ORIGINAL ARTICLE

Photobiomodulation for the treatment of periodontal pockets in patients with type 2 diabetes: 1-year results of a randomized clinical trial

Nídia Castro dos Santos[1] · Naira M. R. B. Andere[1] · Manuela Maria Viana Miguel[1] · Lúcio Murilo dos Santos[1] ·
Milton Santamaria Jr[2] · Ingrid Fernandes Mathias[1] · Maria Aparecida Neves Jardini[1] · Mauro Pedrine Santamaria[1]

Abstract

This study investigated the local effect of photobiomodulation (PBM) for the treatment of periodontal pockets in patients with periodontitis and type 2 diabetes. Thirty-eight periodontal pockets presenting probing depth (PD) and clinical attachment level (CAL) ≥ 5 mm were selected from 19 patients (two pockets/patient). The selected periodontal pockets were randomly assigned to receive mechanical debridement only (control group) or mechanical debridement with PBM (PBM group). Clinical measures, such as PD, CAL, bleeding on probing (BoP), and presence of supragingival biofilm (PI), were collected and compared at baseline, 3, 6, and 12 months. After 12 months, no statistically difference was observed for mean PD and mean CAL when control and PBM groups were compared. The frequency of pockets with PD 5–6 mm was significantly lower for the PBM group at 6 months when compared to the control group. Pockets with PD ≥ 7 mm changed significantly between baseline and 3, 6, and 12 months for the PBM group, while for the control group, statistical significance was only observed between baseline and 6 months. The PBM protocol used in this study did not provide significant changes for PD and CAL in periodontal pockets when compared to mechanical therapy only. However, PBM was more effective in reducing the percentage of moderate periodontal pockets at 6 months in patients with type 2 DM.

Keywords Diabetes mellitus · Periodontitis · Photobiomodulation · Low-level laser therapy · Periodontal pockets

Introduction

Periodontitis is an inflammatory disease, initiated by dental biofilm, that leads to attachment loss, bone resorption, and, eventually, tooth loss [1]. The purpose of periodontal therapy is to remove supra- and subgingival dental biofilm to reduce periodontal inflammatory burden, thus re-establishing tissue homeostasis and stopping the progression of periodontal disease. The gold standard for the treatment of periodontitis is mechanical periodontal therapy, which can be performed by either traditional manual scaling and root planing or ultrasonic debridement [2]. Both the disease initiation or progression and treatment effectiveness of periodontitis can be negatively influenced by systemic, genetic, and behavioral modifiers. [3].

Evidence shows that diabetes mellitus (DM) increases the risk for the initiation and progression of periodontitis [4]. Patients with poor metabolic control frequently present impaired wound healing. The inflammatory mechanisms involved in this process greatly affect diseased periodontal tissues in patients with DM [5, 6]. Several studies show that the expression of local inflammatory factors in the crevicular fluid is increased in patients with poor metabolic control and periodontitis [7–9].

The outcomes of studies that investigated mechanical therapy for the treatment of periodontitis in patients with type 2 DM show that periodontal conditions improve when mechanical periodontal therapy is performed [10–13]. However, impaired wound healing, a significant phenomenon in patients

✉ Mauro Pedrine Santamaria
  mauro.santamaria@unesp.br

1 São Paulo State University (Unesp), Institute of Science and Technology, São José dos Campos, Department of Diagnosis and Surgery, Division of Periodontics, São José dos Campos, SP, Brazil

2 University of Araras (Uniararas), Dental School, Department of Orthodontics, Araras, SP, Brazil

with DM [6], may lead to unfavorable results when conventional periodontal therapy is used in those patients. For this reason, an additional therapy that enhances wound healing, by modulating the host response toward bacterial injury, is of great interest for treating periodontitis in patients with type 2 DM [14–16].

Photobiomodulation (PBM), or low-level laser therapy (LLLT), has been used for a wide range of purposes, including wound healing acceleration [17, 18], tissue biostimulation [19, 20], and pain reduction [21]. This therapy involves the placement of a light source at the visible and near infrared of the spectrum at low density with the purpose of stimulating biological activities at the receptive tissue. Differently from other laser applications that result in ablative and thermal injury, PBM focuses on photon activity to stimulate chemical changes related to the mitochondrial respiratory chain [22]. Cytochrome c oxidase (Cox) is the terminal enzyme of the electron transport chain responsible for electron transfer from cytochrome c to molecular oxygen. This enzyme acts as a photoacceptor and transducer of photosignals in red-to-near-infrared range (620–1100 nm) [23]. The interaction between light and this chromophore increases electron transport, mitochondrial membrane potential, and adenosine triphosphate (ATP) production [24].

PBM has been proposed as an adjunct therapy to mechanical debridement for the treatment of periodontitis to reduce gingival inflammation and promote wound healing [25, 26]. Clinical investigations concerning the additional use of PBM to mechanical periodontal debridement reported improved clinical periodontal parameters and decreased pro-inflammatory markers in normoglycemic patients and controlled diabetic patients [27–30]. Moreover, favorable results were reported when PBM was applied to enhance wound healing on the oral mucosa of diabetic animals [31, 32]. Nevertheless, there is no consensus in the literature regarding the efficacy of PBM in the treatment of periodontitis in patients with type 2 DM.

The aim of this study was to compare the local effects of periodontal debridement with and without adjunct PBM for the treatment of periodontal pockets in patients with periodontitis and type 2 DM through a 1-year randomized clinical trial.

Materials and methods

Sample size calculation

Sample size calculation considered a mean probing depth (PD) reduction of 1 mm between groups, with a standard deviation of 0.8 mm. Seventeen periodontal pockets in each group would provide 95% power with a 5% significance level. With a hypothetical attrition rate of 15%, 19 periodontal pockets were included in each group [33].

Study population

Individuals with type 2 DM and moderate to severe generalized periodontitis [1], who volunteered to receive periodontal treatment, were selected from the population referred to the Periodontal Clinic at São Paulo State University (Unesp), Institute of Science and Technology (São José dos Campos, SP, Brazil). Detailed dental and medical records were obtained. Individuals who met the following inclusion criteria were selected: diagnosis of type 2 DM for ≥ 5 years; treatment of diabetes with oral hypoglycemic agents or insulin supplementation; glycated hemoglobin (HbA1c) levels from 6.5 to 11%; age ≥ 35; at least 15 teeth (excluding third molars and teeth indicated for extraction); and moderate to severe generalized periodontitis [1]. The exclusion criteria were medical conditions that required antibiotic prophylaxis, periodontal therapy in the previous 6 months, antimicrobial and/or anti-inflammatory therapies in the previous 6 months, systemic conditions other than diabetes that could affect the progression of periodontitis, the current use of medication that could interfere with the periodontal response to treatment, pregnancy or lactation, current smoking. Informed consent was obtained from all individual participants included in the study after a thorough explanation of the nature, risks, and benefits of the clinical investigations. The Institutional Review Board at São Paulo State University (Unesp), Institute of Science and Technology approved the study protocol (CAAE 28968714.7.0000.0077). The ClinicalTrials.gov identifier of the present study is NCT02817152.

Randomization and allocation concealment

In this split-mouth double-blind randomized clinical trial, two periodontal pockets with PD and clinical attachment level (CAL) ≥ 5 mm in single-rooted teeth from different quadrants were selected in each patient. The study coordinator (MPS) used a computer program to randomize the selected 38 periodontal pockets to a control group (ultrasonic periodontal debridement only) or a PBM group (ultrasonic periodontal debridement + photobiomodulation). For blinding, one investigator (NMRBA) was responsible for the treatment of the patients and another investigator (NCCS) was responsible for the clinical measurements. The randomization parameters and blinding were performed according to the CONSORT statement 2010 [34].

Treatment protocol

All patients received supragingival biofilm and calculus removal, extraction of hopeless teeth, dental decay removal, and provisional restoration, as well as oral hygiene instructions. After the initial therapy phase, all patients received full-mouth ultrasonic periodontal debridement (Cavitron,

Dentsply, York, PA, USA) with specific inserts (UI25KSF10S, Hu-Friedy). All diseased sites were instrumented in one session and were checked with a periodontal probe for complete subgingival biofilm and calculus removal. After periodontal debridement, one previously selected periodontal pocket received additional PBM.

One previously randomly selected periodontal pocket with a PD and CAL ≥ 5 mm received PBM. The selected periodontal pocket received 20 s of continuous wave diode laser irradiation with a fiber optic of 600 μm in diameter (TheraLase, DMC Ltda, São Carlos, SP, Brazil), a wavelength of 660 nm, power of 0.03 W, fluency of 22 J/cm^2, an area of 0.028 cm^2, irradiation of 1.1 W/cm^2, and total energy of 0.6 J. The application was performed in two points of laser irradiation (one buccal and one lingual) using punctual contact to reduce reflection, with the tip perpendicular to the gingival tissue [19] (Fig. 1).

Clinical parameters

Periodontal clinical measures were performed by one calibrated operator (NCCS), who was blinded to the treatment allocation. The examiner participated in a calibration exercise in which the PD and CAL of 10 patients were measured twice in a 24-h interval. Then, the measurement was submitted to an intraclass correction test. The agreement for variables was > 90%.

Clinical measures were performed before treatment (baseline), 3, 6, and 12 months after treatment. The primary outcome variable was mean PD. Secondary outcome variables were mean CAL, PD reduction, CAL gain, bleeding on probing (BoP), presence of supragingival biofilm (PI), and frequency of distribution of sites according to PD. All of the clinical measures were assessed using a manual probe (North Carolina-Hu-Friedy).

Statistical analysis

The clinical parameters were computed per subject and per selected pocket. The mean and standard deviation were calculated for each parameter. The normality of the data was analyzed according to the Shapiro–Wilk test. As the data did not present normal distribution for any of the evaluated variables, non-parametric tests were performed for each outcome. The

Friedman test was used to compare differences in periodontal pocket parameters, such as mean PD, mean CAL, percentage of sites with BoP, percentage of sites with supragingival biofilm accumulation, PD reduction, and CAL gain. For the frequency of distribution of sites, Kruskal-Wallis test with Dunn's multiple comparisons was performed for intragroup comparisons and Chi-square test was used to compare the differences between groups.

Results

Thirty-eight periodontal pockets were selected in patients with periodontitis and type 2 DM. All the patients included in this study completed the follow-up of 12 months. Figure 2 shows the flowchart representation of the study. Patients were questioned about the adverse effects of laser therapy, such as discomfort, burning sensation, and pain. No adverse effect was reported.

Demographic data and full-mouth clinical parameters are presented in Table 1. The study population was composed of adults with generalized moderate to severe periodontitis and type 2 DM. Mean glycated hemoglobin (HbA1c) indicated that, on average, patients presented poor metabolic control at baseline, which increases the risk of periodontal disease progression. Full-mouth periodontal parameters showed that patients presented advanced stages of periodontitis and increased inflammatory profile, with more than 50% of sites presenting BoP.

The PBM group presented statistically significant changes in mean PD between baseline and all time points ($p < 0.05$), while for the control group, significant differences were observed at 6 and 12 months, but not at 3 months ($p > 0.05$). No statistically significant difference was observed when comparing the study groups ($p > 0.05$). Mean CAL showed statistically significant changes between baseline and 6 and 12 months for both groups ($p < 0.05$). PD reduction and CAL gain did not present statistically significant difference between groups ($p > 0.05$) (Table 2). Percentages of sites with BoP and Pl accumulation decreased over time for both groups ($p < 0.01$) with no statistically significant difference between groups ($p > 0.05$).

The frequency of distribution of sites according to PD was analyzed using Kruskal-Wallis test (intragroup) and Chi-

Fig. 1 a Periodontal probing after ultrasonic periodontal debridement at baseline. b Application of low-level laser perpendicular to the gingival tissue. c Periodontal probing at 12 months
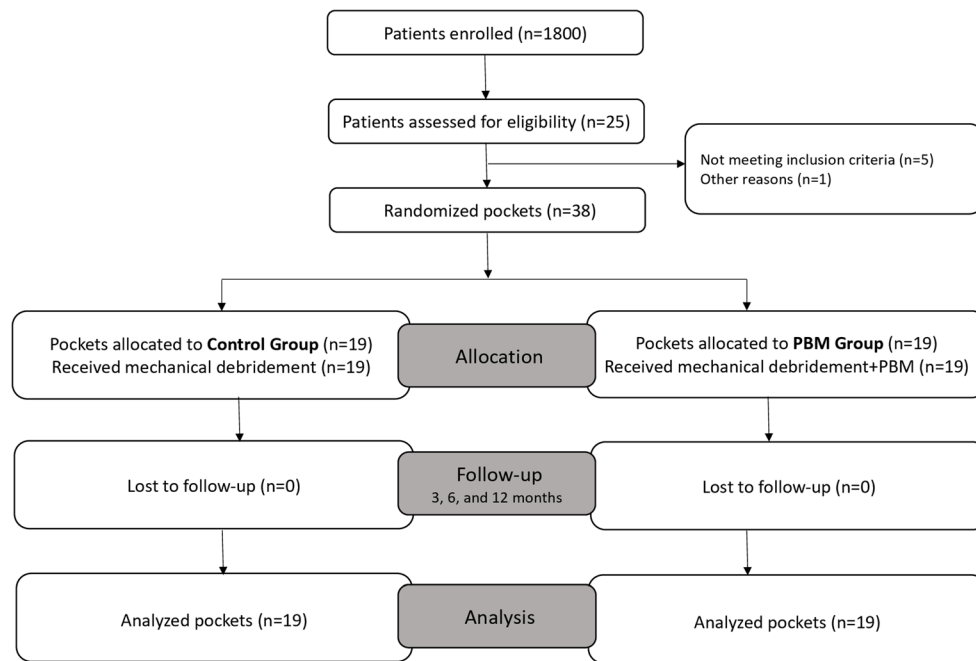
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┌─────────────────────────────────────┐
│      Patients enrolled (n=1800)       │
└─────────────────────────────────────┘
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                  ▼
┌─────────────────────────────────────┐        ┌─────────────────────────────────────┐
│ Patients assessed for eligibility (n=25) │────▶│ Not meeting inclusion criteria (n=5)  │
└─────────────────────────────────────┘        │ Other reasons (n=1)                   │
                  │                              └─────────────────────────────────────┘
                  ▼
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│      Randomized pockets (n=38)        │
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Fig. 2 CONSORT flowchart of the study. PBM, photobiomodulation

Allocation:
- Pockets allocated to **Control Group** (n=19); Received mechanical debridement (n=19)
- Pockets allocated to **PBM Group** (n=19); Received mechanical debridement+PBM (n=19)

Follow-up (3, 6, and 12 months):
- Lost to follow-up (n=0)
- Lost to follow-up (n=0)

Analysis:
- Analyzed pockets (n=19)
- Analyzed pockets (n=19)

square test (intergroup). Statistically significant differences between groups were observed for the percentage of pockets with PD 5–6 mm at 6 months ($p < 0.01$). For the intragroup analysis of deep pockets (PD ≥ 7 mm), the PBM group presented statistically significant reduction in the percentage of pockets at 3 months ($p < 0.001$), and this was also observed at 6 and 12 months ($p < 0.001$) (Table 3).

Discussion

The modest results obtained with current gold standard procedures for adjunctive therapies in the treatment of periodontal conditions have led to the investigation of PBM as a possible alternative. The use of PBM for the treatment of periodontitis

Table 1 Demographic data and full-mouth clinical parameters (mean ± SD) at baseline

Parameters	Patients ($n = 19$)
Mean age (years)	52.26 ± 9.87
Mean number of teeth (n)	20.95 ± 4.49
Gender (F/M)	14/5
Mean HbA1c (%)	8.10 ± 1.83
Mean PD (mm)	4.06 ± 0.93
Mean CAL (mm)	4.54 ± 1.28
Sites with BoP (%)	54.95 ± 25.53
Sites with supragingival biofilm accumulation (%)	69.34 ± 23.82

BoP bleeding on probing, *CAL* clinical attachment level, *F* female, *HbA1c* glycated hemoglobin, *M* male, *PD* probing depth

has been discussed in clinical studies and reviews [25–32, 35–39]. Our study did not detect statistically significant differences between groups for mean PD, the primary outcome of this investigation. Intergroup difference in mean CAL, PD reduction, and CAL gain were also not observed. Although no significant differences were detected between groups, the control and PBM groups presented changes in PD and CAL over time, indicating that both treatments were effective in treating moderate and deep periodontal pockets in patients with type 2 DM. In a systematic review concerning the use of PBM as an adjunctive treatment for periodontitis in patients with type 2 DM, Abduljabbar et al. reported that all the clinical trials using PBM showed improved results in periodontal parameters [39]. However, the follow-up of these studies was up to 12 weeks. In addition, their analyses were based on full-mouth patient-centered parameters, while here we investigated variables related to periodontal pockets.

The frequency of distribution of PD analysis showed that the additional use of PBM decreased the percentage of moderate periodontal pockets at 6 months, with statistically significant difference between groups. This result indicates that the adjunctive use of PBM may be beneficial in the short term. However, at the 12-month follow-up, the significant differences were not sustained. This may be due to the immediate wound healing properties of laser therapy. With the purpose of evaluating tissue biostimulation for root coverage, Fernandes-Dias et al. compared the use of PBM as an adjunct treatment to connective tissue graft (CTG) to CTG alone. In a 6-month follow-up, the authors reported that PBM increased the percentage of complete root coverage when associated with CTG. However, when these patients were reevaluated in a 2-

Table 2 Mean PD, mean CAL, PD reduction, and CAL gain (mean ± SD) for the selected pockets at baseline, 3, 6, and 12 months

		Treatment groups		
Parameters	Timepoints	Control ($n = 19$)	PBM ($n = 19$)	*p* value
Mean PD (mm)	BL	6.5 ± 2.0	6.6 ± 1.6	0.36
	3 M	4.7 ± 1.9	4.4 ± 1.2*	0.65
	6 M	4.1 ± 1.5*	3.9 ± 1.4*	0.65
	12 M	3.8 ± 1.6*	3.6 ± 1.5*	0.49
PD reduction (mm)	ΔBL-12 M	2.7 ± 1.9	3.0 ± 1.8	0.36
Mean CAL	BL	6.7 ± 2.2	6.7 ± 1.6	0.82
	3 M	5.4 ± 2.3	4.9 ± 1.6	0.65
(mm)	6 M	4.9 ± 1.9*	4.5 ± 1.8*	0.25
	12 M	4.7 ± 2.1*	4.2 ± 2.0*	0.17
CAL gain (mm)	ΔBL-12 M	2.0 ± 1.8	2.5 ± 2.1	0.17

BL baseline, *CAL* clinical attachment level, *M* months, *PBM* photobiomodulation, *PD* probing depth

*Statistically significant difference for intragroup comparisons—Friedman test; $p < 0.05$

†Statistically significant difference for intergroup comparisons—Friedman test; $p < 0.05$

year follow-up, PBM did not present additional benefits for root coverage. The results of these studies indicate that there are additional benefits for low-level laser biostimulation in periodontal soft tissues in the short-term, but satisfactory outcomes seem to be equally achieved with or without PBM in longitudinal observation [20, 21]. Although these clinical trials aimed to treat a different periodontal condition than the present study, their findings are in agreement with our outcomes concerning long-term periodontal soft tissue stability.

For the initially deep pockets (PD ≥ 7 mm), PBM greatly decreased the percentage of periodontal pockets, from 47.37% at baseline to 5.26%, at 3 months. Interestingly, the three-month result was maintained at 6 and 12 months. In the control group, there was no statistically significant difference between baseline and 3 months, with 36.84% and 15.79% of

Table 3 Frequency of distribution of sites according to PD measurements (mean ± SD) at baseline, 3, 6, and 12 months

		Sites (%)		
Groups	Timepoint	PD ≤ 4 mm	PD 5–6 mm	PD ≥ 7 mm
Control	BL	0.00	63.16 ± 49.56	36.84 ± 49.56
	3 M	42.11 ± 50.73	42.11 ± 50.73	15.79 ± 37.46
	6 M	57.89 ± 50.73	36.84 ± 49.56	5.26 ± 22.94*
	12 M	78.95 ± 41.89*	10.53 ± 31.53*	10.53 ± 31.53
PBM	BL	0.00	52.63 ± 51.30	47.37 ± 51.30
	3 M	68.42 ± 47.76*	36.84 ± 49.56	5.26 ± 22.94*
	6 M	78.95 ± 41.89*	26.32 ± 45.24†	5.26 ± 22.94*
	12 M	84.21 ± 37.46*	21.05 ± 41.89*	5.26 ± 22.94*

BL baseline, *M* months, *PBM* photobiomodulation, *PD* probing depth

*Statistically significant difference in intragroup analysis compared to baseline—Kruskal-Wallis test with Dunn test post hoc; $p < 0.05$

†Statistically significant difference in intergroup analysis—χ^2 test; $p < 0.01$

pockets, respectively. At 6 months, the percentage of deep pockets decreased to 5.26%, but increased again to 10.53% at 12 months. These results suggest that PBM may provide additional benefits for the treatment of deep periodontal pockets and that these benefits may offer periodontal stability over time. This finding could be explained by in vitro and in vivo observations of fibroblast proliferation and collagen formation when PBM was applied to samples of diabetic cells and tissues [40, 41]. Obradović et al. [42] performed a histological evaluation of human periodontal tissue from diabetic and non-diabetic patients who received adjunct PBM to periodontal therapy. The authors reported that, after PBM application, diabetic periodontal tissue showed less edema, fewer inflammatory cells, and distinguished collagenization. Therefore, wound healing of deep periodontal pockets may be enhanced with PBM, decreasing the percentage of sites with deep periodontal pockets in the short term, and providing periodontal stability in the long-term.

Despite the number of clinical studies investigating the use of PBM for the treatment of periodontal disease already published, the literature still lacks full consensus on the subject. Different laser protocols, including laser parameters and delivery, play a central role in the divergence in study results [25–28]. Kreisler et al. [26] compared scaling and root planing (SRP) associated or not with PBM through a split-mouth clinical study. Twenty-two patients received PBM + SRP in one pocket and SRP alone in another pocket in the contralateral jaw. Laser protocol, as performed, used a GaAlAs diode laser; a wavelength of 809 nm; power of 1 W; for 10 s; and an optic fiber of 600 μm introduced into the periodontal pocket. An intergroup statistically significant difference was found for the PD and CAL, but not for the BoP, GI, and PI. On the other hand, Dukic et al. [27] investigated the effects of PBM through a split-mouth clinical trial. Thirty-five patients each received the treatments in two different periodontal pockets.

The laser protocol was a diode laser; a wavelength of 980 nm; power of 2 W; for 20 s; with an optic fiber of 300 μm introduced into the periodontal pocket. PBM was performed in three sessions: days 1, 3, and 7 after SRP. No intergroup statistically significant difference was observed for any of the analyzed clinical parameters.

To evaluate the additional use of PBM for nonsurgical periodontal therapy in patients with type 2 DM, Koçak et al. [35] performed a parallel clinical trial in which 60 patients were randomly allocated to SRP or SRP + PBM. The laser protocol was a pulsed InGaAlP diode laser; a wavelength of 940 nm; power of 1.5 W; a fluency of 15 (pulse length) and 20 J/cm^2 (pulse interval); for 20 s; with an optic fiber of 300 μm introduced into the periodontal pocket. PBM was performed in one single session. Although the PD, CAL, PI, and GI did not present intergroup statistically significant differences for the whole-mouth analysis, the PD and CAL showed statistically significant changes in deep pockets at 3 months. Patients were controlled diabetics with a mean HbA1c of $6.54 \pm 0.66\%$ (SRP) and $6.91 \pm 0.79\%$ (SRP + PBM) at baseline, which significantly reduced at 3 months.

A systematic review [38] pointed out that PBM tends to be more effective when the laser is applied on the oral epithelium, which could be observed in some clinical trials [19, 22, 27, 28]. Makhlouf et al. [28] investigated the use of adjunct PBM for SRP through a split-mouth clinical trial. Sixteen patients received PBM + SRP in one site and SRP alone in the contralateral site. The laser protocol was performed as described: a wavelength of 830 nm; power of 0.10 W; an area of 0.03 cm^2; a fluency of 3 J/cm^2; for 30 s; perpendicularly to the gingival tissue. PBM was performed in 10 sessions. An intergroup statistically significant difference was found for PD at 5 weeks and 12 weeks, but no statistically significant difference was found at any time point for the GI.

A recurrent question concerning PBM is the contribution of heat as secondary action of lasers, since thermal variance could be the true influencer on cell metabolism in the target tissue. To evaluate the role of this confounding factor, Wang et al. [43] performed a study in humans in which they measured time-dependent temperature increases by laser and by thermal stimulation. No relation could be determinate between hemodynamic and metabolic tissue effects when pure thermal stimulation was performed, whereas significant hemodynamic and metabolic responses were observed when laser was applied, demonstrating that PBM therapeutic properties did not result from tissue-heat interaction.

To the best of our knowledge, this was the first clinical trial with a follow-up of 12 months that evaluated the effects of PBM in periodontal pockets of patients with periodontitis and type 2 DM. The split-mouth design was chosen for this investigation so that the differences inherent to host response were suppressed, prioritizing differences between treatments. This measure is particularly relevant for patients who are likely to present systemic variations that may impact periodontal tissue and that cannot be managed or controlled by periodontists (alterations due to medication, weight gain/loss, etc.). The main weakness of this study is that analyses regarding inflammatory markers were not performed, which limits our understanding of periodontal tissue response to PBM in patients with periodontitis and DM. Future comparisons should focus on other variations of the promising protocols presented in the literature, such as an increased number of application sessions or multiple application points.

In conclusion, the results showed that the PBM protocol used in this study did not provide significant changes PD and CAL in periodontal pockets when compared to mechanical therapy only in patients with periodontitis and type 2 DM. However, PBM was more effective in reducing the percentage of moderate periodontal pockets at 6 months. Additionally, PBM decreased the percentage of deep pockets at 3 months, and this result was maintained at 6 and 12 months.

Compliance with ethical standards

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