Photobiomodulation, Photomedicine, and Laser Surgery
Volume XX, Number XX, 2019

Pp. 1–26
DOI: 10.1089/photob.2019.4710

Photobiomodulation in Periodontology and Implant Dentistry: Part I

Leila Gholami, MSc, DDS,[1] Sohrab Asefi, MSc, DDS,[2] Amirarsalan Hooshyarfard, MSc, DDS,[3]
Anton Sculean, PhD, DDS,[4] Georgios E. Romanos, PhD, DDS,[5]
Akira Aoki, PhD, DMD,[6] and Reza Fekrazad, MSc, DDS[7,8]

Abstract

Objective: Finding evidence-based treatment strategies for low-level light therapy (LLLT) and the correct incorporation of these treatment methods in the clinical practice of periodontics.
Background: Photobiomodulation has been shown to have biostimulatory, anti-inflammatory and analgesic effects that can be beneficial in periodontal and dental implant treatment procedures.
Methods: In this review we have addressed some clinical questions regarding the potential clinical application of low-level light irradiation and its photobiomodulatory effects in periodontology and implantology. The literature was searched for in vivo (animal or clinical) articles written in English in four electronic databases of PubMed, Scopus, Google scholar, and Cochrane Library until April 2019. Only studies with low irradiation doses without any thermal effects used only for their photobiomodulatory purposes were included.
Results: We were able to find relevant studies for all of our questions, and positive effects for the application of light therapy were reported in most of the studies. However, there is still great deal of heterogeneity in terms of study designs and most importantly in light irradiation devices and the parameters used. Owing to this issue it was not possible to reach specific evidence-based irradiation protocols for the questions addressed in this review.
Conclusions: Based on our search results, an obvious positive effect of LLLT on stimulation of healing of periodontal soft and hard tissues and reduction of inflammation can be seen. Future well-designed randomized control studies with the same irradiation settings and systematic reviews evaluating the studies found on the questions mentioned are necessary to reach evidence-based recommendations.

Keywords: low-level light therapy, periodontology, dental implants

Introduction

Low-level light therapy (LLLT) or rather called photobiomodulation (PBM) therapy has attracted special attention recently, and its applications in dentistry and medicine are continuously growing. PBM of tissue can lead to either positive healing responses or sometimes inhibitory biological effects. These are all possible as a result of nonthermal photochemical and biological interactions. Light-emitting diodes (LEDs), broad light sources, and lasers may be used for this purpose. Clinically many different advantages, such as relief and reduction of pain and inflammation and promotion

[1]Dental Implants Research Center, Department of Periodontology, School of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran.
[2]Department of Orthodontics, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran.
[3]Dental Implants Research Center, Department of Periodontology, School of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran.
[4]Department of Periodontology, School of Dentistry, University of Bern, Bern, Switzerland.
[5]Department of Periodontology, School of Dental Medicine, Stony Brook University, Stony Brook, New York.
[6]Department of Periodontology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.
[7]Department of Periodontology, Dental Faculty, Laser Research Center in Medical Sciences, AJA University of Medical Sciences, Tehran, Iran.
[8]International Network for Photo Medicine and Photo Dynamic Therapy (INPMPDT), Universal Scientific Education and Research Network (USERN), Tehran, Iran.

of healing, have been observed. However, the exact mechanisms are not yet fully understood.[1–3]

Laser technology has revolutionized the dental practice. With the wide range of wavelengths and devices now available in dentistry a variety of different applications, from hard tissue ablative or coagulative surgical applications and anti-infective effects using high powers to favorable tissue interactions using low levels of laser energy, are now possible. There has been a great demand in the dental practice to use less invasive methods and reduce the pain and discomfort of patients and promote tissue healing, and laser or light PBM has the potential to be used as an adjunctive method to reach these goals. PBM can be achieved using low levels of laser irradiation and seems to be a promising technique due to its positive effects and biomodulatory interaction with cells and living tissue. It was first used in medicine and physiotherapy, but recently it is also finding its way into routine dental practice.

PBM or laser therapy is performed by using energy densities that do not cause any heat in tissues, but rather result in photochemical and biological interactions.[4] Visible red and also infrared lasers (600–1000 nm) are mainly used for laser therapy, but other wavelengths and lasers, such as Nd:YAG, CO_2, and Erbium family lasers, may also provide such effects with correct adjustment of the parameters.[5] A thorough knowledge and understanding of the laser physics and optical properties of tissue and its optimal therapeutic window is needed to correctly translate the cellular effects of laser interaction with tissue to result in the desired treatment objectives in clinical practice and avoid contradictory results.[6]

Periodontics is a field of dentistry that has adopted laser technology in its surgical and nonsurgical treatments in periodontal and peri-implant tissues either alone or as an adjunctive treatment with many successful results. Different high- and low-level lasers have been used in periodontal treatments with benefits of coagulation, antibacterial effects, root surface detoxification, and smear layer removal, and even bone recontouring or calculus removal is possible with new pulsed high-power devices.[7,8] Obtaining better treatment results in implant surgery and also predictable therapy for peri-implant diseases has been a focus of many researches in this field. Lasers have been employed for dental implantology from its manufacturing stages (e.g., laser sintering) to its surgical placement and most importantly in the treatment of peri-implant infections.[9]

Although these potential applications are now well known and there are a large number of publications and studies addressing the application of lasers or other light sources in periodontology and implant dentistry, there are still controversies in the results and we still lack clear clinical guidelines for many of the applications. Recently, some systematic reviews have focused on lasers in periodontology and implant dentistry. However, they have not specifically addressed potential clinical applications of PBM using low-level light irradiations.[8,10–14]

In this review we aimed to focus only on the status of research in the fascinating field of PBM using low-intensity light and its potential applications in periodontology and oral implantology and try to present some evidence-based answers and guidance for clinical therapies and future well-designed research.

Methods and Search Strategy

The literature was searched for in vivo (animal or clinical) articles written in English in four electronic databases of PubMed, Scopus, Google scholar, and Cochrane until April 2019. Specific clinical questions were designed regarding potential applications of low levels of light in periodontology and implant dentistry. Each question was searched separately by combining the search keyword of ''low-level laser therapy'' OR ''low-power laser therapy'' OR ''low-intensity laser therapy'' OR ''cold laser'' OR ''soft laser'' OR ''photobiomodulation therapy'' OR ''photobiostimulation therapy'' OR ''LED'' with specific keywords chosen for each question. The inclusion criteria slightly varied in some of the questions and are mentioned for each question separately. The inclusion criteria were studies that utilized irradiation doses without any potential thermal effects and only used for photobiomodulatory purposes.

Periodontology and Laser PBM

Clinical Question 1

Can PBM improve periodontal condition as an adjunctive therapy to conventional nonsurgical periodontal treatment?

Evidence search strategy. A literature search was conducted in the four databases mentioned for clinical studies evaluating the use of LLLT as an adjunct to nonsurgical treatment of periodontitis. The keywords previously stated for ''low-level light therapy'' were combined with keyword of ''periodontal disease'' OR ''periodontitis'' OR ''nonsurgical periodontal treatment'' OR ''periodontal treatment '' OR ''periodontal disease'' OR ''adjunct'' OR ''scaling and root planing.''

All clinical studies evaluating adjunctive low-level light therapy plus scaling and root planing (SRP) (root surface debridement) and assessing clinical parameters or biochemical markers related to periodontal inflammation were included. Study populations considered eligible for inclusion included nonsmoking healthy adult patients (≥18 years old) with aggressive periodontitis (AgP) or chronic periodontitis (CP).

Low-level light was defined by including power settings that would not produce a thermal effect but rather a photobiomodulatory result (average output powers of 1 W or less). Therefore, studies in which lasers were used as an adjunctive tool for pocket debridement, pocket wall de-epithelialization, or for photodynamic therapy were also excluded.

A total of 584 studies were found to be potentially eligible by screening the titles. The search results were further screened for relevance and after a more detailed full text analysis of the articles, 26 articles were included that are listed in Table 1.[15–38]

Evidence-based conclusion and recommendations. The gold standard treatment of periodontitis is still considered to be mechanical debridement of the periodontal pockets (SRP). Most studies using lasers in nonsurgical treatment have used high-power lasers as adjuncts for debridement and also for their antiseptic and bactericidal effects. Some laser wavelengths such as Erbium lasers are also able to

Table 1. Characteristics of Included Studies: Effect of Adjunctive Photobiomodulation in Conventional Nonsurgical Periodontal Treatment

Author (year)$^{ref.}$	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Qadri et al. (2005)[15]	2 Wavelengths (630 and 830 nm)	1 Week after SRP Outputs: 10 and 70 mW They treated (1) the buccal papillae with 635 nm laser for 90 sec (0.9 J) and (2) 6 mm more apically with 830 nm for 25 sec (1.75 J), from the buccal and lingual sides. The energy densities were 4.5 and 8.75 J/cm^2 and the power densities 50 and 350 mW/cm^2	Moderate periodontitis	GCF samples for elastase activity, IL-1β, and MMP-8 Subgingival plaque	The clinical variables, i.e., PPD, plaque, and gingival indices were reduced more on the laser side than on the placebo one. The decrease in GCF volume was also greater on the laser side, 0, 12 mL, than on the placebo side, 0.05 mL. The total amount of MMP-8 increased on the placebo side but was slightly lower on the laser side. Elastase activity, IL-1β concentration, and the microbiological analyses showed no significant differences between the laser and placebo sides.
Kreisler et al. (2005)[16]	GaAlAs laser 809 nm	Power output of 1.0 W Continuous wave 600 μm optical fiber Energy/power density: NA	G1: SRP G2: SRP+LLLT	PI, GI, BOP, SFFR, PT, PPD, and CAL	Teeth treated with the laser revealed a significantly higher reduction in tooth mobility, pocket depth, and CAL. No significant group differences, for the PI, gingival index, BOP, and the SFFR. The application of the DL was considered safe and can be recommended.
Vieru et al. (2005)[17]	Infrared DL with 2 laser beams (1) infrared with 830 nm (2) visible red with 630 nm	Energy between 0.5 and 3 J Continuous or pulsed mode with frequency of 4.68 or 9.12 Hz	G1: classic periodontal treatment G2: LLLT as adjunctive	Gingival bleeding time, pain relief time, and bone recovery time	LLLT, as an adjuvant, increased the rate and quality of healing and shortened the healing time. LLLT as an adjuvant led to better results in treatment of periodontal diseases, but the results also depended upon the age and general health of the patient, and existence of any metabolic problems.
Qadri et al. (2007)[18]	HeNe laser 632.8 nm DL (nominally 635 nm)	3 mW size of the aperture (2 mm in diameter) 100 mW/cm^2	G1: SRP+HeNe G2: SRP+DL	PPD, GI, PI, GCF volume, MMP-8, IL-8, and subgingival microflora	The results from this study suggest that there is a difference in the biological effect between lasers of long and short coherence length and that the lasers of longer lengths of coherence have a stronger stimulating effect.
Assaf et al. (2007)[19]	DL 810 nm	Power: 1 W Pulsed mode	G1: US G2: US+DLs	PI, SBI, PD, and relative attachment level	Application of DL energy can reduce bacteria in gingival crevices that may reduce bacteremia after US. The use of DL did not show additional clinical influence on gingival healing after treatment of gingivitis with US.
Pejcic and Zivkovic (2007)[20]	DL 670 nm	Power density 100–200 mW/cm^2, power output of 4–15 mW, spot width of 3 mm	CP with marked clinical symptoms of gingival inflammation G1: SRP+LLLT G2: SRP	Histologically	Based on the results obtained, it can be concluded that laser therapy as an adjunct procedure in the treatment of periodontitis is very successful in the reduction of gingival tissue inflammation.
Ribeiro et al. (2008)[21]	GaAlAs laser 780 nm 630 nm	Laser energy was applied at a wavelength of 780 nm (35 J/cm^2, 70 mW, 20 sec per site) for preoperative analgesia, and SRP were performed with application of laser energy at a wavelength of 780 nm (35 J/cm^2, 70 mW, 20 sec) for analgesia, and at a wavelength of 630 nm (8.8 J/cm^2, 35 mW, 10 sec) for healing	G1: SRP G2: SRP+laser	PD, CAL, and GI VAS	Utilization of the DL as an auxiliary in subgingival SRP did not provide any apparent clinical benefit for teeth with shallow to moderate pockets

(*continued*)

Table 1. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Lai et al. (2009)[22]	He–Ne laser 632 nm	0.2 mW The dose delivered at each application was 1.7 J/cm^2 (2.83 mW/cm^2), and the total dosage for the entire course of treatment was 13.6 J/cm^2	16 Patients moderate to advanced CP G1: SRP+Laser G2: SRP	Supragingival plaque (PL), BOP, PPD, and probing attachment level were recorded at baseline and at 3, 6, 9, and 12 months, while GCF samples and standardized intraoral radiographs for digital subtraction radiography were taken	No statistically significant difference in any clinical parameters or radiographic findings was found between the test and control sites. Changes in GCF volume were significant only at 3 months in the test sites. Within the limits of this pilot study, the use of the low-power He–Ne laser as an adjunct to nonsurgical periodontal therapy in patients with moderate to advanced CP did not seem to provide additional clinical benefits.
Pejcic et al. (2010)[23]	DL 670 nm	Power density of 150 mW/cm^2 spot diameter was 3 mm with 2-min field exposure per session. Laser radiation was performed daily, within the period of 10 days, power density was set to 150 mW/cm^2, energy density to 18 J/cm^2, and later on, until the end of the treatment a presumed optimal dose of 100 mW/cm^2 was used	CP (mild) G1: conservative treatment+LLLT G2: conservative treatment	PI, GI, and BOP	A general conclusion can be drawn that low-level laser irradiation can be used as a successful physical adjuvant method of treatment, which, together with traditional periodontal therapy, leads to better and longer-lasting therapeutic results.
Gómez et al. (2011)[24]	Nd:YAG laser 1064 nm	75 mJ Pulsed mode 60 sec, 1 session 200 μm Contact beam	G1: SRP G2: SRP+Laser	PPD, BOP, PI, GCF, and subgingival microbiota GCF samples were analyzed for IL-1β, TNF-α, and total antioxidative status.	Application of the Nd:YAG laser in the treatment of CP is a viable adjunct to conventional SRP treatment.
Pejcic and Mirkovic (2011)[25]	Semiconductor laser 670 nm	Optical fiber with a spot width of 3 mm, a power density of 150 mW/cm^2, an energy density of 4 J/cm^2, and a power output of 10 mW. Laser irradiation was conducted every day after conservative instrumental treatment of the periodontal pockets for 10 days continuous mode and applied and kept in light contact for 15 sec with the gingival tissues around every tooth (facial and lingual) for ~4 min per quadrant. The laser beam was directed at an angle of 90° in relation to gingival surface, with the laser tip 2 mm from the surface	CP G1: conservative treatment+LLLT G2: conservative treatment	PPD, BOP, CAL, supragingival plaque measurements (PL) and GCF measurements	Based on the results obtained, it can be concluded that the use of LLLT as an adjunct procedure in the conservative treatment of periodontitis is very successful in reducing gingival tissue inflammation.

(*continued*)

Table 1. (Continued)

Author (year)^ref.	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Eltas et al. (2012)[26]	Nd:YAG laser 1064 nm	1 W, 100 mJ, 10 Hz Optic fiber (diameter 200 μm) Contact fiber tip inserted at the bottom of the periodontal pocket and slowly moved from apical to coronal in a sweeping motion during laser light emission This was done mesially, distally, buccally, and lingually during an exposition time of 120 sec	Generalized moderate CP G1: SRP+Laser G2: SRP	PI, GI, PPD, CAL, and GCF samples to determine levels of IL-1β and MMP-8	We found that SRP+Laser treatment of periodontal pockets was more effective than SRP alone in reducing PPD, CAL, GI, and GCF values.
Calderìn et al. (2013)[27]	DL 670 nm	Maximum power of 200 mW. All treatments were performed at a continuous power setting of 200 mW, 60 sec/tooth. SRP+rPT group, adjunctive PT was repeated 5 times in 2 weeks (days 1, 2, 4, 7, and 11)	27 Moderate-advanced CP patients G1: SRP G2: SRP+PT G3: SRP+rPT	FMPS, FMBS, PPD, and CAL were recorded before SRP. GCF samples were used to determine the levels of IL-1β, TNF-α, RANKL, and OPG	PT used in a single or repeated dose does not produce a significant reduction in the clinical parameters essayed levels of IL-1β in GCF were significantly reduced in SRP+PT and SRP+rPT groups compared with the SRP group. SRP+rPT group showed a significant reduction of proinflammatory cytokine TNF-α and RANKL/OPG ratio at 4 weeks post-treatment compared with the SRP+PT and SRP groups. SRP+PT group also showed a significant reduction in TNF-α and RANKL/OPG ratio at 8 weeks post-treatment compared with the SRP group. PT exerts a biostimulative effect on the periodontal tissue. Multiple sessions of PT showed a faster and greater tendency to reduce proinflammatory mediators and RANKL/OPG ratio. Multiple sessions of PT showed a faster and greater tendency to reduce proinflammatory mediators and RANKL/OPG ratio.
Hazeem et al. (2013)[28]	DL 810 nm	Low-density laser irradiation was operated at a frequency of 5.0 Hz and delivered a 0.5 W continuous wave output at 810 nm with a power density of 1.6 J/cm^2 High-density laser irradiation was performed by using a power of 2 W, 25 sec with continuous wave output at a wavelength of 980 nm with a power density of 1193.7 W/cm^2	G1: SRP G2: SRP+low-level laser G3: SRP+high-level laser	PI, GI, BOP, CAL, and PPD	Results were positive and predictable in both lasers irradiation modes. The differences between the changes of the SRP group, and 2 lasers low- and high-density lasers combined with SRP groups at baseline were not significant. Low- and high-level DL can have a beneficial effect in treatment of CP in combination with traditional mechanical treatment.
Dukić et al. (2013)[29]	DL 980 nm	Peak power: 2 W, average power, 0.66 W; time on (laser beam operative), 25 ms; and time off (laser beam inoperative), 50 ms with a continuous timer	Compare with SRP as an adjunctive for chronic periodontitis	API, BOP, PD, and CAL	The results were similar for both groups in terms of API, BOP, PD in deep pockets, and CAL. The LG showed only significant PD gain in moderate pockets during the baseline to 18-week and 6- to 18-week periods, whereas no difference was found between LG and conventional group in the remaining clinical parameters.

(*continued*)

Table 1. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Saafan et al. (2013)[30]	DL 810 nm	200 mW, CW energy of 16 J, and the total exposure time was 80 sec. Spot size was 4 mm circle, so the power density was 0.2 W/cm^2 and the energy density was 16 J/cm^2. Total of 8 sessions	Mild to moderate AgP. G1: SRP+laser G2: SRP	PPD, CAL, PI, MGI, and GR, TGF-β1 was screened by sampling GCF	Significant decrease of PPD and CAL in favor of LG. PI, MGI, and GR showed not significant. TGF-β1 mean percentage showed a significant steady decrease in the LG. Low-power laser parameters in this clinical trial can be used as an adjunct to SRP in treatment of mild to moderate AgP.
Ismaili et al. (2014)[31]	DL 635 nm	Initial laser power: 25 mW; exposure per irradiation area involving one tooth and one interproximal area: 4 min The size of the aperture was 2 mm in diameter allowing the power density of about 100 mW/cm^2	CP G1: SRP+LLLT G2: SRP	PI, PBI, PPD, and GR. GCF was collected and the levels of IL-1α, IL-1β and MMP-9 were determined.	LLLT attenuated periodontal inflammation in CP patients, as judged by clinical parameters and decreased levels of IL-1 in GCF. It remains to be studied whether elevated levels of MMP-9 in GCF might be beneficial for reparation processes.
Nguyen et al. (2015)[32]	940 nm	Power: 0.8 W Continuous pulse mode 0.80 J/sec	Adult periodontal maintenance patient with a history of treatment for CP	PD, CAL, and BOP, and GCF IL-1 levels	In periodontal maintenance patients, adjunctive use of the DL to SRP did not enhance clinical outcomes compared with SRP alone in the treatment of inflamed sites with ≥5 mm probing depth.
Obradovic et al. (2015)[33]	GaAlAs laser 670 nm	5 mW, CW Probe diameter 2 mm. Treatment time 14 min on the gingiva around the teeth 17–11 and 47–41	50 Patients with periodontitis and clinical symptoms of gingival inflammation	PI, GI, periodontal Ramfjord index	Low-power lasers are effective in the elimination of gingival inflammation and improvement of periodontal health. They can be recommended as an adjunct to the basic periodontal therapy.
Gündoğar et al. (2016)[34]	GaAlAs DL 980 nm	0.4 W, CW, energy density of 7.64 J/cm^{2}15 sec 4 Sessions of irradiation	Compare with SRP as an adjunctive for CP	PPD, GI, PI, CAL, and BOP GCF sampling	In the 1st month, PPD levels were significantly lower in the SRP+LLLT group than in the SRP group. At the 3rd and 6th months, CAL, PPD, and GI were significantly lower in the SRP+LLLT group than in the SRP group. Differences in GCF cytokines levels among the group were not statistically significant. LLLT as an adjunct to NSPT has a positive impact on clinical parameters.
Kumaresan et al. (2016)[35]	DL 810 nm	0.7 W in continuous mode with the tip (0.5 mm). The laser was applied at about 0.5–1 mm away from the gingival margin for 20 sec over each surface covering the entire oral cavity	CP patients G1: RSD G2: RSD+LLLT	PPD, CAL, and SBI GCF samples were collected	Within the limitations of this study, LLLT application was found to have additional benefits over RSD with respect to clinical periodontal parameters and GCF periostin levels. Moreover, periostin may be used as a possible biomarker to evaluate the outcome after NSPT.

(*continued*)

Table 1. (Continued)

Author (year)[ref.]	Wavelength	Irradiation parameters	Study population/groups	Evaluations	Main results
Matarese et al. (2017)[36]	DL 810 nm	1 W in pulsating mode at 50 Hz, $t_{off} = 100$ msec, $t_{on} = 100$ msec, and an energy density of 24.84 J/cm^2, with a 300-lm fiber optic delivery system 20 sec for each tooth Single session after instrumentation	Generalized AgP G1: SRP+laser G2: SRP	PD, CAL, BOP, and FMPS Microbiological and inflammatory evaluation GCF was obtained	At 1 year, SRP+DL yielded a significant reduction in some clinical parameters (PD, CAL), whereas microbial and inflammatory mediator changes were not significantly reduced compared with SRP alone. Although in short term SRP+DL determined a reduction in orange complex bacteria and mean GCF level of IL-1β and IL-1β/IL-10 ratio compared with SRP alone.
Petrovic et al. (2018)[37]	980 nm	0.2 W, 6 J/cm^2	60 Subjects with CP G1: SRP G2: SRP+LLT	Subgingival samples for Aa, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* by PCR. Gingival swabs were taken, and direct smears were prepared on slides for cytomorphometric analysis	LLLT as an adjunct to periodontal therapy demonstrates short-term additional bacteriological, cytological, and clinical benefits.
Mastrangelo et al. (2018)[38]	DL 600–1000 nm	0.04–60 J/cm^2 energy density for 3 sec spotlights	30 CP patients G1: SRP G2: SRP+LLLT	PPD BOP IL-1β in GCF	Etiological treatment associated with LLLT improves BOP and inflammation in periodontal disease. Moreover, the IL-1β concentration changes in GCF suggest these cytokines as a predictable marker of gingival inflammation in CP patients.

Aa, *Aggregatibacter actinomycetemcomitans*; AgP, aggressive periodontitis; API, approximal plaque index; BOP, bleeding on probing; CAL, clinical attachment loss/level; CP, chronic periodontitis; CW, continuous wave; DL, diode laser; FMBS, full-mouth bleeding score; FMPS, full mouth plaque score; GCF, gingival crevicular fluid; GI, gingival index; GR, gingival recession; IL, interleukin; LG, laser group; LLLT, low-level light therapy; LLT, low level therapy; MGI, modified gingival index; MMP, metalloproteinase; NA, not available; NSPT, nonsurgical periodontal treatment; OPG, osteoprotegerin; PBI, papillary bleeding index; PCR, polymerase chain reaction; PD, probing depth; PI, plaque index; PL, plaque; PPD, probing pocket depth; PT, periotest; RANKL, receptor activator of nuclear factor κB ligand; rPT, repeated phototherapy; RSD, root surface debridement; SBI, sulcus bleeding index; SFFR, sulcus fluid flow rate; SRP, scaling and root planing; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha; US, ultrasonic scaling; VAS, visual analog scale.

debride the pockets and remove calculus and biofilm. However, the purpose of our question was the adjunctive application of low level of light energy in nonsurgical periodontal therapy to produce biomodulation of the periodontal tissues and possibly enhance tissue regeneration and healing. Therefore, we did not include articles in which either high powers of light or laser were used or even studies that low-level light energy was used to activate photosensitive dyes to produce antibacterial effect as commonly referred to as photodynamic therapy.

In a recent systematic review and meta-analysis by Chambrone et al., 28 articles were included in which the majority had used medium- to high-power infrared lasers as an adjunctive for periodontal therapy.[7] They concluded that in patients with moderate to severe periodontitis (AgP or CP) the nonsurgical treatment by SRP plus infrared diode laser, and the surgical treatment of CP by Er:YAG laser therapy alone may promote statistically significant improvements in probing depth (PD) and clinical attachment levels (CALs). However, these gains are relatively small (<1 mm) resulting in modest clinical relevance compared with SRP alone. In 2017, Ren et al. performed a systematic review and meta-analysis on the photobiomodulatory effect of low-level laser in nonsurgical treatment of CP patients.[14] Eight publications [seven randomized clinical trials (RCTs)] finally met their inclusion criteria of this systematic review and based on their meta-analysis LLLT-mediated SRP resulted in a significant improvement in probing pocket depth (PPD) and levels of interleukin (IL)-1β in the gingival crevicular fluid compared with SRP in the short term. However, no significant intermediate or long-term effect on clinical or biochemical parameters could be found.

In the studies included in this review, some of the researches confirmed no significant difference between adjunctive low-level light treatment group and SRP alone in improvement of clinical periodontal outcomes.[19,21,22,27,32] Nguyen et al. have evaluated adjunctive low-level laser therapy in supportive periodontal therapy phase of inflamed sites with ≥5 mm probing depth in previously treated CP patients, but no additional benefit compared with SRP alone was observed.[32] The majority of the reports have shown more significant improvement in periodontal conditions and some of the measured outcomes by low level light (LLL) irradiation (Table 1). However, most of the studies have recorded and evaluated short-term outcomes. None of the studies have reported any adverse effects.

In some of the included studies, findings for changes in clinical parameters were different from molecular/immunological results and in most cases although the molecular test showed significant differences, the clinical outcomes were not statistically different. For instance, in the study by Calderin et al. no significant change in clinical parameters was observed, although multiple sessions of phototherapy resulted in a greater and faster reduction of proinflammatory mediators such as IL-1β tumor necrosis factor (TNF)-α levels in gingival crevicular fluid (GCF) and the receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio.[27] Also a split-mouth study by Matarese et al. in 2017 showed a significant reduction of probing pocket depth (PDD) and CAL at a 1 year follow-up session, but regarding the microbial (orange complex) and inflammatory mediator changes although was significant reduction in the short-term follow-ups (at 15, 30, and 60 days) the changes were not significant compared with SRP alone after 1 year.[36] A short-term decrease in periodontal pathogenic bacteria levels were also reported by Petrovic et al.[37]

Overall a positive effect is clear for adjunctive phototherapy in nonsurgical periodontal treatment; however, we were not able to reach to a specific treatment protocol since the studies have a great amount of variation in terms of study protocol, irradiation devices, and parameter settings. Despite the relatively large number of articles on this topic the evidence is still insufficient to reach evidence-based conclusions. Further long-term randomized clinical trials with similar designs are needed to determine the appropriate low-level laser or light therapy settings for this kind of treatment.

Clinical Question 2

Can PBM improve periodontal conditions as an adjunct to nonsurgical periodontal treatments in patients with systemic disease or drug consumption?

Evidence search strategy. To find related articles on this issue, the four databases were once again searched with a combination of keywords for low-level laser therapy and keywords of "systemic disease" OR "diabetes" OR "smoker" OR "medication" AND "periodontal" OR "periodontitis."

In vivo clinical human studies or animal studies comparing the effect of adjunctive LLLT in nonsurgical periodontitis treatment of subjects with systemic conditions that can affect periodontal health and healing were considered eligible.

Twenty-three articles were selected in the first round of screening. After full text evaluation 11 articles were selected (Table 2).[39–49]

Evidence-based conclusion and recommendation. Adjunctive application of low levels of laser has been used in some periodontitis patients with systemic conditions/diseases known to be able to modify the course of periodontal disease. It is proposed that the potential biostimulatory effects of this treatment may help enhance healing of periodontal tissues after nonsurgical SRP treatment and affect the periodontal outcomes.

From the 11 studies considered eligible 5 were conducted on patients with diabetes, 3 in smokers, and 3 were animal studies. The animal studies were conducted on animals (rats) that were treated with medication (simvastatin, dexamethasone, 5-fluorouracil chemotherapy drug) and the effect of adjunctive use of low-level lasers in nonsurgical treatment of experimental periodontitis was evaluated. A significant positive effect was reported with adjunctive laser therapy compared with nonirradiated groups in reducing the amount of alveolar bone loss. Multiple sessions of laser therapy were compared with a single session in Theodoro et al.[47] study and reported this method to be more effective (Table 2).

We identified three studies evaluating the adjunctive application of low-level laser in nonsurgical treatment of smokers.[41,48] All the studies concluded that laser therapy applications provided additional benefits in the periodontal treatment of smokers. However, Pamuk et al. did not observe any significant differences between the clinical parameters in LLLT and sham groups of either the smokers or nonsmokers. Overall, they recommended LLLT as an adjunctive treatment of periodontitis in smokers.[48]

Table 2. Characteristics of Included Studies Evaluation Adjunct Photobiomodulation in Nonsurgical Periodontal Treatments in Patients with Systemic Disease or Drug Consumption

Authors (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Garcia et al. (2010)[39]	GaAlAs (660 nm)	0.03 W for 133 sec per point, spot size of 0.07 cm^2 Power density of 0.428 W/cm^2, and energy of 4 J per point (57.14 J/cm^2 per point). The treated area received total energy of 24 J.	Nonsurgical therapy for periodontitis in rats treated with dexamethasone	Radiographic and histometric values	In all groups radiographic and histometric analysis showed less bone loss ($p < 0.05$) in animals treated with SRP+LLLT in all experimental periods.
Obradovic et al. (2011)[40]	GaAlAs (670 nm)	5 mW	150 Patients G1: 50 patients with CP and diabetes mellitus type 1 G2: 50 patients with CP and diabetes mellitus type 2 G3: 50 patients with CP and no diabetes mellitus	Gingival health evaluation was done using GI Löe-Silness	LLLT is efficient in gingival inflammation elimination and can be proposed as an adjuvant tool in basic periodontal therapy of diabetic patients.
Aykol et al. (2011)[41]	GaAlAs DL (808 nm)	0.25 W; spot size, 0.28 cm^2; and continuous wave output The energy density was 4 J/cm^2	Nonsurgical periodontal therapy of smoking and nonsmoking patients	PI, 21 SBI, 22 PD, and CAL GCF samples for matrixmetalloproteinase-1, tissue inhibitor matrix MMP-1, TGF-β1, and basic-fibroblast growth factor levels	There were clinically significant improvements in the laser-applied smokers CAL, PD, and SBI levels compared with smokers to whom a laser was not applied, between the baseline and all time points ($p < 0.001$). No marker level change showed significant differences between the groups ($p < 0.05$).
Obradovic et al. (2012)[42]	GaAlAs (670 nm)	5 mW, 14 min/day, with contact to gingiva	300 Patients G1: periodontitis and T1DM G2: periodontitis and T2DM G3: periodontitis (control group)	GI Smears from both sides of jaws were taken (morphometric analysis)	Parameters were significantly lower after therapy compared with values before therapy. After therapy on the side subjected to LLLT, there was no significantly difference between patients with DM and the control group. LLLT as an adjunct in periodontal therapy reduces gingival inflammation in patients with DM and periodontitis.
Eltas et al. (2012)[43]	Nd:YAG (NDL) laser 1064 nm	1 W 100 mJ, 10 Hz	Smoking and nonsmoking patients with moderate CP	PI, GI, pocket depth (PD), and CAL	Our results supported the idea that NDL applications provide additional benefits in the periodontal treatment of smokers.
Obradovic et al. (2013)[44]	GaAlAs (670 nm)	5 mW, 16 min, 2 J/cm^2 5 consecutive days	300 Patients with CP and diabetes needing tooth extraction (150 and diabetes mellitus type 1, 150 diabetes mellitus type 2) teeth indicated for extraction were assigned into 6 equal groups. In the groups 1 and 4, indicated teeth were extracted before treatment, and in the rest of the groups upon completion of the entire treatment	Histological	LLT showed expressed healing, as 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. It can be concluded that LLLT has shown efficacy in the treatment of periodontitis in diabetics. Because of more pronounced alterations of periodontium in diabetics the use of LLLT is of particular importance.

(*continued*)

Table 2. (Continued)

*Authors (year)*ref.	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Demirturk-Gocgun et al. (2017)[45]	GaAlAs DL 808 nm	0.25 W; continuous mode spot diameter, 6 mm; spot size, 0.28 cm^2 noncontact technique	Type 2 diabetic	BOP, PI, GI, probing depth (PD), and CAL	Use of a low-level laser as an adjunct to SRP showed a minor short-term additional benefit on gingival bleeding, but it did not significantly enhance other clinical parameters.
Swerts et al. 2017[46]	GaAlAs (660 nm)	0.03 W 133 sec/point, power density 0.428 W/cm^2 energy 4 J/point (57.14 J/cm^2/point) Spot size: 0.07 cm^2	Experimental periodontal disease (ligature on the first molar) in simvastatin-modified rats	The tissue oxidative damage by the expressions of tripeptide glutathione, malondialdehyde and carbonylated proteins, radiographic analysis	LLLT was effective as adjuvant treatment for SRP protecting against the occurrence of oxidative tissue damages as well as for reducing ABL.
Theodoro et al. (2016)[47]	(InGaAlP) laser 660 nm	0.035 W, CW 0.0283 cm^2 output fiber diameter, 60 sec in the center of the labial surface and for 60 sec in the center of the lingual surface (4.2 J total energy). The tooth received 74.2 J/cm^2 (2.1 J/point) energy density per point. Single or 4 sessions	Animal study periodontitis induced in rats subjected to 5-fluorouracil chemotherapy 5 Groups: No treatment (5FU) 5FU-SRP SRP-1LLLT 5FU-SRP-4LLLT	The ABL area in the furcation region was analyzed histometrically. TRAP, proliferating cell nuclear antigen, RANKL, OPG, and activated caspase-3 patterns were analyzed by immunolabeling. Prostaglandin E2 was quantified using an ELISA, and TNF-α and IL-6 were assessed using the multiplex method. The prevalence rates of Aa, PG, Pn, Pi, Fn were assessed using the PCR method	SRP-4LLLT group showed lower ABL compared with the 5FU group. Treatment with 5FU worsened EP, and multiple LLLT sessions adjuvant to SRP seemed to improve periodontitis in rats subjected to 5FU chemotherapy. There was reduction in some bacteria (Pn and Aa) with LLLT but overall the action of LLLT alone proved inefficient in reducing the numbers of bacteria.
Pamuk et al. (2017)[48]	940 nm	0.3 W, CW, 3.41 J/cm^2 delivery with a 1.76 cm^2 spot size Applied perpendicularly to the periodontal pocket for 20 sec at a constant distance of 15 mm	30 Patients with CP (15 smokers, 15 nonsmokers) and 30 healthy individuals matched for age, gender, and smoking status as controls. Split-mouth design Cp/SRP+LLLT Cp/SRP+sham Smoker Cp/SRP+sham Smoker Cp/SRP+LLLT control group SC: periodontally healthy smoking age-/gender-matched control group	Silness and Löe PI 24; Löe and Silness GI 25; probing depth; CAL; BOP GCF, TGF-β1, tPA, and PAI-1 levels	LLLT may be understood to play a role in the modulation of periodontal tissue tPA and PAI-1 GCF levels, particularly in smoking patients with CP, and may thus be recommended as an adjunct to NSPT. Although no significant differences were observed for clinical parameters or markers in GCF between the LLLT and sham groups of either the smokers or nonsmokers.
Bunjaku et al. (2017) [49]	Laser 660 nm	10 mW, 8 min/daily, in contact with gingiva for 5 consecutive days	96 Subjects suffering from T2DM 3 Groups: underweight, normal weight, and obese subjects. Before and after NSPT with additional LLLT	hsCRP and HbA1c, PI, GI, CAL, and general periodontal index Baseline, 3 months	NSPT together with LLLT is associated with improved clinical parameters and decreased levels of hsCRP and HbA1c in normal weight patients with diabetes mellitus type 2, but there was low impact on those levels for obese and underweight subjects.

ABL, alveolar bone loss; CAL, clinical attachment loss/level; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; EP, experimental periodontitis; Fn, Fusobacterium nucleatum; NDL, Nd:YAG laser; PAI-1, plasminogen activator inhibitor 1; Pg, Porphyromonas gingivalis; Pi, Prevotella intermedia; Pn, Prevotella nigrescens; SC, smoker control; tPA, tissue plasminogen activator; TRAP, tartrate-resistant acid phosphatase.

In the studies on diabetic patients LLLT was found to have an additional benefit in nonsurgical treatment of periodontitis and reducing gingival inflammation.[40,45] However, Demirturk-Gocgun et al. only reported a minor short-term additional benefit on gingival bleeding, but it did not significantly enhance other clinical parameters (PD, CAL).[45]

In Obradovic et al.'s report in 2012 on patients with diabetes type I and II although clinical parameters and gingival inflammation reduced after treatment in all groups, no significant difference between patients with diabetes mellitus (DM) and the control group was observed.[42]

Obradovic et al. also conducted a histological study in type I and II diabetic patients and found a pronounced healing and absence of inflammatory cells in periodontal tissues after adjunctive LLLT.[44]

In a study by Bunjaku et al. adjunctive LLLT in patients with type II diabetes was found to be associated with a reduction in clinical parameters (PI, GI<FAL) and HbA1c and hsCRP in the normal weight patients, but this was not seen in low weight or obese group of patients.[49]

In the systematic review recently published by Chambrone et al.,[50] two studies of Eltas and Kocak were included that evaluated SRP plus infrared lasers versus SRP alone for the nonsurgical treatment of CP in smokers and patients with diabetes mellitus. We excluded Kocak's study in our report since the average power used was 1.5 W in pulsed mode.[50] Overall, they concluded that the evidence is still lacking and the level of certainty is low. Based on the studies identified here although some benefits were reported for adjunctive LLLT; however, once again considerable variations in study designs and phototherapy parameters are observed. Further well-designed studies are recommended to reach evidence-based protocols to benefit from the application of this technology in treatment of patients with systemic diseases that affect periodontal conditions and treatment results.

Clinical Question 3

Can PBM improve outcomes of periodontal conditions and bone regeneration as an adjunct to periodontal regenerative surgeries?

Evidence search strategy. A literature search was conducted in the four databases mentioned earlier using the keywords for ''low-level laser therapy'' combined with keywords such as ''periodontal'' AND ''surgery'' OR ''periodontal'' AND ''disease'' OR ''periodontal treatment'' OR ''periodontal surgery'' OR ''guided tissue regeneration, periodontal.''

In vivo studies on human or animal subjects evaluating the effect of adjunctive low levels of light used only in periodontal bone regeneration surgeries were included. A total of 98 articles with potential relevance were selected after an evaluation of their titles. These articles were more carefully evaluated by studying their abstract and full text details. Only eight articles fulfilled the inclusion criteria, consisting of six RCT, one animal study, and a case report. Studies utilizing lasers as an adjunctive for debridement during flap and regenerative surgery or used for bacterial disinfection of the defects were not included (Table 3).[51–58]

Evidence-based conclusion and recommendation. In a meta-analysis and systemic review by Behdin et al. in 2015[59] on the effectiveness of laser application in periodontal surgical therapy the evidence was considered insufficient to support adjunctive laser application in reparative/regenerative surgical periodontal treatments. However, they have reported a few studies with positive effects for lasers used as adjunctive biostimulatory tools for periodontal regeneration. In this review we have only included articles evaluating this adjunctive therapeutic effect of phototherapy in regenerative periodontal surgery procedures.

From the six clinical trials included in our search the majority reported that adjunctive LLLT can significantly improve the periodontal treatment outcomes (clinical probing depth [PPD] and CAL).[52–54,56,60]

In all these studies low output power levels (<100 mJ) with energy densities of around 3–4 J/cm^2 were applied and repeated in the first postoperative week.

In a study by Abolfazli et al., reduction of intrabony defect depth was reported.[54] Dogan et al. compared guided tissue regeneration (GTR) surgery alone with GTR plus low-level laser therapy in the treatment of Grade II furcation defects and also reported more improvement in horizontal probing depth of the defects and alkaline phosphatase levels of GCF with adjunctive LLLT compared with GTR alone.[56]

Ozcelik et al. showed that adjunctive application of 4 J/cm^2 of diode laser used together with enamel matrix derivatives (EMD) in the treatment of intrabony defects can improve the effect of EMD.[51] The case report by Bhardwaj et al. also had successful results with 4 mm of CAL gain and 37% bone fill and minimal amount of recession after adjunctive low-level laser in treatment of a periodontal intrabony defect.[57]

A histological animal study by Tao et al. has also revealed positive effects of LED irradiation on inflammation, mucoperiosteal flap healing, and periodontal reattachment.[58] Significant promotion of osteogenesis in open flap debridement with LED light irradiation was also observed. However, in their report a limited enhancement of osteogenesis was observed when barrier membrane or xenograft was simultaneously used for treatment.

Based on the clinical studies included it seems that adjunctive PBM therapy may result in better outcomes of bone healing and periodontal parameters when used in periodontal regenerative therapies of intrabony defects. However, further long-term RCTs with similar laser application protocols will help better evaluate this effect on periodontal bone regeneration to provide evidence-based future guidelines.

Clinical Question 4

Can PBM improve wound healing of periodontal soft tissue as an adjunct to periodontal surgeries?

Evidence search strategy. The four databases were searched with the keywords used for low-level light therapy as previously mentioned and keywords of ''periodontal graft'' OR ''wound healing,'' ''gingival'' OR ''gingival graft'' OR'' gingivectomy'' to identify in vivo animal or human studies that assessed oral soft tissue wound healing after periodontal surgeries with adjunctive application of low levels of light. A total of 19 studies consisting of 16 clinical studies and 3 animal studies were included after thorough evaluation of full texts of relevant studies (Table 4).[61–79]

Evidence-based recommendation and conclusion. Three of the studies were performed on animal modules and all

Table 3. Characteristics of Included Studies: Effect of Photobiomodulation on Periodontal Conditions and Bone Regeneration as an Adjunct to Periodontal Regenerative Surgeries

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Ozcelik et al. (2008)[51]	DL 588 nm	4 J/cm^2	22 Patients Bilateral infra-bony (PD ≥6 mm) EMD+LLLT (T) EMD alone (C)	Immediate postoperative pain (VAS), wound healing, clinical PPDs, CALs	EMD alone or EMD+LLLT leads to probing depth reduction and attachment-level gain. In addition, EMD+LLLT had resulted in less GR ($p<0.05$), less swelling ($p<0.001$) and less VAS scores ($p<0.02$) compared with EMD alone. LLLT may improve the effects of EMD.
AboElsaad et al. (2009)[52]	Diode 830 nm	CW 40 mW Fluence 4 J/cm^2 Energy density of 16 J/cm^2 (on days 3, 5, and 7 postoperatively)	20 Patients with CP and bilateral infra-bony defects G1: bioactive glass G2: bioactive glass+laser (on days 3, 5, and 7 postoperatively)	Clinical PPDs, CALs and standardized periapical radiographs were recorded at baseline and at 3 and 6 months	At 3 months there was a statistically significant difference between the laser and non-laser sites in the parameters investigated. However, at 6 months, no difference was observed. Our results have confirmed the positive effect of soft laser in accelerating periodontal wound healing.
Dilsiz et al. (2010)[53]	Nd:YAG laser 1064 nm	1 W, 100 mJ, 10 Hz	42 Intrabony defects in 21 patients with CP G1: (C)-EDTA+EMP G2: (T)-EMP+LLLT	Probing depth (PD) and gain in CAL Baseline, after 6 and 12 months.	The control group showed a greater reduction in PD and gain in CAL compared with the test group. Both therapies led to improvements of the clinical parameters, and Nd:YAG laser root conditioning as used in this study compared with EDTA root conditioning did not improve the outcome of EMP use.
Abolfazli et al. (2012)[54]	DL 830 nm	40 mW CW 4 J/cm^2 total energy density of 16 J/cm^2 postsurgery and repeated on days 3, 5, and 7	14 Patients with moderate to severe CP were with bilateral intrabony defect (PPD of at least 5 mm and intrabony component of at least 3 mm) G1: OFD and autogenous bone G2: OFD and autogenous bone+LLLT	Clinical PPD, CAL, gingival margin level, alveolar crest level intrabony defect depth baseline and after 3 months	LLLT significantly reduce probing depth. Improved the CAL. Reduced the distance between deepest part of the defect to stent (reduced defect depth). No significant effect on gingival margin level and alveolar crest level. Adjunctive LLLT with autogenous bone can improve the periodontal treatment outcome.
Dogan et al. (2014)[60]	Nd:YAG laser 1064 nm	100 mW, 100 mJ, energy density 4 J/cm^2 300 sec per tooth, 60 sec for each application to a defect	GTR after the application of equine bone and membrane alone or combined with LLLT	PI, 17 SBI, 18 clinical gingival recession level (REC), clinical probing depth (PPD), and CAL	GTR plus LLLT resulted in statistically significant lower REC lower SBI score, more reduction of PPD and CAL gain compared with GTR alone at 6th month control.

(*continued*)

Table 3. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Doğan et al. (2016)[56]	Nd:YAG laser 1064 nm	100 mW energy density 3 J/cm^2. 600 μm therapeutic fibers. 1 cm to the target area. Exposure time 300 sec per each tooth and applied at the time of surgery and on days 1, 2, 3, 5, and 7 postoperatively	33 Furcation grade II defects in CP patients G1: GTR G2: GTR+LLLT	PPD, CAL, HPD and ALP and osteocalcin levels in the GCF were recorded at baseline and at 3rd and 6th months postoperatively	Both treatments led to significantly favorable clinical improvements in furcation periodontal defects. At the 6th month, PPD, CAL, HPD, and ALP values showed significantly more improvement in laser group. LLLT plus GTR may be more effective treatment modality compared with GTR alone.
Bhardwaj et al. (2016)[57]	Diode 810 nm	100 mW CW 4 J/cm^2 5 min to the inner margins of flap in contact mode and the defect was irradiated with LLLT in a noncontact mode for 10 min repeated for 5 days on the outer buccal and lingual flap surfaces	A patient with moderate CP with chronic localized periodontal abscess a periodontal infrabony defect. LLLT+GTR	CAL PPD GR Bone fill	A CAL gain of 4 mm and 37% bone fill was noted radiographically at the end of 12 months combined approach of LLLT and demineralized bone matrix of bovine origin showed a positive outcome with CAL gain, reduction in periodontal probing depth (PPD), minimal recession clinically and linear bone gain and bone fill radiographically was observed.
Tao et al. (2016)[58]	LED 660 $\pm$ 25 nm	Each group received daily 0 or 10 J/cm^2 LED light irradiation. Customized LED devices (1 $\times$ 2 mm^2 in area) that emit 3.5 mW/cm^2 (maximum output 40 mW, continuous mode) visible red light aligned 2 $\times$ 2 at 1 mm intervals mesiodistally and 5 mm intervals buccolingually on a plate connected to an external controller. The plate was placed over the occlusal surface of maxillary molars of each rat	48 Sprague-Dawley rats, large-sized periodontal intrabony defects were created bilaterally on the mesial aspect of the maxillary second molars. 4 Groups G1: open flap debridement alone (OD) G2: barrier membrane alone (MB) G3: xenograft alone (BG) G4: xenograft plus barrier membrane (MG)	Gross observation of wound dehiscence and healing Micro-computed tomography imaging for osteogenesis, histological assessments for inflammatory cell infiltration and periodontal reattachment (1 and 4 week evaluation)	Extent of wound dehiscence was reduced, wound closure was accelerated, epithelial downgrowth was prevented, inflammation was reduced, and periodontal reattachment was promoted in all treatment strategies. Significant reduction of inflammation with LED light irradiation was noted at 1 week in the groups BG and MG ($p < 0.05$). Osteogenesis was significantly promoted only in the group OD at both time points ($p < 0.05$). Our study showed that 660 nm LED light accelerates mucoperiosteal flap healing and periodontal reattachment. However, the enhancement of osteogenesis appeared to be limited while simultaneously treating with a barrier membrane or xenograft.

ALP, alkaline phosphatase; BG, bone graft; EDTA, ethylenediaminetetraacetic acid; EMD, enamel matrix derivative; EMP, enamel matrix protein; GTR, guided tissue regeneration; HPD, horizontal probing depth; LED, light-emitting diode; MB, membrane; MG, membrane-graft; OD, open flap debridement; OFD, open flap debridement; REC, recession.

Table 4. Characteristics of Included Studies: Effect of Photobiomodulation on Wound Healing of Periodontal Soft Tissue as an Adjunct to Periodontal Surgeries

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Amorim et al. (2006)[61]	Diode 685 nm	50 mW, CW beam diameter of 2 μm The irradiation was made in contact mode, scanning an area of about 1 cm^2 during 80 sec Energy density 4 J/cm^2 Irradiated immediately after surgery, and at 24 h, and 3 and 7 days postsurgery	20 Patients with periodontal disease gingivectomy to bilateral maxillary and mandibular premolar teeth Adjunctive LLLT in one side	Probing depth (PD) measurement of attached gingiva Gingival wound healing Healing was evaluated, clinically and biometrically, immediately postsurgery and on days 3, 7, 14, 21, 28, and 35	Biometrical evaluation indicated a significant improvement in healing for the LG at 21 and 28 days. Clinical evaluation showed better repair for the LG, mainly after the 3rd day. LLLT was an effective adjunctive treatment that appeared to promote healing after gingivectomy.
Ozcelik et al. (2008)[62]	Diode 588 nm	120 mW, and the irradiance for 5 min was 4.0 J/cm^2, delivered by applying in the continuous wave mode for 5 min for 7 days	20 Patients with bilateral inflammatory gingival hyperplasias	Wound healing [disclosed by a solution (Mira-2-tones) to visualize the areas in which the epithelium is absent]. Comparison of the surface areas on the LLLT-applied sites and controls were made with an image-analyzing software	Statistically significant differences between the stained surface areas of the LLLT applied and the control sites immediately after the surgery, LLLT-applied sites had significantly lower stained areas compared with the controls on the postoperative 3rd, 7th, and 15th day.
Almeida et al. (2009)[63]	Diode 780 and 660 nm	40 mW, CW 10 J/cm^2, and individually applied (20 sec/site), initially at 1 mm from the graft margins and with a 1-mm distance between sites, contouring the entire extent of the graft. Immediate postoperative and after 48 h. (780 nm) to achieve analgesia, and also at (660 nm) to accelerate the healing.	10 Patients needing bilateral FGG in the mandibular arch	Pain (VAS) Healing of FGG	Low-intensity laser therapy did not improve the healing of gingival grafts and did not influence analgesia.
Vieira et al. (2010)[64]	LED 650 nm	5 W 8 J/cm^2 0, 48 and 72 h after surgery	10 Patients with insufficient keratinized gingiva Needing FGG	Intensity of pain Wound healing of all patients was evaluated by visual inspection (7, 14, and 21 days after surgery).	Significant differences in pain level were found between the control and LGs on days 1 and 2 after surgery ($p < 0.05$). The wound-healing analysis showed that 80% of the irradiated patients and 40% of patients in the control group were healed 14 days after surgery. Laser improved healing and pain (limited sample size).
Ozturan et al. (2011)[65]	DL 588 nm	120 mW, CW 4.0 J/cm^2 for 5 min (before and immediately after surgery), and for 5 min daily 7 days postoperatively	10 Patients with symmetrical total of 74 Miller I and II GR G1: CAF+LILT G2: CAF	GRD, GRW and WKT and CAL measurements after 1 year	The test group presented greater complete root coverage
Firat et al. (2013)[66]	940 nm	0.1 W—CW spot size 0.09 cm^2. 400 lm optical fiber. The optical fiber was positioned at a distance of 5 mm proximal to the wound, and the irradiation time was 9 sec 10 J/cm^2 2 h after surgery, and was repeated on the 2nd, 4th, and 6th days postsurgery (4 sessions)	42 Male Wistar rats Experimental diabetes (using streptozotocin) Full thickness wound in the mucoperiosteum of the hard palates	Histological evaluation of 7, 14, 21 day specimens (inflammation, fibroblast proliferation, keratohyalin granules, and vascularization) Blood samples were collected; total antioxidant capacity was measured using Erel's method	Histopathological findings revealed reduced numbers of inflammatory cells, and increased mitotic activity of fibroblasts, collagen synthesis, and vascularization in the irradiated group. The total oxidative status was significantly decreased in the laser-treated group on the 21st day. LLLT elicits a positive healing effect and can modulate the total oxidant status

(*continued*)

Table 4. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Moslemi et al. (2014)[67]	660 nm	Power: 200 mW for 32 sec immediately postsurgery and on days 1, 2, 4, and 7 after	12 Patients Split-mouth palatal grafts	Donor site epithelialization and healing Number of palliative pills and bleeding	LG showed better epithelialization ($p=0.02$) and healing ($p=0.01$) on day 14 after surgery and showed better epithelialization on day 21 ($p=0.05$). No statistical differences were observed between LG and control group in terms of bleeding and medication.
Dias et al. (2015)[68]	660 nm	30 mW was used for 20 sec, 15 J/cm^2 (3 J/cm^2 per point and an application time of 4 sec per point). Punctual contact immediate postoperative followed by 7 sessions every other day	32 Patients with Class I or II Miller GR G1: CTG+LLLT on donor site G2: CTG	Donor site remaining wound area Scar and colorimetry tissue The presence or absence of scar or keloid TT Postoperative discomfort (D) (baseline and 7, 14, 45, 60, and 90 days after surgery)	The test group presented statistically significant smaller wounds on days 14 and 45. None of the patients presented a scar at the operated area, and colorimetry analysis revealed that there was no statistically significant difference between groups ($p>0.05$). Patients reported mild to moderate discomfort, with low consumption of analgesic pills. We concluded that LLLT irradiation can accelerate wound healing on palatine mucosa after CTG.
Fekrazad et al. (2015)[69]	Red (630 nm), green (532 nm), blue (425 nm) lasers	2 J/cm^2 and a treatment schedule of 3 times/week for 10 days	Oral wound (10 mm × 2 mm) was created aseptically with a scalpel on hard palate of the diabetic Wistar rats	Area of wounds Histological evaluation of full-thickness sample of wound area after 10 days	Significant difference in the mean slope values of wound healing between treatment and control groups and also, between red laser and 2 other lasers, but no significant difference between blue laser and green laser.
Fernandes-Dias et al. (2015)[70]	Diode 660 nm	30 mW was used for 20 sec and the total applied energy density (Fluence) was 15 J/cm^2 (3 J/cm^2 per point and an application time of 4 sec per point). Punctual contact immediate postoperative followed by 7 sessions every other day	40 Patients presenting 40 Miller Class I and II GRs G1: CTG + L G2: CTG	Percentage of root coverage Dentine sensitivity	Test group showed more complete and higher percentage of root coverage than the control group Dentine sensitivity decreased significantly after 6 months in both groups.
Wang et al. (2015)[71]	LED 660 ± 25	3.5 mW/cm^2 Energy density of 5, 10, or 20 J/cm^2 (6, 12, or 24 min of irradiation) Daily 0, 10 (LD), or 20 (HD) J/cm^2 LED	72 Male Sprague-Dawley rats Harvested rat gingival fibroblasts Bilateral 5 × 1.5 mm^2 palatal wounds in 3 groups G1: LD group daily 10 J/cm^2 LED G2: HD group, daily 20 J/cm^2 LED	Cellular viability (Proliferation) Cytotoxicity wound closure (scratch) Healing pattern was assessed by histology, histochemistry for collagen deposition, and immunohistochemistry for TNF-α infiltration mRNA levels of HO-1 TNF-α, the receptor for advanced glycation end products, vascular endothelial growth factor, periostin, type I collagen, and fibronectin	Cellular viability and wound closure were significantly promoted and cytotoxicity was significantly inhibited <5 J/cm^2 LED light irradiation in vitro. The wound closure, re-epithelialization, and collagen deposition were accelerated, and sequestrum formation, and inflammatory cell and TNF-α infiltration were significantly reduced in the LD group. HO-1 and TNF-α were significantly upregulated in the HD group, and most of the repair-associated genes were significantly upregulated in both the LD and HD groups on day 7. Persistent RAGE upregulation was noted in both the LD and HD groups until day 14.
Singh et al. 2015[72]	810 nm	0.3 W CW 4 J/cm^2 10 sec (during 1 week)	10 Subjects with bilateral multiple adjacent maxillary facial GR defects (Miller I and II) were included in this study (20 in test, 20 in control group) T: SCAF + L C: SCAF	GRD, GRW, CAL, and WKT	Significant differences were observed between test and control sites in the change in GRD, GRW, CAL, and WKT measurements and significantly greater complete root coverage after 6 months Low-level laser technique application may enhance the predictability of SCAF procedure

(*continued*)

Table 4. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Ozcelik et al. (2016)[73]	Diode 810 nm	0.1 W CW contact 5 min Total dose of 4 J/cm^2 (at palatal wound area)	52 Patients with isolated recessions were treated. DL was used to de-epithelialize the outer part of the FGG and photobiostimulate the palatal wound area The CTG resulted from the de-epithelialization of a FGG was used G1 de-epithelialization with blade G2 with DL DL was used to de-epithelialize the outer part of the FGG and photobiostimulate the palatal wound area	OHQoL and VAS-discomfort. Root coverage outcomes	Statistically significant differences were found for OHQoL ($p=0.0001$) and VAS ($p=0.0001$) at the 7th day postoperatively favoring LG. Root coverage results did not show a statistically significant difference.
Chawla et al. (2016)[74]	Diode 810 nm	1 W CW DL at 1 mm distance for 5 min	12 Patients with bilateral melanin hyperpigmentation were treated with surgical stripping using a blade	Wound healing was assessed using erythrosine solution on the 3rd, 7th, and 15th day	LLLT promotes wound healing after depigmentation procedure until the 3rd day. On the 7th and 15th day, the difference in healing was not statistically significant.
da Silva Neves et al. (2016)[75]	Diode 660 nm	30 mW total area of irradiation of 0.06 cm^2. G1: 60 J/cm^2 and a time of 60 sec (2 points, 30 J/cm^2 per point, application time of 30 sec per point) and G2: 30 J/cm^2 and a time of 30 sec (2 points, 15 J/cm^2 per point, application time of 15 sec per point) immediate postoperative and every other (7 sessions)	51 Patients presenting buccal GR were randomized into one of the following groups: group 1: CTG procedure for root coverage and PBM 60 J/cm^2 group 2: CTG and PBM application using a 30 J/cm^2 dose group 3: CTG and sham application	Donor site pain (VAS), wound remaining area, scar and TC, TT, and postoperative discomfort (D), evaluated at baseline and 7, 14, 45, 60, and 90 days	There was no statistically significant difference of pain, TT, TC scores among the group. The 60 J/cm^2 group showed faster wound healing 7 days after removing the CTG.
Heidari et al. 2017[76]	Diode 660 nm	200 mW, continuous mode, time of irradiation: 32 sec energy density: 4 J/cm^2, spot size: 0.5 cm. Immediately after FGG surgery, and 1, 2, 4, and 7 days later.	12 Patients (split-mouth) test side, donor and recipient sites received DL control side received the same sequence of irradiation with the laser-off	Wound epithelialization of donor site, clinical wound healing, VAS pain score of donor and recipient sites on 14 and 21 days after surgery	At 14 and 21 days after surgery, the number of donor sites with complete epithelialization was greater in LG compared with the placebo. Clinical healing of the recipient and donor sites, the test and control groups did not show any significant difference during the 45-day period, except on days 1 (for recipient site) and 14 (for donor site), when the test group showed better results (p values 0.01 and 0.03, respectively). PBM after FGG procedure with the parameters used in this study could accelerate the rate of epithelialization at the donor site. Did not reduce postoperative pain.

(*continued*)

Table 4. (Continued)

Author (year)ref.	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Santamaria et al. (2017)[77]	Diode 660 nm	30 mW. The power density was 15 J/cm^2 (3 J/cm^2 per point), delivered by application in continuous wave mode for 4 sec per point (5 points). The tip of the laser device was placed, with slight contact, on the gingival tissue. Immediately after surgery and every other day for 14 days (total of 8 applications)	40 Patients presenting Miller Class I and II G1: CTG+LLLT G2: CTG	Mean percentage of root coverage Number of cases with complete root coverage	LLLT showed no additional benefit in the long term when associated with a CTG in the treatment of Miller Class I and II GRs.
Ustaoglu et al. (2017)[78]	Diode 940 nm	3 W 1.07 W/cm^2 2.8 cm^2 Continuous wave 1 mm Stable 8.6 J/cm^2 8 sec 4 times (48 h interval) 34.4 J/cm^2 2.8 cm	40 Patients requiring FGG	WHI, tissue consistency, color match, and H_2O_2 bubbling test for the evaluation of complete wound epithelialization were recorded on the 3rd, 7th, 14th, and 21st days. The pain-burning level, number of analgesics, and bleeding were recorded for 7 days. Donor area soft TT was measured at baseline and on the 1st month.	Prevalence of complete wound epithelialization was higher in the LLLT group (14th day) Bleeding was lower in the test group (first 2 days) Higher WHI scores were observed in the test group. Color match scores were higher in the test group first 3 visits. Less TT changes LLLT enhances FGG donor site wound healing and preserves TT at palatal donor sites.
Kohale et al. (2018)[79]	Diode 940 nm	100 mW CW 100 mW/cm^2 Aperture diameter 1 cm 1st, 3rd, and 7th day postoperatively	40 Patients with gingival enlargement in the maxillary and mandibular anterior region (bilaterally symmetrical Gingivectomy+LL in one side	Epithelialization disclosed by a solution (Alpha Plac®) Pain (NRS)	Significantly lower than the NRS scores in the control group LLLT-applied sites had significantly lower stained areas signifying improved wound healing compared with the controls on the postoperative 7th and 30th day.

CAF, coronally advanced flap; CTG, connective tissue graft; HD, high-dose; HO-1, heme oxygenase-1; FGG, free gingival graft; GRD, gingival recession depth; GRW, gingival recession width; LD, low-dose; LILT, low intensity laser therapy; LL, low level; NRS, Numeric Rating Scale; OHQoL, oral health-related quality of life; PBM, photobiomodulation; RAGE, receptor for advanced glycation end products; SCAF, semilunar coronally advanced flap; TC, tissue colorimetry; TT, tissue thickness; WHI, wound-healing index; WKT, width of keratinized tissue.

confirm the positive effect of phototherapy on gingival wound healing. In the study by Wang et al. after a daily 10 J/cm^2 LED irradiation better wound closure, re-epithelialization, and collagen were observed, and the amount of sequestrum formation, infiltration of inflammatory cell, and TNF-α decrease significantly.[71]

Fekrazad et al. evaluated three different laser wavelengths on palatal wound healing in a rat model. It was interestingly observed that only the red laser resulted in better wound-healing results when wound area was measured clinically and evaluated histologically.[69] In another histological study on palatal wound healing with and without laser therapy in rats by Firat et al., reduction of the number of inflammatory cells, increase in collagen synthesis, vascularization, and fibroblast cell mitotic activity were reported in the irradiated areas. The laser-treated group also revealed a significant reduction of total oxidative status on the 21st day.[66]

From the total of 16 clinical studies evaluating wound healing, 4 studies evaluated healing in gingivectomy procedures and 10 studies were conducted on patients receiving gingival graft surgeries. In all the gingivectomy studies improved wound healing was reported in the laser-treated sites compared with the nonirradiated controls (Table 4). From the studies conducted on grafts most of the studies reported better wound healing and epithelialization of the donor site, only a study by Almeida et al. evaluated free gingival graft healing and reported no improved healing of gingival grafts and also concluded that LLLT did not influence analgesia in this surgery.[63]

In most of these clinical studies a total dose of around 30 J/cm^2 was applied and reported to be effective in wound healing (by measuring remaining wound area or epithelialization). However, in da Silva Neves study higher energy density of 60 J/cm^2 resulted in better wound healing in the early stages of healing (7th day postoperatively) compared with the 30 J/cm^2 and control.

A few studies have compared root coverage results with the adjunctive application of LLLT with contradictory results.[65,70,72,73,77] Although most studies have reported higher percentage of root coverage with adjunctive PBM in conjunction with connective tissue graft (CTG) in the study by Santamaria LLLT, no additional benefit in terms of percentage of root coverage using CTG was observed.

In a recent systematic review and meta-analysis, the effect of laser therapy as an adjunctive procedure in the treatment of gingival recession with flap graft techniques was investigated. In some of these studies lasers were used for root surface conditioning. This meta-analysis showed an additional clinical advantage in terms of width of keratinized tissue and PD and CAL for the laser-treated groups. However, laser had no additional benefit in terms of amount of root coverage and esthetics results in gingival recession treatments. It must be noted that in the seven studies evaluated in this meta-analysis, study design and laser treatment protocols had great variation. They finally recommended long-term studies for better evaluation of the effect.[80]

Regarding our question on PBM and periodontal soft tissue wound healing it may be concluded that adjunctive LLLT can enhance donor site wound healing as reported in clinical trials and animal studies. Future randomized clinical trials to determine the efficacy of laser as adjunctive phototherapy in recipient site healing and root coverage results and management of postoperative complications and pain level after soft tissue periodontal surgeries such as grafts may be valuable to fully evaluate the potential of PBM in periodontal plastic surgeries.

Clinical Question 5

Does PBM reduce inflammation in periodontitis?

Evidence search strategy. The databases of PubMed, Google scholar, Scopus, and Cochrane were searched using the keywords for LLLT as mentioned and keywords of ''periodontal inflammation'' OR ''inflammation'' OR'' gingival inflammation'' OR ''gingivitis'' OR ''anti-inflammatory.''

In vivo human or animal studies focusing on the effect of low-level light therapy on gingival inflammation by measuring gingival inflammatory indices or markers were included. After title screening 103 studies remained out of which 14 studies met the inclusion criteria after evaluating their full text as previously mentioned we only included studies with low power settings (1 W or less). The included studies characteristics can be found in Table 5.[15,18,20,23,26,27,30,31,81–86]

Evidence-based recommendations and conclusion. Reduction of gingival inflammation is clearly observed after effective nonsurgical and surgical periodontal treatments; however, it is proposed that adjunctive application of low levels of light can also be beneficial in this process. Two animal studies have been conducted on rats, which have reported positive effects for gingival inflammation reduction after low-level laser therapy.[81,86] In one study, Safavi et al. observed that low-level He–Ne laser irradiation leads to a decrease in the inflammation, wound healing was also accelerated, and changes in expression of inflammatory cytokines genes were also reported.

It was observed that expression of IL-1β and interferon (IFN)-γ was significantly inhibited laser-treated group, whereas the gene expression of platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β increased with significant difference. However, in their report no significant difference in gene expression of TNF-α and basic fibroblast growth factor was observed. In Uslu's study myeloperoxidase levels evaluated by western blot were significantly lower in the laser group.

The clinical studies included have evaluated periodontal inflammation changes by studying the effect of PBM on clinical periodontal parameters and also some of the inflammatory markers found in the GCF such as metalloproteinase (MMP)-8, IL-1β, TGF-β1, and COX-2.[26,27,30,87] Positive results were reported for adjunctive PBM therapy in all the studies except for a study by Giannopoulou et al.[82] that reported no additional benefit for low-level diode laser therapy (810 nm) and also photodynamic therapy using 660 nm laser in terms of changes in expression of some of the 13 cytokines and 9 acute-phase proteins in the GCF. Contrary to most of the other reports an increase in GCF MMP-9 levels, after LLLT was reported by Ismaili et al. In this study decreased levels of IL-1 in GCF decreased and they concluded that further study is necessary to better understand whether elevated levels of MMP-9 in GCF might be even beneficial for the repair process in periodontal disease.[31] Inflammatory changes in gingival tissue were also

Table 5. Characteristics of Included Studies: Effect of Photobiomodulation on Reduction of Inflammation in Periodontitis

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Qadri et al. (2005)[15]	LED 653 nm Diode 820 nm	LED 10 mW (50 mW/cm^2) CW 0.9 J, 90 sec Diode 70 mW (350 mW/cm^2) 25 sec CW 1.75 J	17 Patients with moderate periodontitis 2 weeks after SRP Control side: Very low-power LED as placebo Test side: buccal papillae with 635 nm 6 mm more apically with 820 nm on buccal and lingual	Clinical parameters— IL-1β MMP-8 Elastase activity in GCF	PPD, plaque and gingival indices were reduced more on the laser side than on the placebo one ($p<0.01$). The decrease in GCF volume was also greater on the laser side, 0, 12 microl, than on the placebo side, 0.05 microl ($p=0.01$). The total amount of MMP-8 increased on the placebo side but was slightly lower on the laser side ($p=0.052$). Elastase activity, IL-1β concentration, and the microbiological analyses showed no significant differences. Low-level lasers reduced periodontal gingival inflammation.
Pejcic et al. (2007)[20]	DL 670 nm	200 mW/cm^2, and a power output of 4 to 15 mW. 2 min from both the vestibular and oral sides. Spot width of 3 mm, power 100 laser tip 2 mm from the surface. Every day after SRP for 5 days	30 CP patients with marked clinical symptoms of gingival inflammation 2 groups SRP SRP+LLLT	Histological examination of gingiva treated with low-level laser in periodontal therapy	Complete regeneration of gingival tissue with few inflammatory cells and marked collagen tissue homogenization Reduction of tissue inflammation correlates positively with histopathological changes of the gingival tissue
Qadri et al. (2007)[18]	HeNe 632.8 nm, InGaAlP 650 nm, laser	HeNe: 3 mW InGaAlP laser: 180 sec per point, energy 0.54 J) was then performed once a week for 6 weeks	20 Patients with moderate periodontitis (split-mouth laser irradiation of upper jaws)	Pocket depth, GI, PI, GCF volume, matrix MMP-8, IL-8, and subgingival microflora	More pronounced decrease of clinical inflammation was observed after HeNe treatment. MMP-8 levels were considerably reduced on the HeNe side, no difference for IL-8 or microflora. Coherence length appears to be an important factor in laser phototherapy.
Safavi et al. (2008)[81]	He–Ne laser 632.8 nm	3 h after incision, the rats were sedated again and the samples of the case groups (A24 and A48) were exposed to continuous noncontact laser irradiation at the dose of 7.5 J/cm^2 for 300 sec, with the power output of 17 mW. The beam diameter was 0.96 mm	20 Male Wistar rats were randomly assigned into 4 groups (A24, A48, B24, and B48) in which A24 and A48 were cases, and B24 and B48 were controls. Incision was made on gingiva and mucosa of the labial surface of the rats' mandibular incisors	Rats were killed 30 min after the last irradiation of case and control groups, and then excisional biopsy was performed. Gene expression of the cytokines was measured using RT-PCR technique. IL-1β, TNF-α, IFN-γ, TGF-β, bFGF, and PDGF	Low-level He–Ne laser irradiation decreases the amount of inflammation and accelerates the wound-healing process by changing the expression of genes responsible for the production of inflammatory cytokines gene expression of IL-1β and IFN-γ was significantly inhibited in the test groups ($p<0.05$), whereas the gene expression of PDGF and TGF-β were significantly increased ($p<0.05$). The case and control groups did not have a significant difference in the gene expression of TNF-α and bFGF ($p>0.05$).
Pejcic et al. (2010)[23]	DL 670 nm	Power density of 150 mW/cm^2 spot diameter was 3 mm with 2-min field exposure per session. Laser radiation was performed daily, within the period of 10 days, power density was set to 150 mW/cm^2, energy density to 18 J/cm^2, and later on, until the end of the treatment a presumed optimal dose of 100 mW/cm^2 was used	CP (mild) G1: conservative treatment+LLLT G2: conservative treatment		A general conclusion can be drawn that low-level laser irradiation can be used as a successful physical adjuvant method of treatment, which, together with traditional periodontal therapy, leads to better and longer-lasting therapeutic results.

(*continued*)

Table 5. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Pejcic et al. (2011)[25]	Diode 670 nm	150 mW/cm^2, an energy density of 4 J/cm^2, and a power output of 10 mW. Laser irradiation was conducted every day after conservative instrumental treatment of the periodontal pockets for 10 days. The tip was set to continuous mode and applied and kept in light contact for 15 sec with the gingival tissues around every tooth (facial and lingual) for ∼4 min per quadrant	34 CP patients G1: SRP+LLLT G2: SRP	PPD, BOP, CAL, as well as supragingival plaque measurements (PL) and GCF measurements Histological evaluation in gingival 0, 3, and 6 months	6 Months after the therapy, the average PPD, CAL, and CGF reduction in the experimental group with LLLT was significantly greater. Histological findings in gingivae after the laser therapy indicated completely regenerated gingival tissue with few inflammatory cells as well as marked collagen tissue homogenization successful in reducing gingival tissue inflammation.
Eltas et al. (2012)[26]	Nd:YAG 1064 nm	1.0 W 100 mJ, 10 Hz). T Optic fiber (diameter 200 μm moved from apical to coronal in a sweeping motion 120 sec	40 Teeth from 20 patients with CP. G1 SRP + L G2 SRP	PI, GI, PPD, and CAL GCF samples were analyzed for IL-1β and MMP-8. baseline and post-therapy (3 and 9 months after treatment)	There was postoperative improvement of all clinical parameters in both groups, but test side GI, PPD, and CAL recovery was higher than that of the control side ($p < 0.05$). Although levels of IL-1β and MMP-8 in GCF after treatment were lower in the test side than the control side, there was not a statistically significant difference. Adjunctive laser treatment of periodontal pockets was more effective than SRP alone in reducing PPD, CAL, GI, and GCF values.
Giannopoulou et al. (2012)[82]	810 nm 660 nm	Subgingival irradiation 60 sec 810 nm 1 W PDT: 100 mg/mL phenothiazine chloride sterile 660 nm; output power of laser diode of 100 mW, corresponding to an energy density of 3 J/qcm)	G1 SRP G2 SRP+DL G3 SRP+PDT	Cytokines and 9 acute-phase proteins in the GCF. GCF was collected before treatment, after 14 days, and at 2 and 6 months	All 3 treatment modalities resulted in changes in the expression of some of the 13 cytokines and 9 acute-phase proteins in the GCF. DSL and PDT achieved changes in cytokine and acute-phase protein levels comparable with traditional SRP therapy, avoiding any mechanical surface interaction and damage. However, within the limits of the study, no additional benefit could be found with DSL and PDT compared with traditional SRP.
Igic et al. (2012)[83]	635 nm	25 mW, CW power density of 200 mW/cm^2 Exposure time of 120 sec Every day for 5 days. Light contact with the gingival tissues around every tooth (facial and lingual). The laser beam was directed at an angle of 90° to the gingival surface with the laser tip 2 mm from the surface.	130 Children with chronic catarrhal gingivitis G1 basic treatment G2 basic treatment+LLLT G3 healthy gingiva as controls	Inflammation of the gingiva was monitored by cytomorphometric evaluation.	Cytomorphometric analysis showed that after basic treatment the nuclei of the stratified squamous epithelial cells of the gingiva were reduced in size, although not to the size found in healthy gingiva. However, after adjuvant LLLT, the size of the nuclei of the stratified squamous epithelial cells in the gingiva matched the size of the nuclei in the cells in healthy gingiva.

(*continued*)

Table 5. (Continued)

Author (year)ref.	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Pesevska et al. (2012)[84]	630–670 nm	25 mW spot size 0.2 cm^2 Treatment time per papilla 15 sec Energy 0.375 J Energy density (J/cm^2) 1.875 Light contact to the gingival tissue corresponding to the treated pockets in apical-coronal direction in all interdental spaces for 15 sec per site, scanning both lingual and buccal papilla side. The laser irradiation was in continuous mode on both facial and lingual surfaces. Laser treatment was performed on all oral sites at each visit for a total of 16 min per visit (4 min per quad)	60 Patients previously diagnosed with moderate or severe chronic (adult) periodontal disease ($n=20$/group; groups A, B, C, and D. A Healthy control B SRP C SRP + L 5 days D SRP + L 10 days	Papilla biopsies were obtained from subjects and evaluated by ELISA for levels of TNF-α.	The values in the control group were 5.2 ± 3.21 pg/mg and baseline values for the examined groups were 46.01 ± 16.69. Significantly decreased level of TNF-α for groups C and D was found after treatment, whereas group B demonstrated reduction of TNF-α of 31.34%. The results of this study show suppression of TNF-α in gingival tissue after low-level laser treatment as adjunct to SRP. Data may suggest beneficial anti-inflammatory effects of the laser treatment when used as adjunctive periodontal treatment.
Saafan et al. (2013)[30]	Diode 810 nm	200 mW (at the end of the intraoral tip in contact mode) 16 J, 80 sec per defect. The spot size was 4 mm circle; so, the power density was 0.2 W/cm^2, energy density was 16 J/cm^2. 8 sessions every other day	32 Periodontal defects in 8 patients with untreated AgP Split-mouth design	Clinical evaluation included periodontal pocket depth (PPD), CAL, PI, MGI, and GR, was taken at baseline and at 3 months. (TGF-β1in GCF at baseline and at 1, 2, 3, and 4 weeks after SRP)	Showed a significant decrease of PPD and CAL in favor of LG. PI, MGI, and GR showed no significant difference between both groups. TGF-β1 mean percentage showed a significant steady decrease in the LG
Calderìn et al. (2013)[27]	670 nm	200 mW. CW 60 sec/tooth Phototherapy repeated 5 times in 2 weeks (days 1, 2, 4, 7, and 11)	27 Moderate-advanced CP patients SRP SRP+PT SRP+repeated PT treatment	FMPS, full-FMBS, PPD, and CAL were recorded before SRP. GCF samples were used to determine the levels of IL-1β, TNF-α, RANKL, and OPG in GCF.	PT used in a single or repeated doses does not produce a significant reduction in the clinical parameters. Levels of IL-1β in GCF were significantly reduced in SRP+PT and SRP+rPT groups compared with the SRP group. SRP+rPT group showed a significant reduction of proinflammatory cytokine TNF-α and RANKL/OPG ratio at 4 weeks post-treatment compared with the SRP+PT and SRP groups. SRP+PT group also showed a significant reduction in TNF-α and RANKL/OPG ratio at 8 weeks post-treatment compared with the SRP group. PT exerts a biostimulative effect on the periodontal tissue. Multiple sessions of PT showed a faster and greater tendency to reduce proinflammatory mediators and RANKL/OPG ratio.

(*continued*)

Table 5. (Continued)

Author (year)[ref.]	*Wavelength*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Ismaili et al. (2014)[31]	635 nm	100 mW/cm^2, by applying the laser beam to diseased teeth for 9 days	36 CP patients T: SRP+LL C: SRP	Clinical examination was performed at baseline and 10 days after the treatment. GCF samples were collected from the same periodontal site before and after therapy. The levels of IL-1 and matrix MMP-9 in GCF were measured by ELISA.	LLLT decreased clinical parameters of CP. The levels of IL-1α and IL-1β in GCF were decreased ($p < 0.05$), but the level of MMP-9 was increased ($p < 0.01$). After LLLT, the level of IL-1a correlated positively with MMP-9 ($p < 0.05$) and the MMP-9 levels correlated negatively with PI ($p < 0.05$) and PBI ($p < 0.01$). Conclusion: LLLT attenuated periodontal inflammation in CP patients, as judged by clinical parameters and decreased levels of IL-1 in GCF. It remains to be studied whether elevated levels of MMP-9 in GCF might be beneficial for reparation processes.
Pesevska et al. (2017)[85]	630–670 nm	25 mW 0.375 J, 1.875 J/cm^2 15 sec per site Beam spot size 0.2 cm^2	60 Patients previously diagnosed with moderate or severe CP (divided into 3 groups) 20 healthy controls A: control. B: SRP C: SRP+LLLT 5 sessions D: SRP+LLLT 10 sessions	Baseline and post-treatment excisional papilla biopsies RT-PCR for expression of COX-2	Significantly decreased level of COX-2 expression for groups C and D was found after treatment, whereas lowest average expression was found in the group that had the 10 laser treatments.
Uslu et al. (2018)[86]	810 nm	1 W, CW 20 Hz, energy of 10 J/cm^2 spot size of 0.04 cm in diameter and an area of 0.00126 cm^2 power of T-on_ms: 500, T-off_ms: 500, 20s per teeth	Experimental periodontitis by ligature in rats	Inflammatory cell infiltration MPO levels	LLLT reduced inflammation and MPO when applied in addition to SRP

bFGF, basic fibroblast growth factor; DSL, diode soft laser; GCF, gingival crevicular fluid; IFN, interferon; MPO, myeloperoxidase; PDGF, platelet-derived growth factor; PDT, photodynamic therapy; RT, reverse transcriptase.

evaluated by histological evaluation of gingival biopsies in some of the studies.

Pesevska et al. observed in their study that supplemental low-level laser to SRP was able to suppress TNF-α in gingival tissue, and also a significant in level of COX-2 expression was observed in their recent study. In this study they reported lower expression levels of COX-2 in the 10 sessions of laser therapy group than 5 sessions.[84,85]

In addition, in a histological study by Igic, a positive effect was observed when low-level laser therapy was applied as an adjunctive to basic treatment of gingivitis. This study reports a change in size of the nuclei of the stratified squamous epithelial cells in the gingiva to the same size as healthy cells after laser therapy. This also occurred in the group that received only basic periodontal treatment; however, it did not reach the size of normal gingiva in this group.[83] Histological evaluation by Pejcic and Zivkovic reported laser therapy to be successful in gingival inflammation reduction with complete healing and regeneration of gingiva in which only a few inflammatory cells could be found. Marked collagen tissue homogenization was also reported for this group.[20]

Although most studies have clearly demonstrated positive effects of photobiostimulation on inflammation, based on the evaluation of its effects on clinical inflammation indices or measuring inflammatory markers, with the variation in irradiation parameters it is still difficult to propose a specific treatment protocol. Further research in this field with well-designed studies considering the confounding factors that might alter inflammation results in periodontal tissues is recommended. The other effects of PBM on pain control and implantology will be discussed in Part II.[87]

Author Disclosure Statement

No competing financial interests exist.

Funding Information

There was no funding provided for this article.

References

1. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy—an update. Dose Response 2011;9:602–618.
2. Mester E, Mester AF, Mester A. The biomedical effects of laser application. Lasers Surg Med 1985;5:31–39.
3. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng 2012;40:516–533.
4. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys 2017;4:337–361.
5. Tuner J, Hode L. It's all in the parameters: a critical analysis of some well-known negative studies on low-level laser therapy. J Clin Laser Med Surg 1998;16:245–248.
6. Zein R, Selting W, Hamblin MR. Review of light parameters and photobiomodulation efficacy: dive into complexity. J Biomed Opt 2018;23:1–17.
7. Chambrone L, Ramos UD, Reynolds MA. Infrared lasers for the treatment of moderate to severe periodontitis: An American Academy of Periodontology best evidence review. J Periodontol 2018;89:743–765.
8. Mills MP, Rosen PS, Chambrone L, et al. American Academy of Periodontology best evidence consensus statement on the efficacy of laser therapy used alone or as an adjunct to non-surgical and surgical treatment of periodontitis and peri-implant diseases. J Periodontol 2018;89:737–742.
9. Subramani K, Wismeijer D. Decontamination of titanium implant surface and re-osseointegration to treat peri-implantitis: a literature review. Int J Oral Maxillofac Implants 2012;27:1043–1054.
10. De Paula Eduardo C, De Freitas PM, Esteves-Oliveira M, et al. Laser phototherapy in the treatment of periodontal disease. A review. Lasers Med Sci 2010;25:781–792.
11. Lin GH, Suarez Lopez Del Amo F, Wang HL. Laser therapy for treatment of peri-implant mucositis and peri-implantitis: An American Academy of Periodontology best evidence review. J Periodontol 2018;89: 766–782.
12. Prados-Frutos JC, Rodríguez-Molinero J, Prados-Privado M, Torres JH, Rojo R. Lack of clinical evidence on low-level laser therapy (LLLT) on dental titanium implant: a systematic review. Lasers Med Sci 2016;31:383–392.
13. Tang E, Arany P. Photobiomodulation and implants: implications for dentistry. J Periodontal Implant Sci 2013;43: 262–268.
14. Ren C, McGrath C, Jin L, Zhang C, Yang Y. The effectiveness of low-level laser therapy as an adjunct to non-surgical periodontal treatment: a meta-analysis. J Periodontal Res 2017;52:8–20.
15. Qadri T, Miranda L, Tuner J, Gustafsson A. The short-term effects of low-level lasers as adjunct therapy in the treatment of periodontal inflammation. J Clin Periodontol 2005; 32:714–719.
16. Kreisler M, Al Haj H, d'Hoedt B. Clinical efficacy of semiconductor laser application as an adjunct to conventional scaling and root planing. Lasers Surg Med 2005;37: 350–355.
17. Vieru RD, Lefter A, Herman S. Effects of adjunctive laser photobiomodulation in the classical treatment of periodontal disease. Laser Ther 2005;14:161–169.
18. Qadri T, Bohdanecka P, Tunér J, Miranda L, Altamash M, Gustafsson A. The importance of coherence length in laser phototherapy of gingival inflammation—a pilot study. Lasers Med Sci 2007;22:245–251.
19. Assaf M, Yilmaz S, Kuru B, Ipci SD, Noyun U, Kadir T. Effect of the diode laser on bacteremia associated with dental ultrasonic scaling: a clinical and microbiological study. Photomed Laser Surg 2007;25:250–256.
20. Pejcic A, Zivkovic V. Histological examination of gingiva treated with low-level laser in periodontal therapy. J Oral Laser Appl 2007;71:37–43.
21. Ribeiro IW, Sbrana MC, Esper LA, Almeida AL. Evaluation of the effect of the GaAlAs laser on subgingival scaling and root planing. Photomed Laser Surg 2008;26: 387–391.
22. Lai SM, Zee KY, Lai MK, Corbet EF. Clinical and radiographic investigation of the adjunctive effects of a low-power He-Ne laser in the treatment of moderate to advanced periodontal disease: a pilot study. Photomed Laser Surg 2009;27: 287–293.
23. Pejcic A, Kojovic D, Kesic L, Obradovic R. The effects of low level laser irradiation on gingival inflammation. Photomed Laser Surg 2010;28:69–74.

24. Gómez C, Domínguez A, García-Kass AI, García-Nuñez JA. Adjunctive Nd: YAG laser application in chronic periodontitis: clinical, immunological, and microbiological aspects. Lasers Med Sci 2011;26:453–463.
25. Pejcic A, Mirkovic D. Anti-inflammatory effect of low level laser treatment on chronic periodontitis. Med Laser Appl 2011;26:27–34.
26. Eltas A, Orbak R. Effect of 1,064-nm Nd:YAG laser therapy on GCF IL-1β and MMP-8 levels in patients with chronic periodontitis. Lasers Med Sci 2012;27: 543–550.
27. Calderin S, Garcia-Nunez JA, Gomez C. Short-term clinical and osteoimmunological effects of scaling and root planing complemented by simple or repeated laser phototherapy in chronic periodontitis. Lasers Med Sci 2013;28: 157–166.
28. Hazeem MI, Muthenna Shaban Rajab B, Badeia RA. Efficacy of diode laser with different intensities as an adjunct to traditional mechanical treatment of chronic periodontitis. Mustansiria Dent J 2013;10:137–146.
29. Dukić W, Bago I, Aurer A, Roguljić M. Clinical effectiveness of diode laser therapy as an adjunct to nonsurgical periodontal treatment: a randomized clinical study. J Periodontol 2013;84:1111–1117.
30. Saafan A, El-Nahass H, Nasr AS, Radwan R. Effect of low power diode laser 810 nm on TGF-β1 level in GCF in aggressive periodontitis. J Dent Lasers 2013;7:59.
31. Ismaili B, Bokonjic D. Short-term low-level laser therapy attenuates inflammation and production of interleukin-1, but elevates the level of matrix metalloproteinase 9 in chronic periodontitis. J Int Dent Med Res 2014;7:7–13.
32. Nguyen NT, Byarlay MR, Reinhardt RA, Marx DB, Meinberg TA, Kaldahl WB. Adjunctive non-surgical therapy of inflamed periodontal pockets during maintenance therapy using diode laser: a randomized clinical trial. J Periodontol 2015;86:1133–1140.
33. Obradović R, Kesić L, Pejčić A, Igić M, Bojović M, Petrović M. Low power laser efficacy in the therapy of periodontitis. Acta Stomatologica Naissi 2015;31:1504–1513.
34. Gündoğar H, Şenyurt SZ, Erciyas K, Yalım M, Üstün K. The effect of low-level laser therapy on non-surgical periodontal treatment: a randomized controlled, single-blind, split-mouth clinical trial. Lasers Med Sci 2016;31:1767–1773.
35. Kumaresan D, Balasundaram A, Naik VK, Appukuttan DP. Gingival crevicular fluid periostin levels in chronic periodontitis patients following nonsurgical periodontal treatment with low-level laser therapy. Eur J Dent 2016;10:546–550.
36. Matarese G, Ramaglia L, Cicciu M, Cordasco G, Isola G. The effects of diode laser therapy as an adjunct to scaling and root planing in the treatment of aggressive periodontitis: A 1-year randomized controlled clinical trial. Photomed Laser Surg 2017;35:702–709.
37. Petrovic MS, Kannosh IY, Milasin JM, et al. Clinical, microbiological and cytomorphometric evaluation of low-level laser therapy as an adjunct to periodontal therapy in patients with chronic periodontitis. Int J Dent Hyg 2018;16: e120–e127.
38. Mastrangelo F, Dedola A, Cattoni F, et al. Etiological periodontal treatment with and without low level laser therapy on IL-1β level in gingival crevicular fluid: an in vivo multicentric pilot study. J Biol Regul Homeost Agents 2018;32:425–431.
39. Garcia VG, Fernandes LA, de Almeida JM, et al. Comparison between laser therapy and non-surgical therapy for periodontitis in rats treated with dexamethasone. Lasers Med Sci 2010;25:197–206.
40. Obradovic R, Kesic L, Jovanovic G, Petrovic D, Goran R, Mihailovic D. [Low power laser efficacy in the therapy of inflamed gingive in diabetics with parodontopathy]. Vojnosanitetski Pregled 2011;68:684–689.
41. Aykol G, Baser U, Maden I, et al. The effect of low-level laser therapy as an adjunct to non-surgical periodontal treatment. J Periodontol 2011;82:481–488.
42. Obradovic R, Kesic L, Mihailovic D, Jovanovic G, Antic S, Brkic Z. Low-level lasers as an adjunct in periodontal therapy in patients with diabetes mellitus. Diabetes Technol Ther 2012;14:799–803.
43. Eltas A, Orbak R. Clinical effects of Nd: YAG laser applications during nonsurgical periodontal treatment in smoking and nonsmoking patients with chronic periodontitis. Photomed Laser Surg 2012;30:360–366.
44. Obradovic R, Kesic L, Mihailovic D, et al. A histological evaluation of a low-level laser therapy as an adjunct to periodontal therapy in patients with diabetes mellitus. Lasers Med Sci 2013;28:19–24.
45. Demirturk-Gocgun O, Baser U, Aykol-Sahin G, Dinccag N, Issever H, Yalcin F. Role of low-level laser therapy as an adjunct to initial periodontal treatment in type 2 diabetic patients: a split-mouth, randomized, controlled clinical trial. Photomed Laser Surg 2017;35:111–115.
46. Swerts AA, Santos BFE, Bruzadelli SR, Brigagao M, Lima DC, Fernandes LA. Treatment of experimental periodontal disease by laser therapy in simvastatin-modified rats. J Appl Oral Sci 2017;25:387–395.
47. Theodoro LH, Longo M, Ervolino E, et al. Effect of low-level laser therapy as an adjuvant in the treatment of periodontitis induced in rats subjected to 5-fluorouracil chemotherapy. J Periodontal Res 2016;51:669–680.
48. Pamuk F, Lutfioglu M, Aydogdu A, Koyuncuoglu CZ, Cifcibasi E, Badur OS. The effect of low-level laser therapy as an adjunct to non-surgical periodontal treatment on gingival crevicular fluid levels of transforming growth factor-beta 1, tissue plasminogen activator and plasminogen activator inhibitor 1 in smoking and non-smoking chronic periodontitis patients: a split-mouth, randomized control study. J Periodontal Res 2017;52: 872–882.
49. Bunjaku V, Popovska M, Grcev A, et al. Non-surgical periodontal treatment and Low Level Laser Therapy (LLLT) outcomes for patients suffering from type 2 diabetes mellitus, obesity and chronic periodontitis. J Int Dent Med Res 2017;10:214–221.
50. Koçak E, Sağlam M, Kayış SA, et al. Nonsurgical periodontal therapy with/without diode laser modulates metabolic control of type 2 diabetics with periodontitis: a randomized clinical trial. Lasers Med Sci 2016;31:343–353.
51. Ozcelik O, Cenk Haytac M, Seydaoglu G. Enamel matrix derivative and low-level laser therapy in the treatment of intra-bony defects: a randomized placebo-controlled clinical trial. J Clin Periodontol 2008;35:147–156.
52. AboElsaad NS, Soory M, Gadalla LM, et al. Effect of soft laser and bioactive glass on bone regeneration in the

treatment of infra-bony defects (a clinical study). Lasers Med Sci 2009;24:387–395.
53. Dilsiz A, Canakci V, Aydin T. The combined use of Nd: YAG laser and enamel matrix proteins in the treatment of periodontal infrabony defects. J Periodontol 2010;81:1411–1418.
54. Abolfazli N SS, Sadighi SM, Rikhtegaran S. Effect of low-level laser therapy and autogenous bone graft on bone regeneration in the treatment of two wall and three wall intrabony periodontal defects: a clinical study. Laser Med 2012;8:6–14.
55. Emrem Doğan G, Demir T, Orbak R. Effect of low-level laser on guided tissue regeneration performed with equine bone and membrane in the treatment of intrabony defects: a clinical study. Photomed Laser Surg 2014;32: 226–231.
56. Doğan GE, Aksoy H, Demir T, et al. Clinical and biochemical comparison of guided tissue regeneration versus guided tissue regeneration plus low-level laser therapy in the treatment of class II furcation defects: a clinical study. J Cosmet Laser Ther 2016;18:98–104.
57. Bhardwaj S, George JP, Remigus D, Khanna D. Low level laser therapy in the treatment of intra-osseous defect—a case report. J Clin Diagn Res 2016;10:ZD06.
58. Tao CY, Lee N, Chang HC, Yang C, Yu XH, Chang PC. Evaluation of 660 nm LED light irradiation on the strategies for treating experimental periodontal intrabony defects. Lasers Med Sci 2016;31:1113–1121.
59. Behdin S, Monje A, Lin GH, Edwards B, Othman A, Wang HL. Effectiveness of laser application for periodontal surgical therapy: systematic review and meta-analysis. J Periodontol 2015;86:1352–1363.
60. Dogan GE, Demir T, Orbak R. Effect of low-level laser on guided tissue regeneration performed with equine bone and membrane in the treatment of intrabony defects: a clinical study. Photomed Laser Surg 2014;32: 226–231.
61. Amorim JC, de Sousa GR, de Barros Silveira L, Prates RA, Pinotti M, Ribeiro MS. Clinical study of the gingiva healing after gingivectomy and low-level laser therapy. Photomed Laser Surg 2006;24:588–594.
62. Ozcelik O, Cenk Haytac M, Kunin A, Seydaoglu G. Improved wound healing by low-level laser irradiation after gingivectomy operations: a controlled clinical pilot study. J Clin Periodontol 2008;35:250–254.
63. Almeida AL, Esper LA, Sbrana MC, Ribeiro IW, Kaizer RO. Utilization of low-intensity laser during healing of free gingival grafts. Photomed Laser Surg 2009;27: 561–564.
64. Vieira J, Lopes CB, DeMarco AC, de Melo Filho AB, Jardini A. Clinical study of laser biomodulation (650 λ) after free gingival grafts. J Oral Laser Applications 2010; 10:159–163.
65. Ozturan S, Durukan SA, Ozcelik O, Seydaoglu G, Haytac MC. Coronally advanced flap adjunct with low intensity laser therapy: a randomized controlled clinical pilot study. J Clin Periodontol 2011;38:1055–1062.
66. Firat ET, Dağ A, Günay A, et al. The effects of low-level laser therapy on palatal mucoperiosteal wound healing and oxidative stress status in experimental diabetic rats. Photomed Laser Surg 2013;31:315–321.
67. Moslemi N, Heidari M, Fekrazad R, et al. Evaluation of the effect of 660 nm low power laser on pain and healing in palatal donor site: a randomized controlled clinical trial. J Dent Med 2014;27:71–77.
68. Dias SBF, Fonseca MVA, dos Santos NCC, et al. Effect of GaAIAs low-level laser therapy on the healing of human palate mucosa after connective tissue graft harvesting: randomized clinical trial. Lasers Med Sci 2015;30:1695–1702.
69. Fekrazad R, Mirmoezzi A, Kalhori KA, Arany P. The effect of red, green and blue lasers on healing of oral wounds in diabetic rats. J Photochem Photobiol B 2015; 148:242–245.
70. Fernandes-Dias SB, de Marco AC, Santamaria M, Jr., Kerbauy WD, Jardini MA, Santamaria MP. Connective tissue graft associated or not with low laser therapy to treat gingival recession: randomized clinical trial. J Clin Periodontol 2015;42:54–61.
71. Wang CY, Tsai SC, Yu MC, Lin YF, Chen CC, Chang PC. Light-emitting diode irradiation promotes donor site wound healing of the free gingival graft. J Periodontol 2015;86: 674–681.
72. Singh N, Uppoor A, Naik D. Semilunar coronally advanced flap with or without low level laser therapy in treatment of human maxillary multiple adjacent facial gingival recessions: a clinical study. J Esthet Restor Dent 2015;27:355–366.
73. Ozcelik O, Seydaoglu G, Haytac CM. Diode laser for harvesting de-epithelialized palatal graft in the treatment of gingival recession defects: a randomized clinical trial. J Clin Periodontol 2016;43:63–71.
74. Chawla K, Lamba AK, Tandon S, Faraz F, Gaba V. Effect of low-level laser therapy on wound healing after depigmentation procedure: a clinical study. J Indian Soc Periodontol 2016;20:184.
75. da Silva Neves FL, Silveira CA, Dias SB, et al. Comparison of two power densities on the healing of palatal wounds after connective tissue graft removal: randomized clinical trial. Lasers Med Sci 2016;31:1371–1378.
76. Heidari M, Paknejad M, Jamali R, Nokhbatolfoghahaei H, Fekrazad R, Moslemi N. Effect of laser photobiomodulation on wound healing and postoperative pain following free gingival graft: a split-mouth triple-blind randomized controlled clinical trial. J Photochem Photobiol B 2017; 172:109–114.
77. Santamaria MP, Fernandes-Dias SB, Araújo CF, et al. 2-Year assessment of tissue biostimulation with low-level laser on the outcomes of connective tissue graft in the treatment of single gingival recession: a randomized clinical trial. J Periodontol 2017;88:320–328.
78. Ustaoglu G, Ercan E, Tunali M. Low-level laser therapy in enhancing wound healing and preserving tissue thickness at free gingival graft donor sites: a randomized, controlled clinical study. Photomed Laser Surg 2017;35: 223–230.
79. Kohale BR, Agrawal AA, Raut CP. Effect of low-level laser therapy on wound healing and patients' response after scalpel gingivectomy: a randomized clinical split-mouth study. J Indian Soc Periodontol 2018; 22:419.
80. Yan J, Zhang J, Zhang Q, Zhang X, Ji K. Effectiveness of laser adjunctive therapy for surgical treatment of gingival recession with flap graft techniques: a systematic review and meta-analysis. Lasers Med Sci 2018;33:899–908.

81. Safavi SM, Kazemi B, Esmaeili M, Fallah A, Modarresi A, Mir M. Effects of low-level He–Ne laser irradiation on the gene expression of IL-1β, TNF-α, IFN-γ, TGF-β, bFGF, and PDGF in rat's gingiva. Lasers Med Sci 2008;23:331–335.
82. Giannopoulou C, Cappuyns I, Cancela J, Cionca N, Mombelli A. Effect of photodynamic therapy, diode laser, and deep scaling on cytokine and acute-phase protein levels in gingival crevicular fluid of residual periodontal pockets. J Periodontol 2012;83:1018–1027.
83. Igic M, Mihailovic D, Kesic L, et al. Cytomorphometric and clinical investigation of the gingiva before and after low-level laser therapy of gingivitis in children. Lasers Med Sci 2012;27:843–848.
84. Pesevska S, Nakova M, Gjorgoski I, et al. Effect of laser on TNF-alpha expression in inflamed human gingival tissue. Lasers Med Sci 2012;27:377–381.
85. Pesevska S, Gjorgoski I, Ivanovski K, Soldatos NK, Angelov N. The effect of low-level diode laser on COX-2 gene expression in chronic periodontitis patients. Lasers Med Sci 2017;32:1463–1468.
86. Uslu MÖ, Eltas A, Marakoğlu İ, Dündar S, Şahin K, Özercan İ. Effects of diode laser application on inflammation and MPO in periodontal tissues in a rat model. J Appl Oral Sci 2018;26:e20170266.
87. Gholami L, Asefi S, Hoshyarfard A, Sculean A, Romanos GE, Aoki A, Fekrazad R. Photobiomodulation in periodontology and implant dentistry—part II. Photobiomodulation, Photomed Laser Surg 2019. DOI: 10.1089/pho.2019.4731 (in press).

Address correspondence to:
Reza Fekrazad, DDS, MSc
Department of Periodontology
Dental Faculty
Laser Research Center in Medical Sciences
AJA University of Medical Sciences
Lat No 12, Mooj Building, First Behestan,
Pasdaran Street
Tehran 1946883893
Iran

E-mail: rezafekrazad@gmail.com

Received: June 8, 2019.
Accepted after revision: June 27, 2019.
Published online: November 20, 2019.