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ORIGINAL ARTICLE

Efficacy of ILIB on periodontal clinical parameters and glycemic control in patients with periodontitis and type II diabetes—randomized clinical trial

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Abstract

Our study aimed to study the efficacy of ILIB on periodontal parameters and glycemic control in patients with periodontitis and type II diabetes. Twenty-one patients in a randomized clinical trial were divided into 2 groups: control group (CG), conventional periodontal therapy, and test group (TG), conventional periodontal treatment associated with 10 laser applications by the ILIB-Modified (ILIB-M) technique. Fasting blood glucose levels and glycated hemoglobin (HbA1c), visible plaque index (VPI), gingival bleeding index (GBI), and periodontal clinical parameters were evaluated at baseline and after 4 months (T_4). Regarding periodontal parameters, the intragroup analysis showed a statistically significant reduction ($p < 0.05$) between baseline and T_4, for the VPI, GBI, BOP, PD, and CAL indexes. However, in the intergroup analysis, no statistically significant improvements ($p > 0.05$) were observed between the TG and CG for the VPI, GBI, BOP, PD, and CAL indexes. Regarding HbA1C and fasting blood glucose values, no statistically significant improvements were observed in intergroup and intragroup analyses ($p > 0.05$). The Modified ILIB did not improve the periodontal clinical parameters and glycemic control in patients with type II diabetes.

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

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that can affect the supporting periodontal tissue and exacerbate another chronic disease, periodontitis [1–3]. DM patients usually present with more severe periodontal disease [4]. This characteristic can be attributed to changes in function of the immune system, vascularization, sulcular fluid composition, periodontal tissue repairing process, inflammatory response, bone tissue metabolism, and morphology [5, 6]. The use of low-intensity lasers in periodontal disease as an adjunct treatment has been suggested to influence inflammatory response modulation, tissue repair, and analgesia [7]. One of the low-level laser applications is the ILIB technique. The ILIB technique irradiates blood cells, showing effectiveness in the treatment of various chronic and acute conditions [8–10].

The antioxidant effect of ILIB treatment has been related to the stimulation of the enzyme superoxide dismutase (SOD), which is the main endogenous antioxidant system component. SOD is responsible for the dismutation of superoxide anion (O2*-) to hydrogen peroxide (H_2O_2), protecting aerobic organisms against superoxide radical reactivity and toxicity. Superoxide radical reactivity and toxicity are responsible for hydroxyl radical (HO*) formation and subsequent cellular toxicity with reactive oxygen species (ROS) [8–13]. The reduction in the HO* formation and ROS is associated with a decrease in chronic inflammatory responses [9, 12, 13].

Furthermore, ILIB seems to promote a cascade of reactions in the immune system that results in inflammatory

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response modulation, decreased edema and healing time, and analgesic effects [9, 14]. These effects are possibly related to the regulation of expression of growth factors, with an increased production of arginine and nitrous oxide and a decrease in production of the oxygen-free radical [9, 14].

Studies using ILIB as adjunctive therapy in patients with type II diabetes have found a significant effect in reducing blood glucose levels, suggesting this therapy as an effective adjunct treatment in controlling blood glucose levels in patients with type II diabetes [9, 15].

A new form of the ILIB application has emerged, called Modified ILIB (ILIB-M), which is considered easier because it does not require peripheral venous access [8–10, 16]. In this technique, the laser light indirectly irradiates the blood through a guide bracelet placed at the height of the radial artery where a low-intensity laser is attached [8–10, 16].

Although the biological effects of chronic diseases such as inflammation modulation and hemoglobin oxygenation are well studied, there are few studies in the literature regarding the effectiveness of improving the clinical parameters of patients who undergo adjunctive treatment with ILIB. The present study is the first that aims to investigate the efficacy of Modified ILIB for glycemic control and periodontal clinical parameters of patients with periodontitis and type II diabetes mellitus. This study is important because if prediabetes and early diabetes were treated effectively, then the progression of hyperglycemia could be prevented or delayed, which may subsequently lead to reduced progression of periodontitis.

Methods

This study followed the parameters detailed in CONSORT. It was characterized as a randomized-controlled clinical, parallel-group study and blinded trial conducted at the Dentistry Department of Federal University of Rio Grande do Norte (UFRN), in partnership with the Clinical Analysis Laboratory of the UFRN Pharmacy Faculty and the Onofre Lopes University Hospital (HUOL), Natal-RN, Brazil. The study was submitted to the Research Ethics Committee and approved under the protocol number 2,932,923, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. All subjects agreed to participation by signing a Free and Informed Consent Form.

This study population consisted of patients diagnosed with periodontitis and type II diabetes. The subjects of this study were enrolled from January 2019 to June 2019.

Inclusion criteria were as follows: individuals with stage II, III, and IV periodontitis [17]; at least 18 years old; and the presence of at least two sites in different sextants with attachment loss ≥ 3 mm and bleeding on probing. The included participants also presented with a type II diabetes mellitus diagnosis, being prescribed supplementation and/or diet, insulin and/or oral hypoglycemic agents, and glycated hemoglobin levels (HbA1c) ≥ 6.5%. The exclusion criteria were as follows: smokers, people who used drugs that cause gingival hyperplasia, orthodontic appliances users, pregnant women, and lactating women.

For this study, 22 individuals met all inclusion criteria, but one participant was lost due to skin burns, caused by the application of ILIB. Thus, the total sample was 21 participants, of which 11 (52.3%) were in the control group and 10 (47.6%) were in the test group. Sixteen (76.1%) individuals were female and 5 (23.8%) individuals were male. The age range was between 45 and 77 years, with the median age being 61 years.

Data collection was executed by filling out a clinical form with three parts: medical history (including fasting blood glucose and HbA1c values), data collection related to oral hygiene VPI and GBI (visible plaque index and gingival bleeding index), and periodontal evaluation BOP, PD, and CAL (bleeding on probing, probing depth, and clinical attachment level). Data collection was performed by two experienced examiners, who were submitted to interexaminer calibration obtaining a value of 0.97 for quantitative variables following the precepts of the Intra-Class Correlation Index (ICC). Only one researcher was responsible for conducting the treatment, while the other two researchers conducted the evaluations.

Randomization for the study was executed by asking the participants to draw a card from a box to determine their assignment. A box containing 30 cards was used (15 with letter A and 15 with letter B). The participants who took the A card were allocated to the test group, while those who took the B card were assigned to the control group.

After the group assignment and data collection, the individuals underwent one of the two treatments described below:

Treatment A (test group)

Oral hygiene guidance + manual or ultrasound scaling and root planning (SRP) (two sessions, 48 h apart) + irradiation with a low-intensity laser using the Modified ILIB technique. The ILIB utilization protocol consisted of 1 low power laser application from Therapy EC-DMC (Equipment's Ltda., São Carlos, SP, Brazil) with 10 sessions, lasting 30 min each application in lighter-skinned patients and 15 min in black patients (following the manufacturer's recommendation), with an interval of 1 day per session, excluding the weekend. The laser has been configured in wavelength: 660 mm; action mode: contínuos wave; energy density: 6.428 J/cm^2 (Fig. 1). In this technique, a silicone bracelet (supplied by

Laser parameters	
Composition	ASGaINAL
Wavelength	660mm
Wattage	100 mw
Action Mode	Continuous wave
Number of Points Irradiated	Single point
Diameter Tip	0.028 cm
Energy density	6.428 J/cm²
Time	30 minutes
Sessions	10 sessions with break the 48 hours
Application Technique	Laser optic-fiber was positioned in silicone bracelet, at the height of the radial artery, then laser was activated

Fig. 1 Parameters involved in determining the low-power laser application. Natal/RN, 2019. Source: author

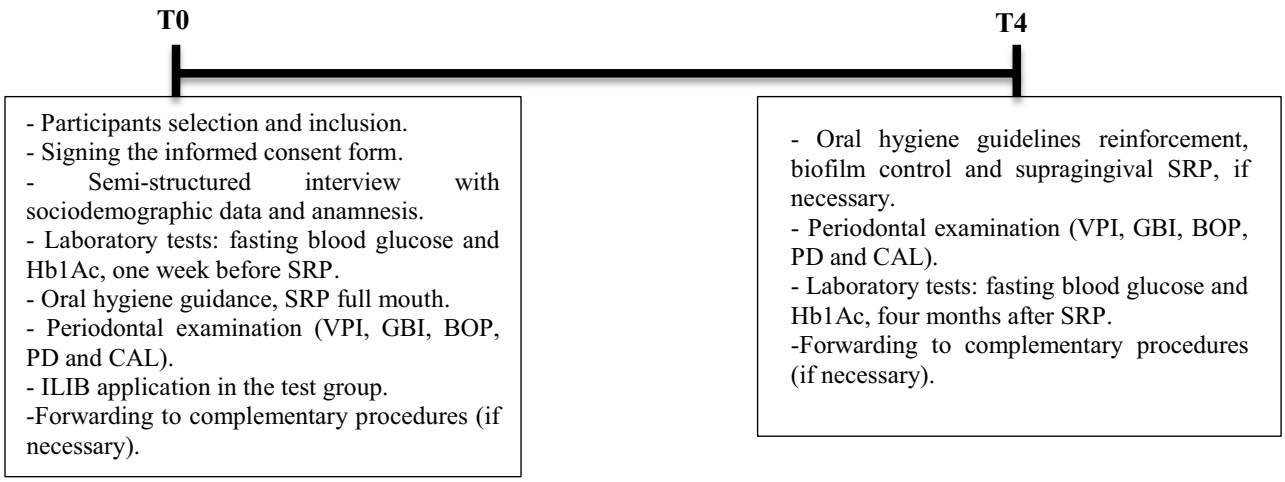
the LASER manufacturer) is fitted on the patient's wrist at the height of the radial artery. The laser tip was applied in contact with the skin. The low-intensity laser tip is then attached to this bracelet (Fig. 2, 3).

Treatment B (control group)

Oral hygiene guidance + manual or ultrasonic manual or ultrasound SRP (two sessions, 48 h apart) (Fig. 2).

The information collected was entered into a spreadsheet in Microsoft Excel and a database was created in the Statistical Package for Social Sciences (SPSS®) program in version 20.0. Non-parametric tests were performed in the normality absence for analysis of the following variables: HbA1c, fasting blood glucose, VPI, GBI, PD, BOP, and CAL.

The Wilcoxon test was applied for intergroup analysis at each point. When a significant difference was observed, the Mann–Whitney test was applied. The 5% ($p < 0.05$) significance level was used for intragroup and intergroup evaluation.



Subtitles: SRP: scaling root planning; VPI: visible plaque index; GBI: gingival bleeding index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; ILIB: intravascular laser irradiation of blood; Source: Author.

Fig. 2 Experimental design. SRP: scaling root planning; VPI: visible plaque index; GBI: gingival bleeding index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; ILIB: intravascular laser irradiation of blood. Source: author

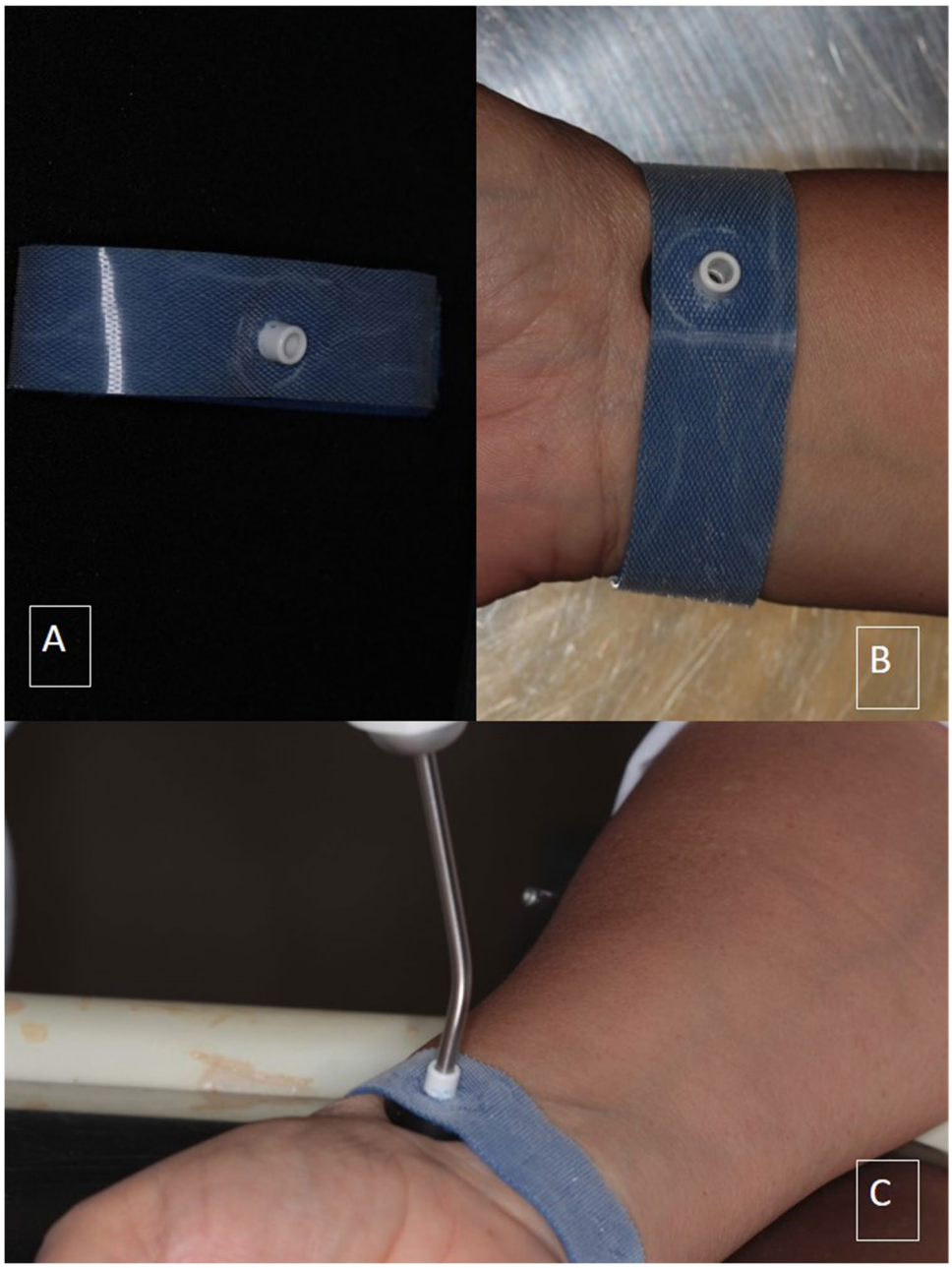


Fig. 3 Bracelet and laser application. **A** Silicone bracelet; **B** silicone bracelet at the height of the radial artery; **C** laser optic-fiber was positioned in silicone bracelet

Results

In this study, all oral hygiene indexes (VPI and GBI) and periodontal parameters (BOP, PD and CAL), had a statistically significant decrease of the median in the intragroup analysis from baseline to T4. However, there was no statistically significant difference in the intergroup analysis between the test and control groups in baseline and T_4 (Table 1).

The patient's glycemic control was determined by their HbA1c and fasting blood glucose values. For HbA1c, the control group showed an increase in the median between the study times, from 6.90 at baseline to 7.30 at T_4. The test group showed no variation in the 8.15 median value between baseline and T_4. For fasting blood glucose, there was an increase in the median of the control group from 124.00 mg/dL at baseline to 153.00 mg/dL at T_4. In the test group, there was also an increase from a median of 133.50 mg/dL at baseline to 157.00 mg/dL at T_4 (Table 2). In the intergroup analyses, there was no statistically significant difference between glycated hemoglobin and fasting glucose (Table 2).

The following confounding variables were evaluated: comorbidities other than diabetes, the use of drugs to control type II diabetes mellitus (oral hypoglycemic agents), or insulin and the diabetic patient's metabolic compensation.

Table 1 Medians comparison (Q_{25}–Q_{75}) for VPI, GBI, PD, BOP, and CAL in the test and control groups in baseline and T_4. Natal/RN, 2020

Study group	Baseline (T_0)	4 months (T_4)	p^1
	VPI		
Control group	58.33 (53.01–88.88)	33.00 (25.00–66.66)	0.033
Test group	58.88 (36.35–71.87)	27.08 (19.87–50.34)	0.005
p^2	0.573	0.291	
	GBI		
Control group	62.50 (44.00–100.00)	22.00 (11.11–45.83)	0.004
Test group	57.13 (34.33– 69.07)	33.48 (19.15 –43.28)	0.047
p^2	0.437	0.468	
	BOP		
Control group	87.50 (50.00–100.00)	38.80 (21.29–50.00)	0.007
Test group	57.80 (49.10–78.57)	35.44 (24.13–50.13)	0.005
p^2	0.258	0.832	
	PD		
Control group	5.00 (3.50–6.00)	3.00 (2.50–4.00)	0.003
Test group	5.00 (4.87–5.50)	2.50(2.00–3.24)	0.005
p^2	0.883	0.429	
	CAL		
Control group	7.50 (6.50–8.50)	5.50 (4.00–7.00)	0.003
Test group	7.50 (6.37–9.50)	5.00 (4.00–6.00)	0.005
p^2	0.915	0.697	

p^1 indicates the intragroup p value between the evaluated periods by the Wilcoxon test ($p < 0.05$). p^2 indicates the intergroup p value (test and control) by the Mann–Whitney test. *VPI* visible plae index; *GBI* gingival bleeding index; *BOP* bleeding on probing; *PD* probing depth; *CAL* clinical attachment level. Source: author

For the other comorbidities present and the use of drugs to control type II diabetes variables, no statistical difference was observed in the intragroup and intergroup analyses. When assessing the metabolic compensation confounding variable, a statistically significant reduction was found in the intragroup analysis for the GBI, BOP, PD, and CAL parameters. In the intergroup analyses, there was no statistically significant difference ($p^2 > 0.05$) for metabolic compensation at baseline or T_4 for GBI, PD, and CAL (Table 3). However, in the BOP baseline, a statistically significant result ($p^2 = 0.042$) was observed in the intergroup analysis, in which the metabolically compensated patients presented 61.40% BOP, while the non-metabolically compensated patients presented 86.60% BOP (Table 3).

Discussion

Diabetic patients present with more aggressive periodontal disease, and for this reason, several studies seek adjuvant therapies to periodontal disease treatment. This was a pioneering study on the use of ILIB-M as an adjunct to basic periodontal treatment in diabetic patients. It was observed that ILIB-M use did not result in statistically significant improvements in periodontal parameters or glycemic control. Although, there was a reduction in the periodontal clinical parameters after periodontal treatment.

In our study, there was no statistically significant association ($p < 0.05$) when comparing the GBI, BOP, PD, and CAL periodontal parameters between test and control groups. Cheng et al. [17] carried out a systematic review with meta-analysis, which verified the use of photobiomodulatory therapy as adjunctive treatment to scaling and root planning wherein they found a reduction in BOP and PD ($p < 0.05$) after 3 months. When comparing the use of ILIB-M as an adjunct to periodontal treatment, we found different results than Cheng et al. [17], with no improvement in BOP and PD [18]. However, the results of our study concerning CAL do agree with Cheng et al. [17] who found no evidence to prove that clinical attachment gain with photobiomodulatory therapy use in adjuvant therapy to basic periodontal treatment [18].

There was a statically significant reduction ($p < 0.05$) in the intragroup analysis in both test and control groups regarding GBI, BOP, PD, and CAL periodontal indexes between baseline and T4. This result confirms the effectiveness of basic periodontal treatment with scaling and root

Table 2 Medians comparison (Q_{25}–Q_{75}) for HbA1c and fasting blood glucose in the test and control groups in baseline and T_4. Natal/RN, 2020

Group study	Baseline (T_0)	4 months (T_4)	p^1
	Glycated hemoglobin (HbA1c)		
Test group	8.15 (6.20–9.77)	8.15 (6.22–12.20)	0.646
Control group	6.90 (6.10–10.30)	7.30 (6.50–10.40)	0.944
p^2	0.647	0.647	
	Fasting blood glucose		
Test group	133.50 (104.75–272.00)	154.00 (97.00–263.25)	1.00
Control group	124.00 (107.00–272.00)	153.00 (93.00–174.00)	0.109
p^2	0.673	0.398	

p^1 indicates the intragroup p value in the periods evaluated by the Wilcoxon test ($p < 0.05$). p^2 indicates the intergroup p value (test and control) by the Mann–Whitney test. Source: author

Table 3 Medians (Q_{25}–Q_{75}) for GBI, PD, BOP, and CAL of the sample with metabolic control T_0 and T_4. Natal/RN, 2020

Metabolically compensated	Baseline (T_0)	4 months (T_4)	p^1
	GBI		
Yes	51.31 (32.67–66.51)	22.00 (11.80–38.68)	0.007
No	71.05 (46.09–93.75)	39.56 (19.63–48.95)	0.036
p^2	0.176	0.180	
	BOP		
Yes	61.40 (43.33–84.97)	30.39 (23.35–48.50)	0.003
No	86.60 (58.63–99.30)	40.90 (26.25–61.30)	0.012
p^2	0.042	0.384	
	PD		
Yes	5.00 (4.25–5.75)	2.50 (2.00–3.75)	0.001
No	5.00 (5.00–5.87)	2.75 (2.50–3.75)	0.011
p^2	0.578	0.631	
	CAL		
Yes	7.00 (6.50–8.50)	4.50 (4.00–6.00)	0.001
No	7.75 (6.25–8.37)	5.50 (3.87–6.37)	0.012
p^2	0.746	0.560	

p^1 indicates the intragroup p value between the evaluated periods by the Wilcoxon test ($p<0.05$). p^2 indicates the intergroup p value (test and control) by the Mann–Whitney test. *VPI* visible plate index; *GBI* gingival bleeding index; *BOP* bleeding on probing; *PD* probing depth; *CAL* clinical attachment level. Source: author

planing and oral hygiene instruction for diabetic patients, resulting in decreased gingival inflammation and increased CAL. These findings corroborate the studies by Farman and Joshi [19], who claim that basic periodontal therapy to control periodontitis is effective [19].

Diabetic patients with periodontal disease present with an exacerbated inflammatory response and more severe clinical characteristics. Thus, the complete remission of clinical characteristics is more difficult in this patient group [1, 20]. In this study, there was a statistically significant reduction between baseline and T4 for the test and control groups in median BOP. However, even with this reduction, the median value for BOP in the control group was 38.80% and 35.44% in the test group. This shows that even after periodontal treatment, the patients still had active periodontal disease, considering that the recommended value for the periodontal health classification is less than 10% BOP [3, 21]. In this regard, the importance of periodontal support treatment for the adequate control of periodontitis in diabetic patients is highlighted [4].

Concerning the metabolic compensation, a statistically significant difference ($p=0.042$) was observed for BOP in the baseline between the compensated and non-compensated diabetic patients. The metabolically compensated group had a BOP median of 61.40%, while the non-compensated group had a BOP median of 86.90%. This difference corroborates with studies by Mauri-Obradors et al. [1]; Ziukaite; Slot; Van Der Weijden [2], who report exacerbation of inflammatory response as a result from periodontitis in non-metabolically compensated diabetic patients [1, 2].

The BOP increase associated with metabolic decompensation occurs because hyperglycemia promotes excess glucose in the bloodstream and consequently in the body's tissues [3]. This increase in glucose induces mitochondria to undergo an increase in stress and respiratory burst [3, 5]. This reaction can activate several pro-inflammatory mediator cascades. Advanced glycation end-products (AGEs) also form, which bind to their receptor, RAGE, activating a pro-inflammatory events cascade [3]. This cascade can exacerbate several inflammatory diseases, including periodontitis [3].

In this study, no improvement of glycemic control was observed in relation to the use of ILIB-M. Individuals who received ILIB-M showed no glycemic control improvement, with Hb1Ac being maintained at 8.15%.

Kazemikhoo and Ansari [9] conducted a study evaluating the efficacy of unmodified ILIB for glycemic control in patients with type II diabetes and found a 190 ± 17 reduction in the baseline to 165 ± 20 in T1 regarding the plasma glucose level reduction ($p=0.0018$) [9]. In the Kazemikhoo and Ansari [21] study, T1 assessment was performed immediately after the ILIB application without assessing the treatment longevity. However, the present study found results different to those of Kazemikhoo and Ansari [21], with an increase in fasting blood glucose values in patients who received ILIB-M from 133.50 mg/dl at baseline to 154.00 mg/dl. This difference in findings can be justified by the variation of the techniques used in the studies by Kazemikhoo and Ansari [21] and Kazemikhoo et al. [9].

Kazemikhoo and Ansari [21] and Kazemikhoo et al. [9] used the unmodified ILIB technique. In this technique, peripheral venous access is recommended for laser application directly to blood cells [8, 9, 11, 14, 15, 22]. In the present study, the ILIB-M technique was used, where the laser is applied through the epidermis with a bracelet aid located at the height of the radial artery to irradiate blood cells [14, 15].

During this study, some limitations may have interfered with the final outcome, such as the lack of standardization in medical treatment for type II diabetes mellitus. The patients in this study were treated by different doctors, and the treatment for this clinical condition depends on the individual preference of each professional. Another possible study limitation may be related to the low rate of patient adherence to medical treatment for diabetes, either using the appropriate medication or reducing sugar consumption.

During the application of ILIB-M, it was observed that the patient may have performed small movements of their arm which can interfere with light absorption by the target cells, causing losses in the final result.

Patients with darker skin present a complex melanin chain, causing greater laser light absorption with little reflection [22]. Due to this characteristic, burns on the skin of these patients may occur [22, 23, 24]. For this reason, we suggest an application time of 15 min, according to the laser manufacturer's recommendation, for dark-skinned patients. In our study, we excluded a dark-skinned patient because she presented with a skin burn after 30 min of ILIB application, characterized by hyperpigmented lesion with area of central excoriation and presence of a healing crust.

Future studies are needed that include an evaluation of SOD levels in various tissues and body fluids to assess the real ILIB-M effect in the chronic process reduction.

Conclusion

In conclusion, the use of the Modified ILIB technique did not provide a statistically significant improvement when comparing the periodontal parameters GBI, BOP, PD, and CAL and glycemic control, through Hb1Ac and fasting glycemia over 4 months. However, periodontal treatment was efficient in improving VPI, GBI, BOP, PD, and CAL in diabetic individuals, which reinforces the importance of controlling periodontitis in this population.

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Declarations

Ethics approval This study was submitted to the Research Ethics Committee and approved under the protocol number 2,932,923, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Conflict of interest The authors declare no competing interests.

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