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ORIGINAL ARTICLE

# Nonsurgical periodontal therapy with/without diode laser modulates metabolic control of type 2 diabetics with periodontitis: a randomized clinical trial

**Emrah Koçak[1] · Mehmet Sağlam[2] · Seyit Ali Kayış[3] · Niyazi Dündar[4] · Levent Kebapçılar[5] · Bruno G.Loos[6] · Sema S. Hakkı[1,4]**

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**Abstract** In order to evaluate whether nonsurgical periodontal treatment with/without diode laser (DL) decontamination improves clinical parameters, the levels of IL-1β, IL-6, IL-8, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM) in gingival crevicular fluid and metabolic control (HbA1c) in chronic periodontitis (CP) patients with diabetes mellitus type 2 (DM2). Sixty patients with DM2 and CP were randomly assigned into two groups to receive scaling and root planing (SRP, $n=30$) or SRP followed by diode laser application (SRP + DL, $n=30$). Clinical periodontal and gingival crevicular fluid (GCF) parameters were assessed at baseline, 1, and 3 months after periodontal treatment. HbA1c levels were evaluated at baseline and 3 months post-therapy. Total amounts of cytokines and molecules were analyzed by ELISA. Nonsurgical periodontal treatment with/without DL appeared to improve clinical, biochemical parameters, and glycemic control in DM2 patients (BMI < 25 kg/m$^2$) with CP. The SRP + DL group provided better reductions in probing depth (PD) and clinical attachment level (CAL) parameters compared to the SRP group ($P<0.05$). Significant reductions were found in the total amounts of GCF levels of IL-1, IL-6, IL-8, ICAM, and VCAM after treatment ($P<0.05$). HbA1c levels decreased significantly at 3 months after treatment ($P<0.05$). SRP + DL reduced HbA1c levels more significantly compared to SRP alone (0.41 vs. 0.22 %, $P<0.05$). SRP, especially in combination with DL, shows improvement of glycemic control for DM2 patients with CP.

**Keywords** Diode lasers · Chronic periodontitis · Nonsurgical periodontal debridement · Diabetes mellitus · Metabolic control · Cytokines · Cell adhesion molecules

✉ Mehmet Sağlam
dtmehmetsaglam@gmail.com

[1] Department of Periodontology, Faculty of Dentistry, Selcuk University, Konya, Turkey

[2] Department of Periodontology, Faculty of Dentistry, Izmir Katip Celebi University, Izmir, Turkey

[3] Department of Biostatistics, Faculty of Medicine, Karabük University, Karabuk, Turkey

[4] Research Center of Dental Faculty, Selcuk University, Konya, Turkey

[5] Department of Endocrinology and Metabolism Disease, School of Medicine, Selcuk University, Konya, Turkey

[6] Department of Periodontology, Academic Center for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University Amsterdam, Amsterdam, The Netherlands

## Introduction

Type 2 diabetes mellitus is the most common type of diabetes, caused by a combination of resistance to insulin action and a compensatory insulin secretory response [11, 33]. Diabetes mellitus type 2 (DM2) was mainly characterized by hyperglycemia and hyperlipidemia, which are strongly involved in the development of many diabetic complications including retinopathy, neuropathy, nephropathy, cardiovascular complications, delayed wound healing, and periodontitis [4, 48]. It has been indicated that DM2 and chronic periodontitis are involved in a two-way relationship, as DM2 increasing the risk for chronic periodontitis (CP) and periodontal inflammation negatively affecting glycemic control [36]. It has been reported that patients with diabetes tend to have a higher prevalence and more severe forms of periodontitis than non-diabetics [23]. Additionally, individuals with poor

control of diabetes experienced more periodontitis than well-controlled diabetics [46, 55].

Periodontitis may have an even greater influence on the systemic inflammatory condition in individuals with diabetes. It has been shown in several studies that elevated circulating levels of interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), prostaglandin E2, and RANTES can worsen insulin resistance and thereby impair glycemic control [1, 19, 39, 51]. Periodontitis is also associated with endothelial dysfunction which plays a key role in the pathogenesis of diabetes [34]. The term endothelial dysfunction defines a condition in which the endothelium loses its physiological properties such as the tendency to promote vasodilation, fibrinolysis, and anti-aggregation [3]. Measurement of elevated plasma levels of cellular adhesion molecules (CAMs), including E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1), can be used for the detection of endothelial dysfunction [35].

Considering the potential relationship between DM2 and CP, researchers have hypothesized that periodontal treatment could directly and positively affect metabolic control in patients with DM2. Some meta-analysis have reported improvement in glycemic control after the successful control of periodontal infection [8, 12, 15, 54], whereas other reports have not found such a beneficial effect [9, 11, 16, 25, 45].

Diode laser has promising features for periodontal treatment [2], and it has been also reported that diode laser (DL) has in vitro bactericidal and detoxification effects [21] and the ability to completely remove the pocket epithelium at 2 W [43]. While some studies have demonstrated that DL used as an adjunct to periodontal therapy may promote benefits additional to those of conventional scaling and root planing (SRP) therapy [29, 37, 44], others have not found additional benefits when using the DL with periodontal treatment [13, 50, 59].

The aim of this study is to evaluate whether nonsurgical periodontal treatment with/without DL decontamination improves clinical parameters, the levels of IL-1β, IL-6, IL-8, ICAM, and VCAM in gingival crevicular fluid and metabolic control (HbA1c) in CP patients with DM2.

## Material and methods

This study was a randomized, single-blind, controlled, and clinical trial of a 3-month duration, using a parallel design. A total of 60 subjects with DM2 and CP (30 males and 30 females, between the ages of 35 to 60 years) were consecutively recruited into the present study between April 2011 and October 2013 in the Department of Periodontology, Faculty of Dentistry, Selcuk University, Konya, Turkey. Patients with DM2 were recruited from the Department of Endocrinology and Metabolism Disease, School of Medicine, Selcuk University, Konya, Turkey. All the patients had a confirmed diagnosis of DM2 (5.7 %≤glycated hemoglobin (HbA1c) ≤8.5 %) with no alteration in the diabetes treatment in the last year prior to the study, and were authorized by their physician (LK) to undergo periodontal therapy. The study protocol was approved by the Ethics Commission of Selcuk University for human subjects (2013/57). All participants provided written informed consent before their enrollment into the study. All participants had a diagnosis of chronic periodontitis. To be included in the study, patients with CP: (1) were 30≤years old, (2) had 17≥teeth, and (3) had 8≤sites with probing depths (PDs) ≥5 mm [18]. Patients were excluded if they had any other systemic diseases, received antibiotic therapy within the preceding 6 months, used immunosuppressive medications, or received periodontal treatment within the previous 1 year. Pregnant women, smokers, and alcohol consumers were also excluded. Sixty patients with CP were randomly assigned into two groups to receive SRP alone (SRP, $n=30$) or SRP followed by diode laser application (SRP + DL, $n=30$) by an experienced investigator (SSH) who did not collect data or perform the procedures (1:1 ratio). The randomization process took place in the following way. The 60 patients with DM2 did not refer to us as one cohort, but referred as two at a time in the time period detailed above. Then, the two patient ID cards with the patient names not visible were presented to the senior author (SSH), who subsequently and "blindly" assigned each of the two ID cards to one and another unlabeled, patient file boxes, of which one represented the experimental treatment and the other the control treatment. The treatment mode, represented by the two patient file boxes, was only known to the first author (EK), who after the random assignment of the two patients at a time, treated these patients according to the experimental or control mode. For the whole study period, the statistician was masked for the treatment modes.

The following clinical parameters were evaluated at baseline: (1) plaque index (PI) [49], (2) gingival index (GI) [31], (3) PD, and (4) clinical attachment level (CAL). PD and CAL were measured using a periodontal probe (PCP-UNC 15, Hu-Friedy, Chicago, IL, USA). PI and GI measurements were performed at four sites (mesial, distal, buccal, and lingual) around each tooth; PD and CAL measurements were performed at six sites around each tooth. All clinical examinations performed at baseline were repeated 1 and 3 months after treatments by the same calibrated periodontist (EK).

Blood samples were taken at baseline and at the 3-month recall visit. The percentage of glycated hemoglobin (HbA1c) was determined for all subjects (Trinity Biotech Plc, Co Wicklow, Ireland).

### GCF sampling and analysis

The three deepest pockets with probing depth of ≥5 mm were chosen from two single-rooted teeth and one multi-rooted

tooth for gingival crevicular fluid (GCF) sampling. GCF was collected using filter paper strips (Periopaper, Oraflow Inc., Plainview, NY, USA) from non-adjacent pocket sites. GCF sampling sites were selected according to the baseline measurements, and GCF collection was done with a calibrated Periotron™8000 m (Oraflow Inc.) as previously reported [44]. The three samples from the deepest pockets sides were pooled in an Eppendorf tube together and diluted in phosphate buffer saline up to 650 μl. The strips were stored at −80 °C until assayed.

GCF samples were analyzed for IL-1β, IL-6, IL-8, ICAM (Invitrogen™ Corporation 542 Flynn Road, Camarillo, CA, USA), and VCAM (eBioscience, Bender MedSystems GmbH Campus Vienna Biocenter 2 1030 Vienna, Austria) using commercially available kits in accordance with the manufacturer's instructions.

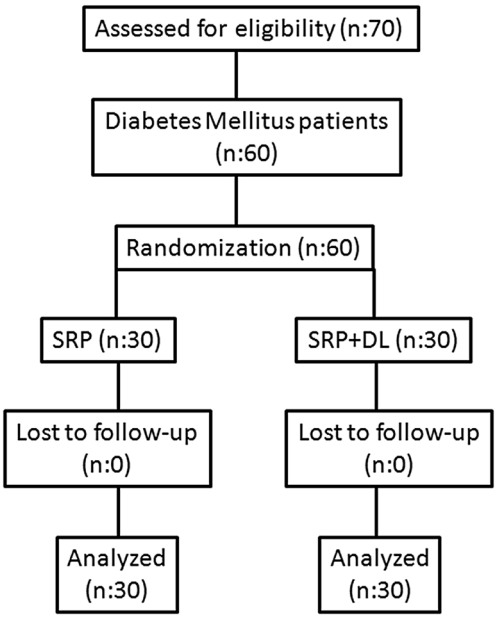


**Fig. 1** Study flowchart

## Clinical treatment

At the first visit, all patients received oral hygiene instructions and supragingival scaling with hand instruments (Hu-Friedy, Chicago, IL, USA) and ultrasonic scalers (Satelec, Merignac, France). One week after the first visit, full-mouth subgingival scaling and root planing under local anesthesia was performed in a single appointment (approximately 80–90 min) for each patient in all groups using an ultrasonic scaler and hand instruments (Gracey Curettes, Hu-Friedy). SRP and DL therapy was performed in the same visit.

Laser treatment was performed by using a 940-nm indium–gallium–aluminum–phosphate diode laser (Ezlase, Biolase, Irvine, CA, USA). A single-dose laser therapy was applied

**Table 1** Demographic and metabolic characteristics of the two study groups at baseline

| | SRP ($n=30$) | SRP + DL ($n=30$) |
|---|---|---|
| Age (years) | 53.1 (5.1) | 51.7 (5.2) |
| Gender | | |
| Male | 15 | 15 |
| Female | 15 | 15 |
| BMI | 24.1 (1.7) | 24.9 (1.5) |
| Metabolic data (medians and IQR) | | |
| Fasting plasma glucose (mg/dl) | 113 (104–138) | 121 (111–142) |
| HbA1c (mean) (%) | 6.5 (0.6) | 6.9 (0.7) |
| Total cholesterol, median (IQR), (mg/dl) | 131 (90–198) | 139 (97–177) |
| HDL-cholesterol, median (IQR), (mg/dl) | 48 (39–53) | 47 (37–53) |
| LDL-cholesterol, median (IQR), (mg/dl) | 103 (90–122) | 113 (101–138) |
| Triglyceride, median (IQR), (mg/dl) | 131 (90–198) | 139 (97–177) |
| Periodontal measurements | | |
| Number of teeth | 21.9 (2.5) | 23.2 (1.8) |
| PD (mm) | 3.7 (0.3) | 3.6 (0.3) |
| Sites with $5 \leq PD < 7$, mean sites/person | 13.8 (4.6) | 15.4 (2.1) |
| Sites with $7 \leq PD$, mean sites/person | 1 (1.7) | 0.8 (1.7) |
| CAL (mm) | 2.9 (0.4) | 2.8 (0.5) |
| PI | 1.8 (0.1) | 1.8 (0.1) |
| GI | 1.8 (0.2) | 1.8 (0.1) |

Values represent number of patients (%) or means (standard deviations), or medians (interquartile ranges)

as previously reported [44] (Perio pocket setting 1.5 W (average) with a pulse interval of 20 ms and pulse length of 20 ms delivering 20 and 15 J/cm$^2$ of energy, respectively). Irradiation was accomplished with a 300-μm fiber optic delivery system (Ezlase, Biolase, Irvine, CA, USA). The optic fiber was inserted into the periodontal pocket base in parallel alignment with the root surface, the device was activated, and the fiber was slowly moved from apical to coronal in a sweeping motion during the laser light irradiation. This was done mesially to distally at the buccal aspect for 10 s and distally to mesially at the lingual aspect for 10 s, reaching a total of 20 s for each tooth. The periodontal therapy and laser applications were performed by the same investigator (EK).

### Sample size calculation and statistical analysis

HbA1c change was set as the primary outcome, and sample size was estimated based on a pilot study ($n=10$), conducted as a preliminary to the present study, using the recorded mean difference and standard deviation (SD) in HbA1c change between the experimental and control groups (ΔHbA1c for the SRP group = 0.09 ± 0.23, ΔHbA1c for the SRP + DL group = 0.42 ± 0.18). It was decided to employ a sample size of 30 in each group with power analysis at $\alpha=0.05$ and $\beta=0.01$ (99 % statistical power). The secondary outcomes were PD and CAL. All variables showed a non-normal distribution. Therefore, non-parametric tests were employed for the purpose of data analysis. The Kruskal-Wallis test was used for multiple group comparisons, and the Mann–Whitney *U* test was employed for post hoc tests. The Wilcoxon Signed Rank test was used for analysis of repeated measures. The statistical analyses were performed using the R software (Minitab Release 14, Minitab, Philadelphia, PA, USA).

## Results

The outline of the study is described in a flowchart (Fig. 1). The baseline demographic data of the participants are provided per study group in Table 1.

### Whole-mouth clinical parameters (PD, CAL, PI, and GI)

The results of whole-mouth clinical parameters at baseline, 1, and 3 months in the treatment groups are displayed in Fig. 2. At baseline, no statistically significant differences in clinical parameters were found among the treatment groups. Whole-mouth clinical parameters showed

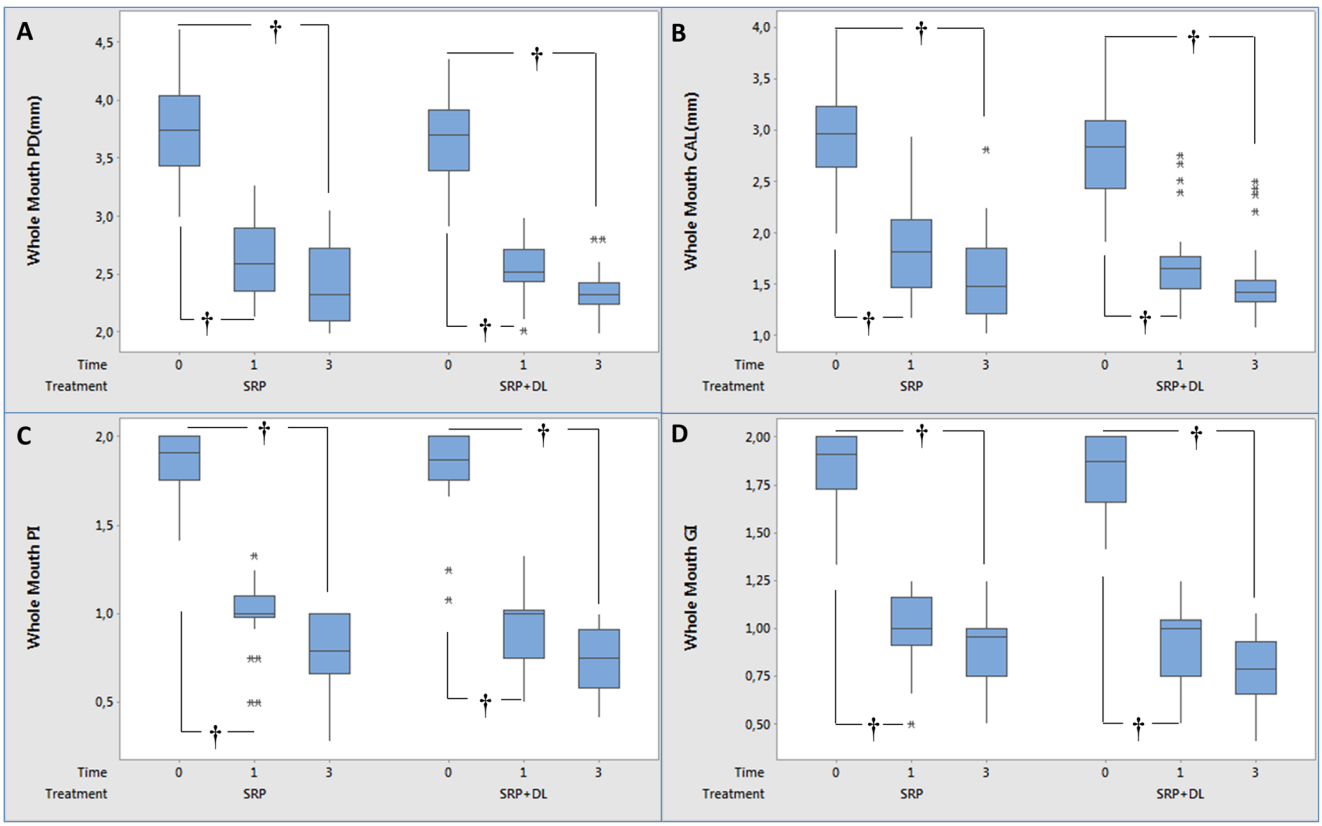


**Fig. 2** Comparison of whole-mouth clinical parameters. **a** Whole-mouth PD (mm). **b** Whole-mouth CAL (mm). **c** Whole-mouth PI. **d** Whole-mouth GI. *Dagger* represents significant difference compared to the first and third months within the group

statistically significant reduction at all time points after treatment compared with baseline in both groups ($P<0.05$). However, there was no statistically significant difference in any analyzed whole-mouth clinical parameter changes between the groups at any time points ($P>0.05$).

### Site-specific results (PD and CAL)

**GCF sampled sites** The site-specific PD and CAL values were significantly reduced in both groups at all time points after treatment compared with baseline ($P<0.05$) (Fig. 3a, b). PD reductions (baseline $5.59\pm0.68$ mm and $5.67\pm0.73$ mm for the SRP and SRP + DL groups, respectively) were significantly greater in the SRP + DL group ($\Delta0–1=3.35\pm0.59$, $\Delta0–3=3.84\pm0.68$) compared to the SRP group ($\Delta0–1=2.72\pm0.42$, $\Delta0–3=2.98\pm0.42$) ($P<0.05$). However, CAL reductions were similar between the SRP and SRP + DL groups ($P>0.05$).

**Analysis of moderately deep pockets (5 and 6 mm)** The PD and CAL values for moderately deep pockets were significantly reduced in both groups at all time points after

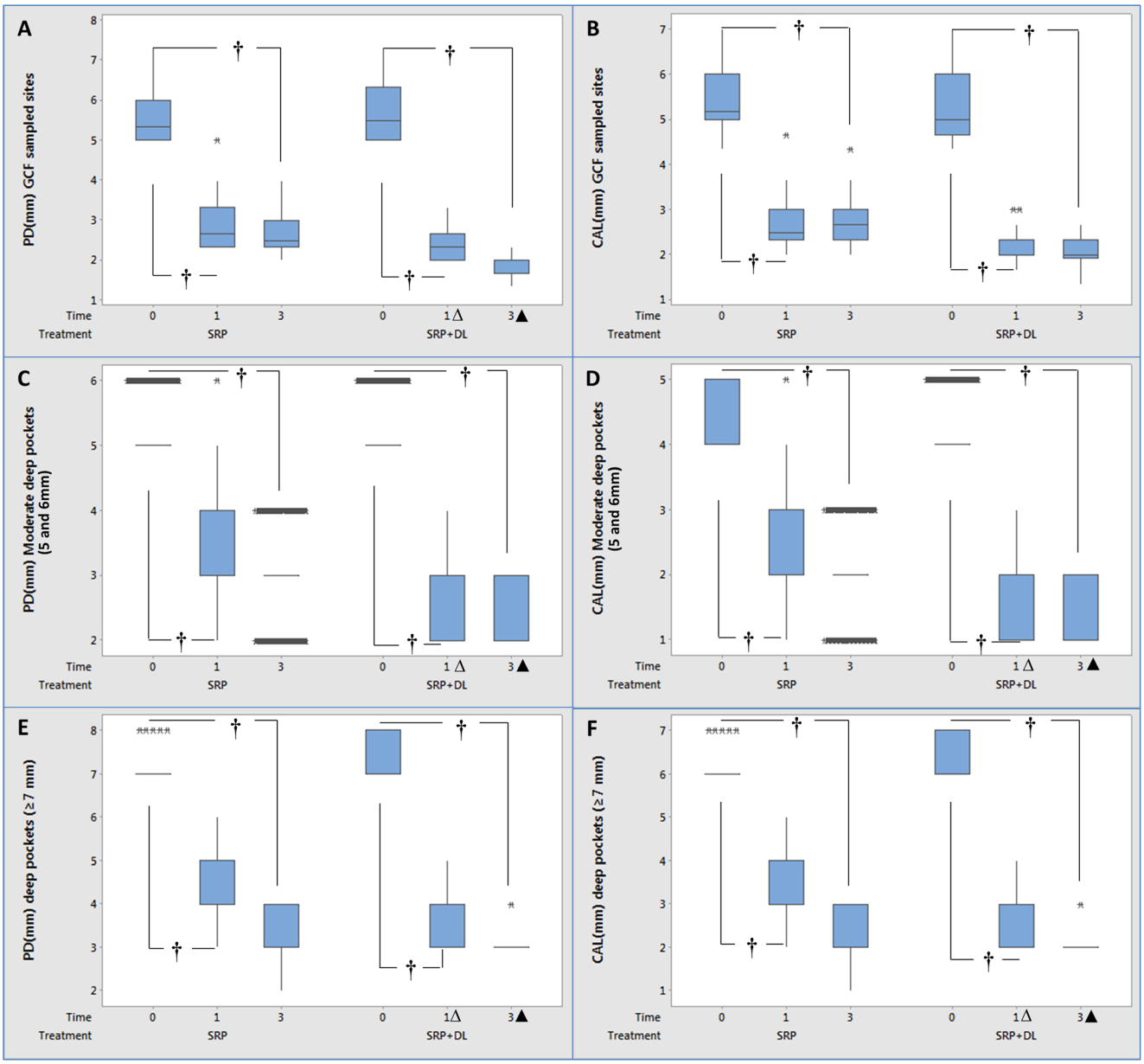


**Fig. 3** Comparison of PD and CAL parameters (mm) (GCF sampled sites, moderate deep pockets, and deep pockets). **a** PD (mm) values of GCF sampled sites. **b** CAL (mm) values of GCF sampled sites. **c** PD (mm) values of moderate deep pockets. **d** CAL (mm) values of moderate deep pockets. **e** PD (mm) values of deep pockets. **f** CAL (mm) values of deep pockets. *Dagger* represents significant difference compared to the first and third months within the group. *White triangle* and *black triangle* represent significant difference between groups at the first month and third month respectively ($P<0.05$)

treatment compared with baseline ($P<0.05$) (Fig. 3c, d). PD (baseline 5.22 ± 0.41 mm and 5.22 ± 0.41 mm for the SRP and SRP + DL groups, respectively) and CAL (baseline 4.29 ± 0.45 mm and 4.23 ± 0.42 mm for the SRP and SRP + DL groups, respectively) reductions were significantly greater in the SRP + DL group (Δ0–1 = 2.49 ± 0.52, Δ0–3 = 2.55 ± 0.52 for PD, Δ0–1 = 2.50 ± 0.54, Δ0–3 = 2.56 ± 0.53 for CAL) compared to the SRP group (Δ0–1 = 1.79 ± 0.61, Δ0–3 = 2.24 ± 0.49 for PD, Δ0–1 = 1.86 ± 0.63, Δ0–3 = 2.30 ± 0.54 for CAL) ($P<0.05$).

**Analysis of deep pockets (≥7 mm)** The PD and CAL values for deep pockets were significantly reduced in both groups at all time points after treatment compared with baseline ($P<0.05$) (Fig. 3e, f). PD (baseline 7.16 ± 0.37 mm and 7.26 ± 0.45 mm for the SRP and SRP + DL groups, respectively) and CAL (baseline 6.16 ± 0.37 mm and 6.26 ± 0.45 mm for the SRP and SRP + DL groups, respectively) reductions were significantly greater in the SRP + DL group (Δ0–1 = 3.57 ± 0.50, Δ0–3 = 4.23 ± 0.42 for PD, Δ0–1 = 3.57 ± 0.50, Δ0–3 = 4.23 ± 0.42 for CAL) compared to the SRP group (Δ0–1 = 2.51 ± 0.56, Δ0–3 = 3.64 ± 0.55 for PD, Δ0–1 = 2.51 ± 0.56, Δ0–3 = 3.64 ± 0.55 for CAL) ($P<0.05$).

## Evaluation of biochemical parameters

### *HbA1c (%)*

HbA1c values were significantly reduced in both groups at 3 months after treatment compared with baseline ($P<0.05$) (Fig. 4). HbA1c reductions (baseline 6.54 ± 0.66 % and 6.91 ± 0.79 % for the SRP and SRP + DL groups, respectively) were significantly greater in the SRP + DL group (Δ0–3 = 0.41 ± 0.19 %) compared to the SRP group (Δ0–3 = 0.22 ± 0.25 %) between baseline and 3 months ($P<0.05$).

### *GCF volume (μl)*

GCF volumes were presented in Fig. 5a. Changes in GCF volumes were significant at all time points after treatment compared to baseline in both groups ($P<0.05$). GCF volume changes were similar between the SRP and SRP + DL groups ($P>0.05$).

### *GCF IL-1β, IL-6, and IL-8 levels (pg/30s)*

GCF IL-1β levels were presented in Fig. 5b. There were significant reductions in both groups ($P<0.05$), and the levels of IL-1β reductions were similar between the SRP and SRP + DL groups ($P>0.05$).

GCF IL-6 levels were presented in Fig. 5c. There were significant reductions in both groups ($P<0.05$). The levels of IL-6 reductions were significantly greater in the SRP + DL group compared to the SRP group between baseline and all time points after treatment ($P<0.05$).

GCF IL-8 levels were presented in Fig. 5d. The IL-8 levels were significantly reduced in both groups at the first month after treatment compared with baseline ($P<0.05$) but increased in all treatment groups at 3 months after treatment compared with the first month ($P<0.05$). There were significant differences at the first and 3 months after treatment compared to baseline in the SRP group ($P<0.05$). There were significant differences only at the first month after treatment compared to baseline in the SRP + DL group ($P<0.05$). The levels of IL-8 changes were similar between the SRP and SRP + DL groups ($P>0.05$).

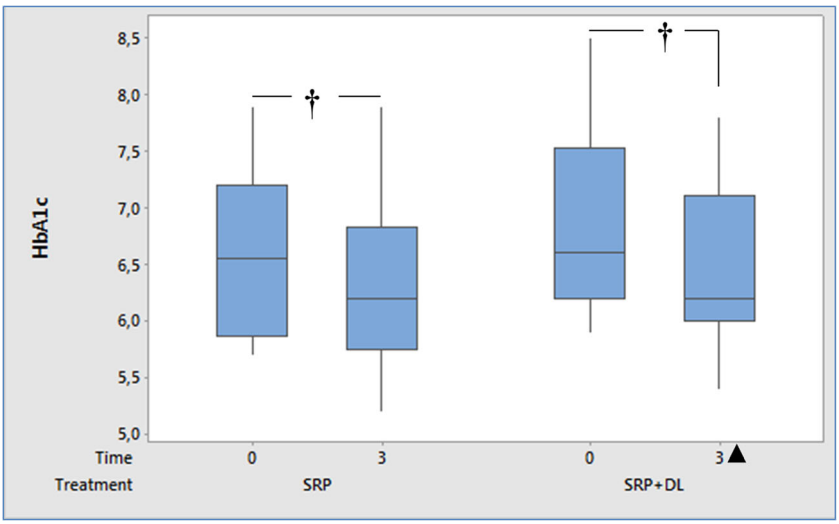


**Fig. 4** Comparison of HbA1c levels (%). *Black triangle* represents significant difference between groups at the third month ($P<0.05$). *Dagger* represents significant difference compared to the third months within the group

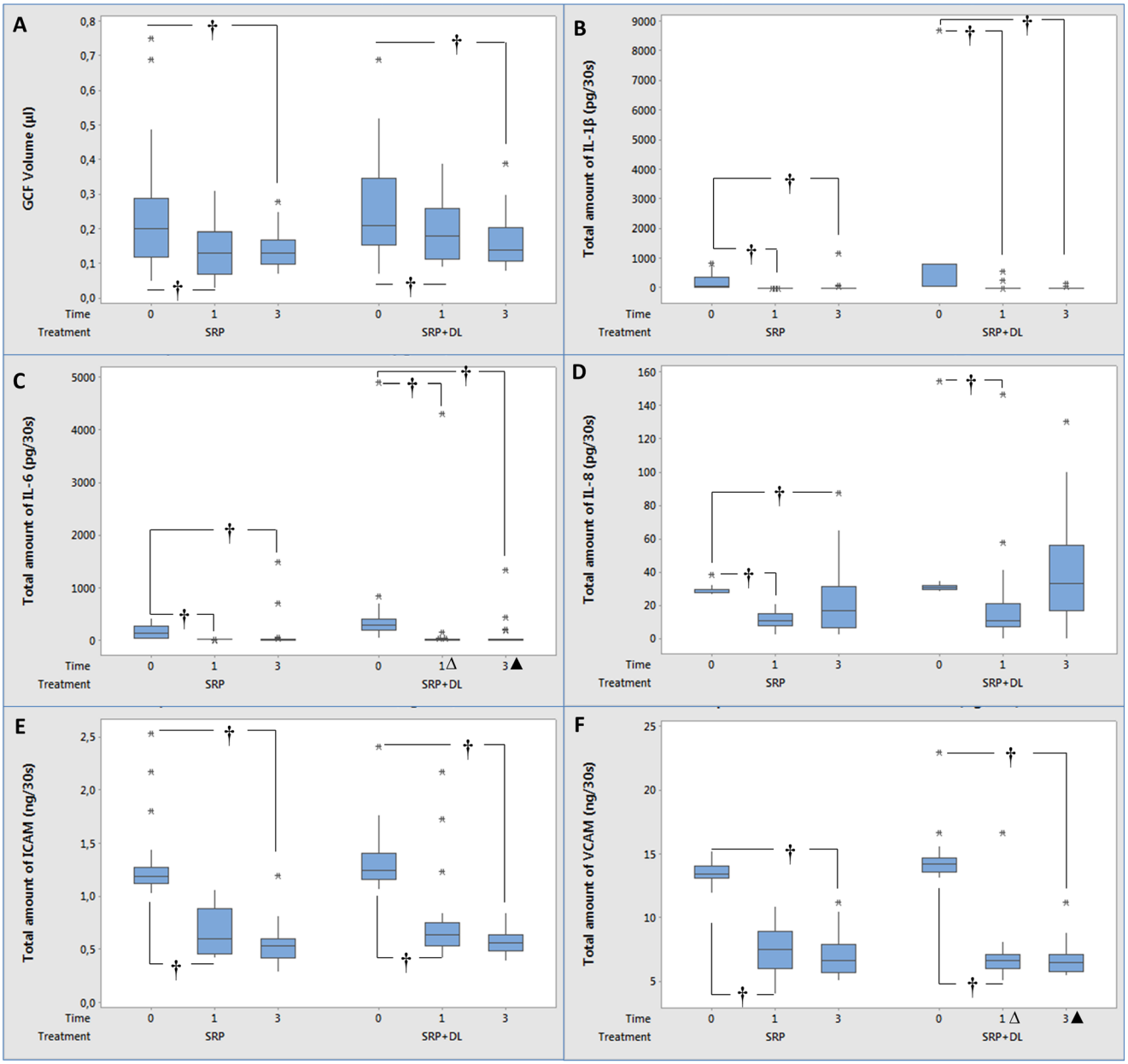


**Fig. 5** Comparison of GCF volume and biochemical parameters in GCF. **a** GCF volume values (µl). **b** Total amount of IL-1β (pg/30s). **c** Total amount of IL-6 (pg/30s). **d** Total amount of IL-8 (pg/30s). **e** Total amount of ICAM (ng/30s). **f** Total amount of VCAM (ng/30s). *Dagger* represents significant difference compared to the first and third months within the group. *White triangle* and *black triangle* represent significant difference between groups at the first and third months, respectively ($P < 0.05$)

*GCF ICAM, VCAM levels (ng/30s)*

GCF ICAM levels were significantly reduced in both groups at all time points after treatment compared with baseline ($P < 0.05$) (Fig. 5e); instead, the levels of ICAM reductions were similar between the SRP and SRP + DL groups ($P > 0.05$), whereas GCF VCAM levels were significantly reduced for both groups ($P < 0.05$) (Fig. 5f), and it also found the levels of VCAM reductions were significantly greater in the SRP + DL group compared to the SRP group only ($P < 0.05$).

## Discussion

The major finding in the present study is that in both study groups, the percent of HbA1c was reduced, on an average from 6.54 to 6.31 % for the SRP group and from 6.91 to 6.49 % for the SRP + DL group at the 3-month post-operative time point. This finding corroborates previous observations that periodontal therapy is able to lower %HbA1c in DM2 [24, 27, 28, 38]. It is important to note that the current patients had a mean BMI <25 Kg/m$^2$, and were non-smoking, which

are both factors favoring a good response to periodontal therapy, and thus favorably affecting HbA1c levels [5].

In the current study, DM2 patients showed significant improvements in all clinical periodontal parameters at 1 and 3 months after SRP or SRP + DL treatments compared to baseline. While there were no significant difference in PI and GI values between the SRP and SRP + DL groups, superior results were observed for the SRP + DL group compared to the SRP group in PD and CAL parameters. Our results for PD and CAL parameters were in agreement with those obtained by other researchers [14, 29, 37, 42, 44, 57]. A recently published meta-analysis indicated that adjunctive use of the DL with SRP provided significant improvements only in GI and bleeding scores compared to SRP alone, and it was concluded that the evidence considering the adjunctive use of the DL is judged to be moderate for changes in PD and CAL [50]. It has been demonstrated that DL as an adjunct in periodontal therapy significantly reduced gingival inflammation compared to SRP alone in DM2 patients [41]. In a histological study from the latter investigators, a faster healing response was observed when SRP was combined with DL in DM2 patients [40]. Also, Romanos et al. [43] reported that DL led to a complete epithelial removal in soft periodontal tissues compared to conventional hand instruments in pigs. In another study, Kreisler et al. [29] suggested that higher reduction in PD was probably related to the de-epithelization of the periodontal pockets leading to an enhanced connective tissue attachment. Thus, these observations can explain a somewhat better response to periodontal treatment in the SRP + DL group. Contrary to our findings, some researchers suggested that DL did not provide any additional clinical benefit when compared with conventional treatment [6, 13, 59]. These controversial reports might be the result of different wavelengths, application power densities, type of laser fiber, and application time.

Meta-analyses of intervention studies suggest that additional trials are needed to clarify the effect of periodontal treatment on HbA1c levels [12, 15, 54]. Another recent systematic review and meta-analysis showed that nonsurgical periodontal treatment improves metabolic control in patients with both periodontitis and diabetes [8]. A recent randomized clinical trial reported that nonsurgical periodontal therapy did not improve glycemic control in DM2 patients with moderate to advanced chronic periodontitis [16]. In their study, residual plaque levels of 72 % and bleeding scores of 42 % after nonsurgical periodontal therapy are far below the consensus for expected outcomes [58]. According to these results, it was indicated that the periodontal therapy failed to clinically control the periodontal infection and associated inflammatory burden. Therefore, no conclusions can be drawn about the effect of clinically effective periodontal therapy on HbA1c in that study [5, 7]. For the same study, BMI was 34.7 (67.5) kg/m$^2$ in the treatment group. Borgnakke et al. suggested that this high obesity levels would have masked any anti-inflammatory effect of successful periodontal treatment [5]. In this present study, we observed that both SRP and SRP + DL treatments reduced HbA1c levels. We also observed that SRP + DL treatment provided better reductions in HbA1c levels compared to SRP treatment. Considering the comments for the study of Engebretson et al. [16], there were remarkable improvements in clinical parameters and baseline mean BMIs were below 25 kg/m$^2$ (the normal BMI) in both groups in our study.

In present study, SRP and SRP + DL treatments significantly reduced GCF levels of IL-1β in DM2 patients. Reduction of the GCF IL-1β level after nonsurgical periodontal treatment in DM2 patients was demonstrated in previous studies [10, 38]. We did not observe any significant effect of DL as an adjunct to nonsurgical periodontal treatment on reducing GCF IL-1β levels. This result is in agreement with those obtained by Qadri et al. [42], Lui et al. [32], and Sağlam et al. [44] who did not demonstrate any significant effect of DL as an adjunct to nonsurgical periodontal treatment on reducing GCF IL-1β levels compared to SRP alone.

Kardesler et al. demonstrated that the total amount of IL-6 was reduced after periodontal treatment, and this finding possibly reflects a great transient reduction in this inflammatory molecule at 1 month after therapy in the diabetics. It was also suggested that the clinical improvements might be related to the reductions in the levels of IL-6 in the GCF [26]. In this study, SRP and SRP+DL treatments significantly reduced GCF levels of IL-6 in DM2 patients. SRP+DL treatment provided better reductions in IL-6 levels compared to SRP treatment as we reported in our previous study in systemically healthy patients [44], it has been indicated that there is a quantitative relationship between this IL-6 and glycemic control [53]. IL-6 and TNF-α, which are inducers of acute phase proteins such as CRP, have been shown to impair intracellular insulin signaling. Therefore, it has been proposed that reductions in the levels of these cytokines as a result of periodontal treatment could lead to improved diabetes control theoretically [52].

The GCF IL-8 levels were significantly reduced at the first month compared to baseline but increased at 3 months compared to the first month after SRP and SRP + DL treatments in our study. Engebretson et al. [17] reported that GCF IL-8 levels were lower in chronic periodontitis patients with DM2 as compared to systemically healthy chronic periodontitis patients. They also indicated that there was no association between GCF IL-8 and glycemic control. Sfakianakis et al. indicated that IL-8 is involved in cell proliferation and angiogenesis in wound healing [47]. The increasing GCF IL-8 level in our study may be related to improved wound healing in the periodontium because of

improved glycemic control. Sağlam et al. also reported increased GCF IL-8 levels after SRP and SRP + DL treatments, and they associated this situation with wound healing including cellular sources such as epithelial cells [44]. They did not observe any significant additional effect of DL on this cytokine, and we also did not observe any additional effect of DL on IL-8 levels in this study.

It has been suggested that periodontal therapy improved endothelial function and reduced cell adhesion molecules [56]. Lalla et al. observed reductions in serum ICAM and VCAM levels after periodontal treatment compared to baseline in diabetic patients, but these reductions did not reach the level of significance [30]. Hannigan et al. reported that GCF ICAM levels significantly decreased after periodontal treatment compared to baseline, but they did not find any significant change in GCF VCAM levels after treatment [20]. In our study, GCF ICAM and VCAM levels significantly decreased after SRP and SRP + DL treatments in DM2 patients. SRP + DL treatment provided better reductions in VCAM levels compared to SRP treatment. It was reported that ICAM-1 is induced by proinflammatory cytokines (e.g., IL-1β, TNF-α) and VCAM-1 is induced by IL-1β [22]. Reduced GCF ICAM and VCAM levels seem to be related to resolution of inflammation in our study.

## Conclusion

In this present study, the investigator (EK) who took all clinical measurements and performed periodontal treatments was non-masked, and this may introduce some bias. To control sources of bias, an experienced researcher (SSH) who did not collect data or performed the procedures conducted random allocation of patients in the test or control groups. Based on the baseline data, the groups were very similar, confirming that the randomization in our study might have been effective. Both SRP and SRP + DL treatments provided a significant improvement in clinical periodontal status, evaluated biochemical parameters in GCF, and glycemic control in patients with DM2 and CP. The results of this study suggest that the use of a 940-nm indium–gallium–aluminum–phosphate diode laser (Perio pocket setting: average 1.5 W with a pulse interval of 20 ms and pulse length of 20 ms delivering 20 and 15 J/cm$^2$ of energy, respectively) as an adjunct to scaling and root planning produces significant better improvement in the site-specific PD and CAL clinical parameters compared to SRP alone. A remarkable finding of this study was that SRP + DL (0.41 %) was superior in decreasing HbA1c levels compared to SRP alone (0.22 %) in DM2 patients with CP. This result needs to be confirmed in further randomized controlled double-blinded clinical trials before a generalized recommendation of dental lasers as an adjunct to conventional nonsurgical therapy in periodontal treatment of DM2 patients with CP.

**Compliance with ethical standards**

**Conflict of interest** The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article. This study was supported by the Research Project Coordination of Selcuk University (project no. 11202014) and The Scientific and Technological Research Council of Turkey (TUBITAK/SBAG-114S229). Author BGL is supported in part by a grant of the University of Amsterdam (focal point "Oral Infections and Inflammation").

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