LOW-LEVEL LASER PERIODONTAL THERAPY IN DIABETIC PATIENTS: A RANDOMIZED CONTROLLED CLINICAL TRIAL - PILOT STUDY

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Objectives We aimed to evaluate the effects of low-level laser therapy as an adjunct to non-surgical periodontal therapy in patients with periodontitis and compare the effect on periodontal healing in diabetes mellitus and non-diabetes mellitus patients.

Methodology Ten patients with periodontitis stage II grade B were divided into two groups; Group 1 included 5 non-diabetes mellitus patients with periodontitis, and Group 2 included 5 type-2 diabetes mellitus patients with periodontitis. A 13 mW low-level laser was used in a continuous wave and non-contact mode as an adjunct to scaling and root planning (SRP) in a split-mouth study design “OPTODAN” (Scientific Development with periodontitis). A 13 mW low-level laser was used in a continuous wave and non-contact mode as an adjunct to scaling and root planning (SRP) in a split-mouth study design “OPTODAN” (Scientific Development.

Results Statistically, significant improvement was evident in the gingival index, probing depth, and relative clinical attachment level when comparing test and control sides in all patients 1-month post-therapy. There was improvement in gingival index amongst type-2 diabetes mellitus patients in the test group. However, non-diabetes mellitus patients demonstrated superior results especially in probing depth and relative clinical attachment level.

Conclusion The use of low-level laser therapy as an adjunct in periodontal therapy showed overall improvement in gingival inflammation, probing depth, and clinical attachment level. In comparison to non-diabetes mellitus patients, type-2 diabetes mellitus patients demonstrated significant improvement in gingival inflammation with low-level laser therapy.

KEYWORDS
Periodontitis, Diabetes Mellitus, Lasers, Periodontal Pockets, Photobiomodulation

1. INTRODUCTION

The applications of Photobiomodulation (PBM) or Low-Level Laser Therapy (LLLT) are gaining popularity in the field of dentistry. These lasers have wavelengths that range between 600 and 1,100 nm and interact with tissues via non-thermal photochemical and biological mechanisms. The low-level laser (LLL) light is absorbed in the mitochondria by chromophores including the protein cytochrome-c oxidase which then increases the internal activity and three events occur as a result: An increase in adenosine triphosphate (ATP), the main energy source for the majority of cellular functions which accelerates the healing process; modulation of reactive oxygen species (ROS) which activates transcription factors positively impacting cellular repair and healing; and temporary release...
of nitrous oxide (NO), a potent vasodilator, which improves circulation as well as lymphatic drainage. Therefore, clinically these lasers are known to reduce pain, inflammation and promote wound healing. Due to these properties, researchers are constantly striving to find different therapeutic applications of this non-invasive treatment modality [1].

Periodontitis is a multifactorial chronic inflammatory disease that causes progressive destruction of tooth-supporting tissues (gingiva, periodontal ligament, and surrounding bone), eventually resulting in loss of tooth support. The main etiological factor is microbial plaque accumulation at the gingival margin. When allowed to become chronic, drastic consequences in the periodontium occur causing inflammatory changes in the gingiva, which initially appear as redness and bleeding on probing (BOP). With persistence of inflammation and progression of tissue damage; clinical attachment loss (CAL), bone loss and periodontal pocket formation are evident. Several anaerobic gram-negative species are considered the culprits of periodontal disease, mainly; Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum [2,3]. The basic principle of periodontal therapy is to restore function and avoid further progression of the periodontal disease by removing or altering the causative factors [4]. Conventional treatment for periodontitis consists of non-surgical methods that involve debridement of the inflamed tissues to control the periodontal infection and allow healing of the periodontium [5,6]. Disruption of biofilm by the mechanical removal of subgingival plaque reduces the bacterial load and facilitates resolution of inflammation as well as decrease the probing depth (PD). Considering that LLL is effective in reducing gingival inflammation, swelling, as well as inducing wound healing and providing pain relief, a lot of research is directed towards understanding if the adjunctive use of these lasers could promote accelerated healing and periodontal tissue regeneration. In a study, Obradović et al. achieved better therapeutic results when LLLT was combined with scaling and root planing (SRP) compared to SRP alone [7].

Various systemic conditions influence the periodontium. Diabetes mellitus (DM) is a prevalent metabolic disorder affecting nearly 90% of the world's population. It could be due to a defect in the secretion of insulin from beta-cells of the pancreatic islets of Langerhans, a defect in insulin action or a combination of both. Type-2 diabetes mellitus (T2DM) results from the body’s ineffective use of insulin. Insulin resistance is a cardinal feature of T2DM. Diabetes is a risk factor for periodontal disease and there is strong evidence suggesting a two-way relationship between T2DM and periodontal disease; with diabetes increasing the risk of periodontal disease, and periodontal disease adversely affecting glycemic control [8].

The exact mechanism linking both conditions is still not yet fully understood, but it is believed that chronic hyperglycemia produces advanced glycation end products (AGEs) which bind to specific receptors on different cells such fibroblasts, macrophages and endothelial cells. As a result, macrophages are transformed into hyperactive cells that increase the production of inflammatory cytokines, tumour necrosis factor-alpha (TNF-α), and interleukins 1β and 6 (IL-1β, IL-6) which leads to periodontitis. Moreover, the production of AGEs increases the permeability and molecule adhesion in endothelial cells, while fibroblasts will show decreased collagen production which also contributes to periodontal disease. There is growing evidence supporting the fact that periodontal disease adversely affects glycemic control; it is now acknowledged that due to untreated periodontal disease, the systemic inflammatory burden may be increased in patients with DM. Due to this, they have an altered or delayed healing as compared to non-DM patients. There are relatively few studies that evaluate the adjunctive effect of LLLT in T2DM patients with periodontitis [9]. Therefore, this study sought to evaluate the effectiveness of LLL as an adjunct to non-surgical periodontal therapy (NSPT) in patients with T2DM, by observing changes in clinical parameters such as plaque index (PI), gingival index (GI), PD, and CAL.

2. MATERIALS AND METHODS

Study design
A randomized controlled cross-sectional study using a split-mouth design was planned. The study was approved by the local research and ethics committee; MOHP/RAK/SUBC/NO: 31-2017-UG-D. The study sample consisted of 10 patients aged 35-50 years diagnosed with periodontitis that were recruited from the Ras Al Khaimah College of Dental Sciences (RAKCODS) clinic, Ras Al Khaimah, United Arab Emirates. The sample was divided into two groups; Group 1: 5 Non-DM patients with periodontitis, and Group 2: 5 DM patients with periodontitis. The inclusion criteria for Group 1 were (i) Non-DM patients diagnosed with Stage II Grade B periodontitis (ii) Presence of 4-5mm periodontal pockets on the mandibular 1st molars. For Group 2, the inclusion criteria were (i) T2DM patients diagnosed with Stage II Grade B periodontitis (ii) Presence of 4-5mm periodontal pockets on the mandibular 1st molars. According to the 2017 World Workshop Classification of Periodontal and Peri-Implant Diseases, Stage II Grade B periodontitis patients were selected for this study, as these cases are of moderately progressing periodontitis with pocket depths of < 5mm and a clinical attachment loss of 2-3 mm and there were no teeth lost due to periodontal disease. Although Glycated hemoglobin (HbA1c) blood levels were not obtained from the patients, they were asked if their blood glucose levels were controlled over the past 3 months, and all patients admitted that they had controlled levels (<7%). This was also confirmed...
by the screening glucometer tests for average blood glucose levels performed just before the initiation of the treatment which had a range of (126-146mg/dl). A patient with average blood glucose levels<150mg/dl corresponds to<7% HbA1c levels [10,11]. The exclusion criteria for both groups were (i) Use of antibiotics or corticosteroid therapy 3 months before the study (ii) Patients with acute systemic illness (iii) Pregnant women (iv) Patients suffering from any hemorrhagic disorder or autoimmune disease (v) Smokers or tobacco chewers (vi) Patients who underwent periodontal treatment 3 months before the study.

All participants were given information about the study and informed consent was obtained from all participants.

Clinical examination
Clinical examination included measurements of Plaque Index (PI) (Silness and Loe), Gingival Index (GI) (Loe and Silness), Probing Depth (PD), and Relative Clinical Attachment Level (RCAL). Acrylic stents were fabricated to be used to standardize the probe angulation and as a fixed reference point (Figure 1a).

PD and RCAL were measured using acrylic stents on the mesial, mid buccal and distal surfaces of the mandibular 1st molars using the University of North Carolina (UNC-15) periodontal probe. Acrylic stents were used to ensure accurate measurements, reproducibility, as well as minimize errors while probing (Figure 1b).

Treatment protocol
Patients in both groups received thorough clinical examination, oral hygiene instructions (OHI), full mouth scaling, polishing and root planning. In each patient, the right and left mandibular first molars were then randomly allocated to either Control (SRP alone) or Test (SRP+LLLT) side. A low-level diode laser “OPTODAN” (Scientific Development and Production Center “VEND”, Saratov, Russia) with a 980 nm wavelength and a power setting of 13 mW was used in a continuous wave, non-contact mode with the help of a metallic knob delivery system having an optical diameter tip of 5 mm (Figure 2a). The knob was used in a “brushstroke” motion on the gingival margin and attached gingiva of the buccal surface on the tooth (Figure 2b).

Either SRP or SRP+LLLT was applied to the test side on the 1st, 4th and 7th day respectively. On the first day, the laser application was for 2 minutes with an energy density of 8.2 J/cm². The second application, on day 4 was for 4 minutes delivering a total energy density of 16.4J/cm². The third application, on day 7 was for 5 minutes, with an energy density of 20.5J/cm². Re-evaluation of all clinical parameters was performed after 1 month of the laser therapy.

The pain intensity felt by the patients during the treatment and 1 week postoperatively was determined with the help of a visual analogue scale (VAS), where the patients were told to rate the pain experienced on a scale of 0 to 10, with 0=no pain, 1-3=mild pain, 4-6=moderate pain, and 7-10=severe pain. Patients were on a maintenance protocol and given routine oral hygiene instructions. No antibiotics were prescribed post treatment, as they were not indicated in these cases since only non-surgical periodontal therapy was performed. Moreover, antibiotics can modify the oral flora and host response thereby altering the effect of LLLT by causing an ecological disturbance and inducing the selection of resistant strains as well as increasing their number, causing more amoxicillin resistant strains to be present [12].

Statistical analysis
The statistical significance of various periodontal indices that were elaborated between both groups was examined using the paired t-test. Using the following formula (postoperative index - preoperative index) the absolute change in every periodontal index at 1-month post-therapy about the baseline was calculated. The site with the deepest PD and RCAL in both groups was used to measure all parameters.

A p-value <0.05 was deemed statistically significant, and the valid data was analyzed using Statistical Package for the Social Sciences Statistics “SPSS Statistics” (International Business Machines Corporation “IBM”, Chicago, IL, USA) for Microsoft Windows operating system (Microsoft Inc., Redmond, WA, USA).

3. RESULTS

The comparison of the mean values and change from day 0 to day 30 as well as standard deviation between parenthesis of PI, GI, PD, and RCAL in all patients within the test and control sides is described in Table 1.
The values of PI in the test side were 1.20±0.23 at baseline and 0.17±0.16 at 1 month, while the values in the control side were 1.22±0.21 at baseline and 0.48±0.47 at 1 month, so the differences were not statistically significant (p-value 0.806 and 0.078).

Regarding the absolute change in the values of PI, the difference has shown no statistical significance either (p-value 0.065).

The GI has decreased from 1.67±0.47 to 1.05±0.15 in the test side and from 1.77±0.60 to 1.42±0.31 in the control side group after 1 month; the difference showed no statistical significance at baseline (p-value 0.685) but was statistically significant at 1 month (p-value 0.003). The difference shows statistical significance in the absolute change of the GI values as well (p-value 0.016).

With regard to the PD, there was a reduction from 4.50±0.70 mm to 3.60±0.94 mm in the test side at 1 month. The PD remained unchanged; 5.00±0.94 mm in the control side at 1 month, the difference was not statistically significant at baseline (p-value 0.196) and was statistically significant at 1 month (p-value 0.003). The difference in the absolute change in the values of PD was also statistically significant (p-value 0.001).

The RCAL was 9.70±1.05 and 9.40±0.96 mm in the test and control sides respectively at baseline; and at 1 month the RCAL was 8.80±1.03 and 9.40±0.96 mm in the test and control sides respectively. Therefore, no statistically significant gain in RCAL compared to the baseline in the test and control sides (p-value 0.517 and 0.196), while the difference in the absolute change in the values of RCAL was statistically significant (p-value 0.001).

Table 2 demonstrates the comparison of VAS values on both sides. The differences between the test and control sides as well as the difference in the absolute change were all not statistically significant, either intraoperatively or postoperatively (p-value 1.000).
The mean values of PD and RCAL showed statistical improvement in non-DM patients with periodontitis compared to T2DM patients with periodontitis (p-value 0.047). The mean values of GI indicate a statistically significant improvement was obtained in T2DM patients with periodontitis post-therapy (p-value 0.049), with an absolute change of 0.85 compared to 0.40 in non-DM patients with periodontitis which was statistically significant as well (p-value 0.048).

4. DISCUSSION

The biostimulatory and bioinhibitory effects of laser are governed by the Arndt-Schultz law, which states that weak stimuli excite the biologic activity, while stronger stimuli will have an inhibitory effect. The treatment dose is probably the most important variable in laser treatment and should always be kept in mind when using PBM. If the anticipated response is not achieved then the clinician may need to re-evaluate the dose to ensure it is within the optimal range. The intended target for PBM treatments is to remain within the therapeutic window, which includes both biostimulatory and bioinhibitory effects [13].

In the present study, the treatment protocol was according to Prokhonchukov et al. [14]. The success of the periodontal treatment depends on the elimination of periodontal pathogens and their toxic byproducts from the dental root surface and periodontal soft tissue [15]. Currently, nonsurgical periodontal therapy remains the “gold standard” of care to treat periodontal diseases [16,17]. However, patients with systemic conditions like DM demonstrate an altered or delayed healing. LLLT has shown to be effective in the treatment of impaired microcirculation, improves wound healing, pain relief, fracture healing, and reduction of inflammation as well as swelling [18,19,20]. Yet, there are a few articles about the study of LLLT in periodontal diseases in patients with DM. Therefore, we aimed to assess the adjunctive effects of LLLT with a diode laser in combination with SRP in T2DM patients with periodontitis.

Although not our primary objective, we compared the effect of the LLL on both test and control sides in all patients (n=10) in group 1 and group 2, which exhibited a significant improvement in GI, PD and RCAL on the test side (LLLT + SRP) when compared to the control side (SRP alone) at 1 month. A VAS was used to determine pain perception by the patients intraoperatively and 1 week post-operatively. There was no statistically significant difference between the control and test sides in both groups, which indicates that the level of discomfort was similar in both groups. There was no statistically significant difference in PI and VAS when comparing the control and test sides for both groups after 1 month. In a systematic review and meta-analysis on the PBM effect of LLL in the non-surgical treatment of periodontitis patients, Ren et al. found that LLLT-mediated SRP resulted in a significant improvement in PD and levels of IL-1β in the gingival crevicular fluid compared with SRP alone in the short term [21]. There are a lot of studies where the adjunctive application of LLLT with SRP has shown to improve BOP and inflammation in periodontitis patients as compared to basic periodontal therapy alone [22]. Most of the studies on LLLT as an adjunct to SRP have recorded and evaluated short-term outcomes demonstrating positive effects overall. However, researchers have still not been able to reach a specific treatment protocol [23]. The adjunctive application of LLLT in periodontitis patients with systemic conditions or diseases is able to modify the course of periodontal therapy. Upon comparison of the change (Day 0 - Day 30) in the test side (LLLT+SRP) of both groups, non-DM patients (Group 1) showed statistically significant improvement in PD and RCAL post-therapy as compared to T2DM patients (Group 2), while there was a statistically significant improvement in GI in T2DM patients (Group 2) as compared to non-DM patients (Group 1). Obradovic et al. studied the effect of LLLT on gingival inflammation using the GI by Loe & Silness; they concluded that LLLT is efficient in gingival inflammation elimination and can be proposed as an adjunctive tool in basic periodontal therapy of DM patients [24]. He performed another histological study in 2013, where he found that LLLT expressed healing and is evident by the absence of inflammatory cells. Tissue edema could not be seen and the number of blood vessels was reduced. In the gingival lamina propria, pronounced collagenization and homogenization were present. They then concluded that LLLT showed efficacy in the treatment of periodontitis in DM patients. Because of the more pronounced alterations of the periodontium in DM, the use of LLLT is of particular importance [7]. Demirturk-Goegun et al. found the additional benefit of the LLLT as an adjunct to SRP on gingival bleeding, but did not find any significant improvement on other clinical parameters [25]. Al-Sharif et al. stated that the mean values of GI, PI, and PD reduced significantly after-treatment of the two groups; SRP and SRP with laser groups. However, the SRP with laser group gained a greater reduction in the measured parameters in DM patients with periodontitis [26]. Seda et al. in their randomized controlled trial concluded that the adjunctive use of LLLT with NSPT in DM patients have positively affected the clinical and biochemical parameters, which was similar to the results of our study [27].

5. CONCLUSION

Within the limitations of this study, LLLT being used as an adjunct in periodontal therapy reduced gingival inflammation, decreased probing depth, and improved clinical attachment level. Non-DM patients with periodontitis had statistically significant improvement in both PD and RCAL, while DM patients with periodontitis had statistically.
significant improvement in GI only. Moreover, other parameters demonstrated strong correlation, yet no statistically significant result was reached. Most likely, this is due to the small sample size and short follow-up periods.

6. RECOMMENDATION

The efficacy of LLLT on periodontal pockets in DM patients is promising. Future randomized controlled clinical trials with larger sample sizes and longer follow-up periods are highly recommended to assess the extent and effectiveness of LLLT as an adjunct to NSPT in DM patients.

7. LIMITATION OF THE STUDY

This study was performed during the COVID-19 pandemic. The sample size is relatively small because of the strict selection criteria applied and the limited number of patient flow to the students’ clinic because of the COVID-19 restrictions. Also, the study had to be completed before end of May; the end of the academic year.

CONFLICT OF INTEREST

All authors declare that there is no financial/personal interest or belief that could affect their objectivity.

REFERENCEs

14. OAJ: statistical analysis, preparation of results. JAK: study design, result writing, review of the discussion, overall writing up, preparation of the manuscript.
15.撰稿团队: JAK: background writing, clinical work, preparation of results and manuscript. HZ: study design, background review, results. JD: clinical work, results, discussion. WH: background writing, clinical work, preparation of results. OAJ: statistical analysis, preparation of results. JAK: study design, result writing, review of the discussion, overall writing up, preparation of the manuscript.

STATEMENT OF HUMAN RIGHTS

We would like to thank the clinical staff of the RAK College of Dental Sciences for the continuous support and help while conducting this research.

AUTHOR CONTRIBUTIONS

FAH: background writing, clinical work, preparation of results and manuscript. HZ: study design, background review, results. JD: clinical work, results, discussion. WH: background writing, clinical work, preparation of results. OAJ: statistical analysis, preparation of results. JAK: study design, result writing, review of the discussion, overall writing up, preparation of the manuscript.
Questions

1. In periodontitis, the inflammatory cytokines, such as TNF-α, IL6 and IL 1β are thought to be released by which of the following cells?
   a. T-Lymphocytes;
   b. Mast cells;
   c. Neutrophils;
   d. Macrophages.

2. Which of the following activities is/are associated with the use of Low-level laser in the treatment of periodontitis?
   a. Increase the phagocytosis process;
   b. Increase in cellular repair and healing;
   c. Promotes local hemostasis;
   d. Reduces glycemia.

3. When using photobiomodulation, which of the following laws govern the biostimulatory and bioinhibitory effects of a low level laser?
   a. Arndt-Shultz Law;
   b. Newton’s Law;
   c. Snell’s Law;

4. What is the typical wavelength range for a diode laser used?:
   a. 1500-2000 Nm;
   b. 2900-3000 Nm;
   c. 600-1100 Nm;
   d. 500-550 Nm.