiotics application on patients with periodontal diseases and poorly controlled T2DM [28]. The purpose of this study was to evaluate the effects of non-surgical periodontal therapy alone and in conjunction with subgingival minocycline administration on changes of periodontal parameters and serum chronic reactive protein (CRP), IL-6, HbA1c, and sRAGE in patients with poorly controlled diabetes mellitus (DM) and chronic periodontitis. Latent growth curve modeling was used to test changes in clinical and laboratory variables following periodontal treatments.

Materials and methods

Patient selection

We recruited 28 patients with type II diabetes mellitus from DM clinics in Shin-Kong Memorial Hospital, Taipei, Taiwan. The diagnosis of poorly controlled T2DM was defined by a diabetic specialist (Lai SM) using a cutoff value of HbA1c of ≥8.5% for more than 5 years. To be recruited into this study, patients had to have at least 20 teeth remaining in the mouth and five or more teeth with a probing depth of ≥5 mm, and could not have taken any antibiotics nor received any periodontal treatment during the past 6 months. Exclusion criteria were allergy to tetracycline or any related antibiotic, being pregnant or intending to become pregnant during the study period, being smokers, and being unwilling to sign the consent form and accept periodontal therapy.

Study design

Fourteen patients with T2DM were randomly allocated to the scaling and root planning (SRP) group and 14 patients to the SRP in conjunction with subgingival antibiotics (2% minocycline gel, Periocline, Sun Star, Osaka, Japan) therapy group (SRP+minocycline). Random allocations were carried out using random numbers generated by the statistical software package Stata 9.0 (StataCorp, College Station, TX, USA). This was a single-blind, parallel-group study. The allocation sequence was concealed from the periodontist (SJL) who was responsible for treating patients and collecting clinical and laboratory data.

All enrolled patients were treated with SRP in quadrant by quadrant on a weekly basis. Non-surgical periodontal therapy included oral hygiene instruction and full mouth scaling and root planing for four consecutive appointments. One month after scaling and root planing, patients in the SRP+minocycline group received a 4-week regimen of subgingival minocycline [26]. The tip of a specially designed syringe containing the 2% minocycline gel was inserted into the base of periodontal pockets at the experimental sites, and then the antibiotic gel was gently pushed out of the syringe until the antibiotic gel flowed over the gingival margin while the tip was slowly withdrawn from periodontal pockets. The patient was instructed not to drink or eat for 30 min after gel injection. Over the following 3 weeks, the experimental sites received additional subgingival minocycline administration once a week, whereas the control sites received only supragingival plaque control.

Data of clinical parameters, which included probing depth (PD), bleeding on probing (BOP), plaque score (PS), clinical attachment level (CAL), and plasma levels of IL-6, CRP, HbA1c, and sRAGE were collected at the baseline appointment and at the 3- and 6-month follow-up visits after non-surgical therapy by the same periodontist (SJL). This study was approved by the Institutional Review Board at the Shin-Kong Medical Center (96E-021).

Measurement of probing depth, bleeding on probing, and clinical attachment

PD was measured by the first author (SJL) from the free gingival margin to the base of the periodontal pocket using a UNC #15 (HuFriedy, Chicago, IL, USA) periodontal probe. Measurements were taken at six sites per tooth at baseline, 3 months, and 6 months for all teeth within each subject. BOP was measured as a binary variable (yes versus no) for each site, and then a summary score presented as the percentage of sites with bleeding was calculated for each patient. For plaque scores (PS), disclosing solution was applied to all tooth surfaces, and the O'Leary Index [29] was recorded. CAL is the distance between the cemento-enamel junction and the bottom of the periodontal pocket, and it was measured at six sites around the teeth with the periodontal probe.

Measurement of IL-6, CRP, sRAGE, and HbA1c data in plasma

Three milliliters of venous blood was drawn from the antebrachial fossa of patients and processed to quantify IL-6, CRP, and sRAGE levels at baseline and at 3 and 6 months after non-surgical periodontal treatments. The current value of HbA1c was retrieved at the baseline point and 3 and 6 months after treatment from medical records in the hospital to ensure that the results of HbA1c reflected glycemic control over the previous 2–3 months. Concentrations of plasma CRP, sRAGE, and IL-6 were measured by CRP, sRAGE, and IL-6 enzyme immunoassay systems (Quantikine® HS; R&D Systems, Minneapolis, MN, USA). The sensitivities of CRP, sRAGE, and IL-6 for enzyme immunoassay were 0.78 ng/ml, 78 pg/ml, and 0.156 pg/ml, respectively. For each patient, gingival crevicular fluid (GCF) samples were taken from three or four sites with 5-mm pocket depth or more for measuring IL-6 concentration in GCF. In total, GCF samples were taken from 109 sites of 109 teeth within 28 patients. Gingival fluid samples were collected from the mesiobuccal and mesiolingual surfaces of selected teeth with Periopaper strips (HARCO Electronics, Irvine, CA, USA) of standard dimensions. Prior to sampling, the test area was air-dried and isolated with gauze. The first paper strip was slipped into a gingival pocket 1 mm subgingivally for 5 s and discarded immediately in order to avoid contamination by saliva. A second paper strip was inserted in the selected site for another 30 s. The remaining paper strip was then dipped in a 200-ll phosphate-buffered saline container and stored at −80°C for further IL-6 analysis. A Periotron HAR-6000 (Periotron 6000, HARCO Electronics) was used to accurately estimate gingival fluid volume by daily adjustment, and this value was adjusted in a calibration function using human serum as the standard. Results were calculated as the mean of triplicate measurements in each sample taken from each site at each time point.

Sample size calculation

Sample size calculation was undertaken by assuming 3 mm in mean pocket depth reduction in the test group with 0.7 mm standard deviation and 2 mm in the control group with 0.7 mm standard deviation, 90% statistical power, and 5% significance level. This is because little information was available in periodontal literature about the expected differences in other main outcomes, HbA1c and sRAGE. Statistical software Stata showed that the required sample size for each group was 11, and we recruited 14 patients to account for potential dropouts and missing data.

Statistical analysis

As there were three repeated measurements for the clinical and biochemical variables in this study, latent growth curve modeling (LGCM) was used to test for differences in changes from the baseline because the LGCM is a flexible statistical method in modeling nonlinear changes [30–32]. LGCM is a special application of structural equation modeling for repeated measurements. Individual growth curves (i.e., changes over time) are estimated for each subject, and variations in the baseline values (i.e. intercepts) and subsequent changes (i.e. slopes) within the sample are treated as latent variables. This approach is similar to multilevel or random effects modeling for longitudinal data where latent variables for the intercepts and slopes are modeled as random effects [33, 34]. One problem with the analysis of repeated measurement of periodontal data is that most change in the outcome occurs between baseline and the first follow-up, and as a result, a flexible methodology, such as LGCM, is required to model the sudden changes in the outcome in the first follow-up and residual changes in subsequent follow-ups [35]. Random effects modeling usually uses polynomial terms for time to capture nonlinear change, and this approach is not practical because there were only three repeated measurements in this study. Furthermore, the interpretation of the polynomial terms is not always straightforward. In LGCM, we can fix the factor loadings for the baseline and final measurements to 0 and 1, respectively, and allow the factor loading for the intermediate measurement to be estimated [34, 35]. This is a simple and elegant way to capture a nonlinear change pattern. Readers can find detailed explanation for LGCM modeling strategy in [34, 35]. For PD and IL-6 measured at the 109 sites, a multilevel LGCM was used in order to take into account the clustered structure of the data. The variations in the intercept and slope (i.e., equivalent to

random effects in the random slopes model in multilevel analysis) were estimated at the subject level, but only the variations in the intercept were estimated at the site level. The random effects for the intercept and slope were allowed to be correlated in the single-level LGCM and on the subject level in the two-level LGCM. Descriptive and univariate statistical tests were conducted using SPSS version 13 (SPSS, Chicago, IL, USA). LGCM was undertaken using the statistical software package Mplus version 5.21 (Muthen & Muthen, Los Angeles, CA, USA). The statistical significance level was set to 5% throughout the study.

Results

Demographic information and descriptive statistics

Demographic information of the researched subjects is given in Table 1. Both SRP and SRP+minocycline groups showed a significant pocket reduction which ranged between 1.74 and 2.02 mm in the 3- and 6-month follow-ups (Table 2). Nevertheless, the two-level LGCM showed no significant differences in changes in pocket depth or IL-6 at site level between the SRP and SRP+minocycline groups over 6 months. There was a significant reduction in

Table 1 Demographic characteristics of patients in the 6-month trial

	SRP (n=14)	SRP + minocycline (n=14)
Age (years)		
Mean ± SD	59.0±6.5	56.6±7.8
Age range (years)		
Young/old	40/68	43/69
Gender (n)		
Male/female	5/9	3/11
BMI		
Mean ± SD	25.7±3.3	26.8±3.9
CRP (pg/dL)		
Mean ± SD	1,477.8±1,393.9	1,509.3±1,370.3
sRAGE (pg/dL)		
Mean ± SD	732.6±327.4	733.1±422.0
IL-6 (mg/dL)		
Mean ± S.D	1.51±0.52	1.68±1.53
HbA1c (%)		
Mean ± SD	9.9±2.2	9.3±0.8

There is no baseline difference in the four main outcomes (CRP, sRAGE, IL-6, and HbA1c) between the test and control groups using t test
SRP scaling and root planing, *SRP + minocycline* scaling and root planing in conjunction with subgingival minocycline administration, *CRP* C-reactive protein, *sRAGE* soluble receptor of advanced glycation end products, *IL*-6 interleukin-6

Table 2 Three-month and 6-month treatment effect of probing depth, bleeding on probing, plaque index, and clinical attachment level

	PD(mm)			BOP (%)			PS (%)			CAL (mm)		
	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months
SRP	5.15±0.52	3.36±1.12*	3.13±1.10*	36.43±19.58	15.64±14.47*	15.93±14.24*	47.93±7.99	27.07±7.50*	18.79±2.94*	5.84±0.67	3.78±0.98*	3.98±0.90*
SRP + minocycline	5.13±0.47	3.39±0.91*	3.11±0.92*	45.00±11.66	11.50±8.37*	12.71±7.16*	42.93±7.00	17.86±6.55*	19.29±4.48*	5.80±0.88	4.15±0.95*	3.76±0.81*

SRP scaling/root planning, *PD* probing depth, *BOP* bleeding on probing, *PS* plaque score, *CAL* clinical attachment level
*$p<0.05$ (compared to baseline data)

BOP in both groups, but no significant difference between the two groups was found. Results of PS suggested that patients in this study showed moderate to high compliance to our plaque control program, although they did not achieve an ideal level as expected (15%). Both groups also showed a significant gain in CAL, but no significant difference between the two groups was found.

Plasma IL-6, HbA1c, CRP, sRAGE

The LGCM showed that IL-6 in plasma increased in the SRP group but decreased in the SRP+minocycline group (Fig. 1), although the difference was not statistically significant (0.469 pg/ml, p=0.172; Table 3). As the distributions of sRAGE, HbA1c, and CRP were quite skewed, a natural log transformation was used (Figs. 2, 3, and 4). The LGCM for log-transformed sRAGE showed that there was a small overall reduction in the log sRAGE in the SRP group (−0.147, p=0.162) during the 6 months of observation, but there was little change in the SRP +minocycline group (Table 3). The difference between the two groups was not statistically significant (0.129, p= 0.420; Fig. 2). The LGCM for log HbA1c showed that there was little change between the baseline and 3 months, and most change occurred between 3 and 6 months (Fig. 3). There was a significant overall reduction in the log HbA1c in the SRP group (−0.082, p=0.033), and there was a smaller change in the SRP+minocycline group. Using 0.66% reduction [22] of HbA1c level as the cutoff value, 9 of 14 patients in the SRP group and 8 of 14 patients in the SRP+minocycline group showed improved HbA1c levels (Table 4). The difference between the two groups was not statistically significant (0.031, p=0.473; Table 3). There was little change in log CRP in plasma for either the SRP or SRP+minocycline group (Fig. 4 and Table 3).

Discussion

Periodontal non-surgical therapy for diabetic patients

The short-term non-surgical treatment response of patients with stable diabetes was found to be similar to that of non-diabetic controls, with similar trends in improved PDs, attachment gain, and altered subgingival microbiota [22]. Patients with well-controlled diabetes with regular supportive therapy were also shown to maintain long-term treatment results after a combination of non-surgical and surgical treatments [36]. However, less favorable treatment outcomes may occur in long-term maintenance therapy with poorly controlled diabetes in patients who may be predisposed to more rapid recurrence of initially deep pockets [37]. Our study showed that conventional SRP and SRP + minocycline can achieve periodontal pocket reduction in patients with poorly controlled T2DM. Our previous 18-week clinical trial suggested that SRP with adjunctive subgingival administration of minocycline ointment has a significantly better and prolonged effect compared to SRP alone on the reduction of probing depth and clinical attachment loss. The better result of the SRP+minocycline group may be explained by the antimicrobial effects of the drug [26].

Compared to the first randomized, single-blind, controlled clinical trial in patients with poorly controlled

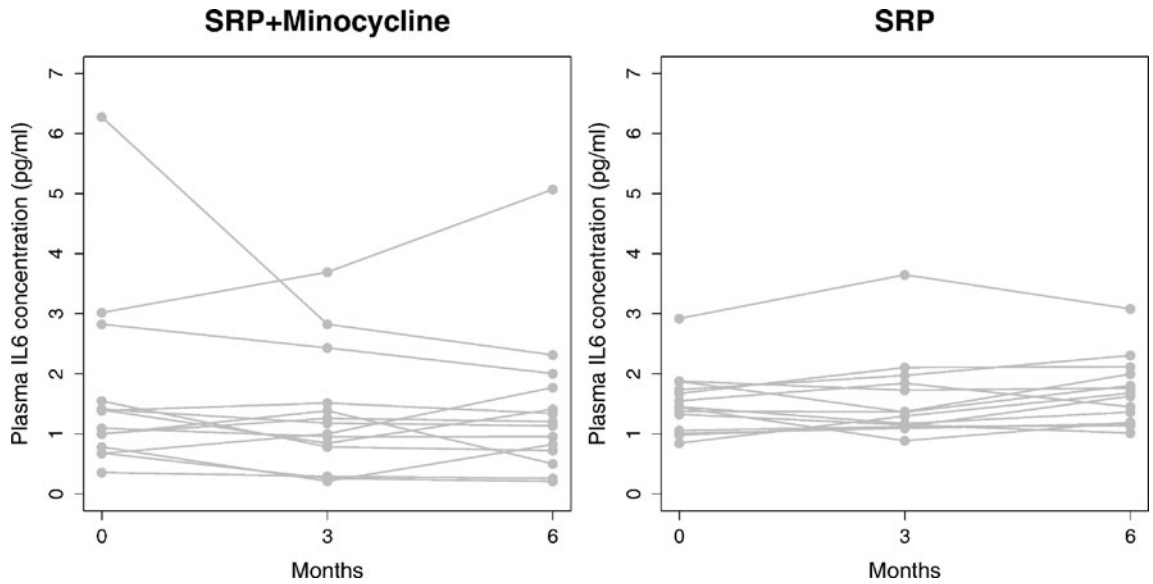

Fig. 1 Mean changes in plasma levels of IL-6 for every patient

Table 3 Results from LGCM for serum biomarkers

			Coefficients	SE	*p* value
IL-6					
$IL6_0$	←	SLOPE	0		
$IL6_3$	←	SLOPE	0.752	0.092	<0.001
$IL6_6$	←	SLOPE	1		
INTERCEPT	←	Group	0.158	0.414	0.702
SLOPE	←	Group	−0.469	0.343	0.172
Intercepts					
INTERCEPT			1.496	0.292	<0.001
SLOPE			0.158	0.243	0.515
Covariance					
INTERCEPT	↔	SLOPE	−0.536	0.224	0.016
Residual variances					
INTERCEPT			1.114	0.321	0.001
SLOPE			0.665	0.228	0.004
$IL6_0$			0.086	0.023	<0.001
$IL6_3$			1.276	1.108	<0.001
$IL6_6$			0.237	0.105	<0.001
sRAGE					
$sRAGE_0$	←	SLOPE	0		
$sRAGE_3$	←	SLOPE	0.705	0.141	<0.001
$sRAGE_6$	←	SLOPE	1		
INTERCEPT	←	Group	−0.052	0.194	0.788
SLOPE	←	Group	0.129	0.149	0.42
Intercepts					
INTERCEPT			6.486	0.137	<0.001
SLOPE			−0.147	0.105	0.162
Covariance					
INTERCEPT	↔	SLOPE	−0.021	0.041	0.619
Residual variances					
INTERCEPT			0.238	0.071	0.001
SLOPE			0.103	0.044	0.018
$sRAGE_0$			0.027	0.007	<0.001
$sRAGE_3$			0.027	0.007	<0.001
$sRAGE_6$			0.027	0.007	<0.001
HbA1c					
$HbA1c_0$	←	SLOPE	0		
$HbA1c_3$	←	SLOPE	−0.226	0.698	0.746
$HbA1c_6$	←	SLOPE	1		
INTERCEPT	←	Group	−0.032	0.048	0.505
SLOPE	←	Group	0.031	0.043	0.473
Intercepts					
INTERCEPT			2.241	0.042	<0.001
SLOPE			−0.082	0.038	0.033
Covariance					
INTERCEPT	↔	SLOPE			
$HbA1c_0$	↔	$HbA1c_3$	−0.01	0.004	0.016
Residual variances					
INTERCEPT			0.014	0.004	0.002
SLOPE					

Table 3 (continued)

			Coefficients	SE	*p* value
$HbA1c_0$			0.013	0.003	<0.001
$HbA1c_3$			0.013	0.003	<0.001
$HbA1c_6$			0.013	0.003	<0.001
CRP					
CRP_0	←	SLOPE	0		
CRP_3	←	SLOPE	0.5		
CRP_6	←	SLOPE	1		
INTERCEPT	←	Group	−0.032	0.048	0.505
SLOPE	←	Group	0.031	0.043	0.473
Intercepts					
INTERCEPT			0.227	0.388	0.56
SLOPE			−0.107	0.252	0.67
Covariance					
INTERCEPT	↔	SLOPE	−0.101	0.152	0.507
Residual variances					
INTERCEPT			0.89	0.286	0.002
SLOPE			0.032	0.158	0.837
CRP_0			0.2	0.153	<0.001
CRP_3			0.2	0.153	<0.001
CRP_6			0.2	0.153	<0.001

The significance test for each parameter in the model is based on the *z* ratio of the estimate over its standard error (SE) by assuming a normal distribution. The latent variable INTERCEPT represents the variations in baseline value for SRP group, while SLOPE represents the variations in the change. For all models, the only covariate is the variable Group coded as 1 for SRP + minocycline and 0 for SRP. The two latent variables, INTERCEPT and SLOPE, are allowed to be correlated. INTERCEPT represented the baseline values and SLOPE the mean changes for SRP. The regression coefficients for Group represented the differences between SRP + minocycline and SRP in baseline (INTERCEPT←Group) or overall changes from baseline (SLOPE←Group)

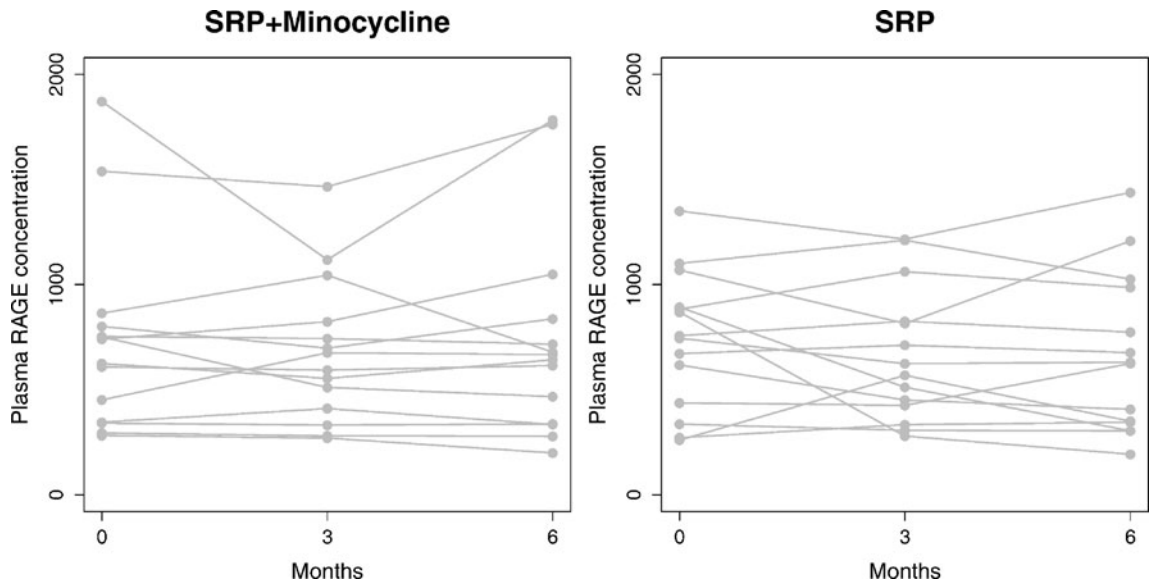

Fig. 2 Mean changes in plasma levels soluble receptor of advanced glycation end products (*sRAGE*) for every patient

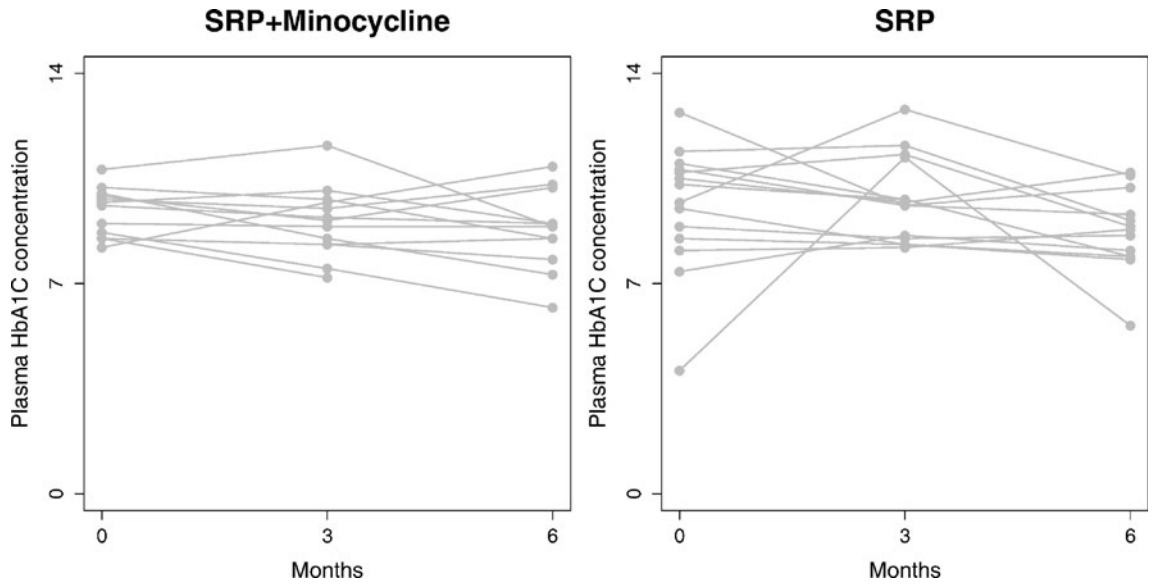

Fig. 3 Mean changes in plasma levels of HbA1c for each patient

T2DM [24], the results of PD reduction were quite similar. In that study, approximately 60% of the deep pockets remained unchanged after 4 months of healing. Another study which associated the effect of non-surgical periodontal therapy with systemic levels of CRP also showed a similar clinical reduction in PD [38].

Effect of SRP on HbA1c control

Recently, Janket et al. [21] conducted a meta-analysis of ten intervention studies to quantify the effects of periodontal treatment on HbA1c levels among diabetic patients. Results showed that the actual decrease in HbA1c levels was 0.38% in all studies, 0.66% when restricted to T2DM patients, and 0.71% if antibiotics were prescribed. However, none was statistically significant. In a recent study on the effect of periodontal therapy on the glycemic control of type I diabetes mellitus patients [25], the mean glycemic control improved in 35% and worsened in 28% of the study subjects during the study period. The change in HbA1c was assessed using both a positive or negative change of >0.5% and any change in HbA1c. It was found that the reduction of HbA1c was significantly associated with the baseline HbA1c, but not with the baseline periodontal health status or periodontal healing. From our clinical trial, LGCM for log-transformed HbA1c values showed that there was a slight change between the baseline and 3 months, and most change occurred between 3 and 6 months in both the SRP and SRP+minocycline groups ($p<0.05$). In total, 64.3% patients in the SRP group and 57.1% in the SRP +minocycline group showed improved HbA1c levels (Table 4). While the number of our patients was limited, our results seem to suggest beneficial effects of SRP and SRP + minocycline on glycemic control.

Table 4 Ratio of plasma HbA1c reduction of >0.66% of both groups comparing 6-month with baseline data

HbA1c% reduction>0.66%	
SRP	9/14 (64%)
SRP + minocycline	8/14 (57%)

Changes of IL-6 and CRP in plasma

There is a scientific basis for the increased susceptibility to periodontal disease seen in people with diabetes, including clinical, cellular, and immunologic aspects [39]. The inflammatory response of periodontal tissues to plaque challenge is complex and involves networks of cytokines functioning in synergy. It is likely that alterations in immunologically active molecules as a result of diabetes may alter cytokine networks in the periodontium. Emerging concepts of diabetes as low-grade systemic inflammation precedes a diagnosis of T2DM [40]. IL-6 levels are elevated in the plasma of obese patients and those with T2DM. Hyperglycemia also results in increased levels of IL-6. [41]. In the present study, SRP and SRP + minocycline therapies improved the soft tissue conditions of patients with PD and BOP reduction; however, neither SRP nor SRP + minocycline significantly reduced the amount of plasma concentrations of IL-6 or CRP. These results are contradictory to a recent randomized clinical controlled trial study of IL-6 and CRP [42] and a pilot study investigating the effect of SRP on systemic levels of CRP, fibrinogen, and white blood cell counts in subjects

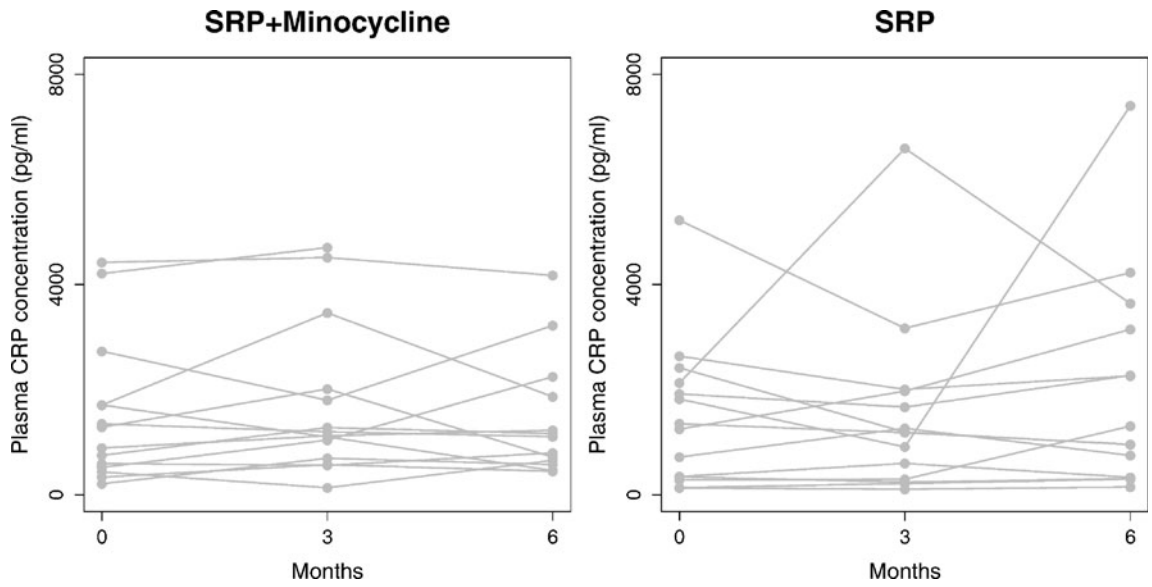

Fig. 4 Mean changes in plasma levels of chronic reactive protein (*CRP*) for each patient

with and without coronary heart disease (CHD) [38]. We inferred that our non-responsive outcome of plasma CRP and IL-6 may have been due to patients in our study having poor glycemic control. A study comparing high-sensitivity serum CRP levels in T2DM patients with CHD showed that there was a positive correlation between serum CRP and glycated hemoglobin in T2DM patients with and without CHD [43]. Although our data of glycemic control reflected a significant treatment effect of SRP on HbA1c reduction, a Pearson correlation showed no correlation of CRP and HbA1c in our samples throughout the entire study (p=0.299, data not shown). We speculated that the status of poorly controlled DM may nullify the periodontal treatment effects on CRP reduction or that the concentration of CRP is only slightly influenced by glycemic control in T2DM subjects [44].

Plasma sRAGE changes

The extent of hyperglycemia is critical for the formation of both reversible HbA1c and irreversible AGE-protein adducts (such as carboxymethyllysine and pentosidine) glycoxidation products [45]. These cellular effects of AGEs are largely mediated by their specific engagement of RAGE, triggering NADPH oxidase activation and recruiting multiple downstream pathways, culminating in the nuclear transcription factor, nuclear factor (NF)-κB activation, increased expression of cytokines and effectors (metalloproteinases) of an immuno-inflammatory response, and induction of oxidative stress [45, 46]. For the relationships of serum biomarkers to periodontal deterioration, serum AGEs were significantly associated with deterioration of periodontitis [8]. Many of the effects of AGEs are receptor-dependent and involve a multi-ligand member of the immunoglobulin superfamily of cell surface molecules. The best integral membrane protein of these is the RAGE [47]. It appears that RAGE plays a central role in oral infection, exaggerated inflammatory host responses, and destruction of alveolar bone in diabetes. It was suggested that antagonists of RAGE might have a valuable adjunctive therapeutic role of inhibiting periodontal destruction found in diabetics. Blockade of AGE–RAGE interactions can be achieved by truncated sRAGE, which is naturally produced by an alternative splicing of RAGE messenger RNA or the ectodomain shedding of the membrane-associated receptor [48, 49]. Experimental studies suggested that sRAGE can act as a decoy for RAGE ligands and thus has cytoprotective properties against AGE actions [50]. In a study of diabetic mice with blockade of RAGE, the level of alveolar bone loss was diminished with sRAGE in a dose-dependent manner [47]. Our research showed that neither treatment modalities of SRP or SRP + minocycline affected the plasma sRAGE concentration in our limited number of subjects. It can be assumed that both clinical modalities have a limited effect on AGE–RAGE interactions in patients with poorly controlled DM.

In summary, probably due to the small sample size, this study did not find significant influence of SRP or SRP + minocycline in changes of plasma levels of IL-6, CRP, or sRAGE. However, the results of the present study suggest that SRP or SRP + minocycline may contribute to improving glycemic control in patients with poorly controlled diabetes.

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Conflict of interest The authors declare that they have no conflict of interest.

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