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Review

Photobiomodulation in Periodontology and Implant Dentistry: Part II

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Abstract

Objective: Finding evidence-based treatment strategies for low-level light therapy 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 photobobiomodulatory 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 a great deal of heterogeneity in terms of study designs and most importantly in light irradiation devices and the parameters used. Due 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 low-level light therapy 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

Clinical Question 6

Can photobiomodulation reduce post-periodontal surgery pain?

Evidence search strategy. The terms ‘‘Periodontal surgery’’ OR ‘‘Pain’’ OR ‘‘Visual analog scale’’ were used combined with the low-level laser therapy keywords as previously stated. An electronic search of the four databases was performed. The inclusion criteria considered for finding relevant articles to answer this question were human clinical studies evaluating the adjunctive effect of low levels of light therapy on pain after periodontal flap or graft surgeries. Title screening resulted in 32 articles, out of which only 6 met our inclusion criteria (Table 1).[1–6]

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Table 1. Characteristics of Included Studies: Effect of Photobiomodulation Post-Periodontal Surgery Pain

Author (year)$^{\text{Ref.}}$	*Wave length*	*Irradiation parameters*	*Study population/groups*	*Evaluations*	*Main results*
Ozcelik et al. (2008)[5]	Diode 588 nm	Energy density 4 J/cm^2 in each site CW 5 min, 2 times from buccal, 2 times from lingual/ For 5 days	22 periodontitis patients with deep intra-bony defects (EMD alone EMD+LLLT)	CAL PPD, BI gingival recession swelling VAS scores	LLLT may improve the effects of EMD and reduce gingival recession and postoperative pain and swelling.
Almeida et al. (2009)[6]	Diode laser 2 Wave lengths 780 nm 660 nm	40 mW, 10 J/cm^2 CW: 20 sec Immediate postoperative and 48 h Noncontact (1 mm)	10 Patients undergoing bilateral free gingival grafts	Healing process and analgesia (VAS) in individuals undergoing free gingival grafts	Low-intensity laser therapy did not improve the healing of gingival grafts and did not influence analgesia.
Etemadi et al. (2011)[1]	Laser 660 nm	25 mW, 4.5 J, so a band of gingiva just beneath the marginal gingiva of the central incisor, lateral incisor, and canine were irradiated by swiping motion for 3 min every other day starting the day after surgery and continuing for 4 times	40 Patients, periodontal flap surgery on upper anterior sextan (20 cases: randomly received LL in left or right side of the treated section and 20 controls received only periodontal dressing)	Pain sensation (VAS) DH using VAS	Reduced pain after periodontal surgery, but did not have any effects on DH
Sanz-Moliner et al. (2013)[2]	Diode laser (810 ± 20 nm)	1 W, CW 4 J/cm^2 per surface 400 μm fiber Noncontact (contact was also used for inner flap epithelial removal)	13 Patients with generalized severe chronic periodontitis needing contralateral flap (MWF MWF+DL)	Pain (PS), PM consumption, TE, TC 1 week after surgery	Statistically significant differences were seen for TE ($p = 0.041$), PM ($p < 0.001$), and PS ($p < 0.001$) favoring test sites. TC showed no difference
Doshi et al. (2014)[3]	Diode laser 660 nm	25 mW, CW 4.5 J/cm^2 for 3 min for 3 consecutive day Noncontact	30 Patients needing periodontal flaps in 2 sites	VAS and verbal rating scale for pain and DH	Postoperative DH and pain after periodontal surgery can be reduced by using LLLT
Heidari et al. (2018)[4]	Diode laser 940 nm	0.5 W, CW 20 J/cm^2 each side (40 J/cm^2) 112 sec on the buccal and lingual of the flap 2.8 cm^2 Noncontact 3 mm	30 Patients needing periodontal flaps in 2 sides of mandible	VAS analgesic medication consumption	Laser adjunct treated sites had lower pain and the number of analgesics taken by patients after un-displaced flap surgery

BI, bleeding index; CAL PPD, clinical attachment level probing pocket depth; CW, continuous wave; DH, dentin hypersensitivity; DL, diode laser; EMD, enamel matrix derivative; LL, low level; LLLT, low-level laser therapy; MWF, modified Widman flap; PGF, peri-implant crevicular fluid; PM, pain medication; PS, pain scale assessment; TC, tissue color; TE, tissue edema; VAS, visual analog scale.

Evidence-based recommendations and conclusion. One of the well-known applications of photo biomodulation is its ability to exert analgesic effects.[7] Periodontal surgeries can result in postoperative pain in patients mostly in the first few hours after surgery. Therefore, low-level light therapy may be considered a suitable treatment method for controlling this kind of pain after surgical trauma, especially with its ability to effect the pain, inflammation, and immune axis that has been reported in the literature.[8]

Almost all the studies included in our review showed a significant favorable effect for phototherapy after periodontal surgeries and reported reduction of pain scores as visual analog scale (VAS) scores and/or amounts of pain medication consumption. Only in one study by Almeida et al., low-level laser irradiation of free gingival grafts did not show a significant analgesic effect and reduction in VAS pain scores.[6]

However, low-level light therapy with energy levels ranging from 4 to 20 J/cm^2 seems to produce favorable post-periodontal surgery analgesics. Further clinical trials with similar settings are still necessary to find the most effective dose and clinical protocol.

Laser Photobiomodulation in Implant Dentistry

Clinical Question 1

Does photobiomodulation promote bone formation around titanium implants?

Evidence search strategy. To find suitable articles that have focused on the biostimulatory effect of phototherapy on bone formation around dental implants a comprehensive electronic search was conducted by using key words of ''bone formation,'' ''Bone implant contact'' ''bone healing'' OR'' Dental implant'' and the ones described earlier for low-level light therapy in the four data bases of PubMed, Google scholar, Scopus, and Cochrane.

From the 97 articles chosen based on titles, 16 articles were finally included after evaluation of full texts. Any in vivo studies that had evaluated the effect of low-level light irradiation on bone formation around Titanium (Ti) surfaces were included.

Evidence-based recommendation and conclusion. There are many in vitro studies that have shown biostimulatory effects for low-intensity light therapy on cells and their osteogenic differentiation on Ti surfaces by measuring changes in different bone formation markers.[9–11] Further studies have focused on testing this effect in animal or clinical settings to correctly translate these findings to clinical implication.

The majority of studies evaluating bone formation around Ti implants were conducted on animals, since it makes it possible to more clearly examine bone formation from a clinical and histological point of view. Most of these studies reported positive effects in terms of promotion of bone formation around Ti implants, and higher bone implant contacts (BICs) were reported (Table 2).[12–27]

Many researchers have confirmed that low-level light therapy can promote bone formation by stimulatory effects on osteoblasts, which can lead to greater osteo-integration of Ti implants. This has been evaluated in different study designs and laser irradiation parameters.

In a study in sheep, Jakse et al. found no significant regenerative effect after sinus lift procedure with autologous graft (iliac crest) under low level laser (LLL) irradiation; however, they also considered it to be possibly effective in osseointegration of dental implants inserted after sinus augmentation.[17] Another animal study was also conducted by Soares et al. on implants integration in auto and xenografts in rabbits.[21] They observed an increased bone formation in the bone-implants interface after LLL irradiation. However, it was noted that bone formation was significantly increased in autografts but was not statistically significant with xenografts. The experimental animals (sheep and rabbit) used, laser wavelength (680 or 780 nm), and output energy densities (3–4 or 16–21 J/cm^2) were different between these two studies, which might have led to the different results obtained.

Lopes et al. have also showed some positive effects for adjunctive photo therapy. In their study, calcium-hydroxyapatite absorption and implant integration were significantly increased by application of LLL irradiation.[18]

Pereira et al. have irradiated Ti implants inserted in tibia of rabbits with low-intensity laser with a 48-h interval for 14 days. According to their results with laser therapy, BIC had a significant increase at 3–6 weeks evaluation times. However, it did not affect the area of bone formed within the threads.[19] In 2004, Khadra et al. reported many positive effects of LLL irradiation. According to their findings, irradiated implants had a greater bond to bone based on tensile pullout test results. A greater amount of calcium and phosphorus content on the irradiated implant surfaces were observed compared with the nonirradiated group, and bone maturation was also faster in irradiated bone.[14]

In another animal study by Kim et al., expression of osteoprotegrin (OPG), receptor activator of nuclear factor kappa-B ligand (RANKL), and RANK was shown to be influenced by low-level laser irradiation and an increase of metabolic bone activity and bone tissue cell activity was observed.[16]

In an interesting research by de Vasconcellos et al. in 2016 in rats, low levels of infrared diode laser were found to be able to improve the initial phase of bone formation and the osseointegration process of Ti scaffolds in osteopenic and normal rats.[25]

In a recent study, Mikhail et al. have evaluated the radiodensitometric changes in bone density along the bone-implant interface. They observed that the rate of increase and mean differences was significantly higher in the laser group.[27] Their conclusion was that low-intensity laser irradiation significantly promoted bone healing and increased the speed of the osseointegration process.

Overall, it seems that energy densities of around 10–20 J/cm^2 performed every other day for 2 weeks may be considered an effective treatment procedure in terms of promoting bone formation around Ti implants. Although there is once again great variation observed in the irradiation protocols used in the current available studies, further research with similar and improved study designs will still be valuable.

Clinical Question 2

Can photobiomodulation influence Ti implant stability?

Evidence search strategy. Once again, the literature was searched by using key words of ''dental implant stability,''

Table 2. Characteristics of Included Studies: Effect of Photobiomodulation on Promotion of Bone Formation Around Titanium Implants

Author (year)$^{\text{Ref.}}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Dörtbudak et al. (2002)[12]	690 nm	100 mW for 1 min (6 J) immediately after drilling and insertion of implants	Sandblasted and etched (FrialitA-2 Synchro) implants	Iliac crest of 5 male baboons	Histomorphometric: 1—osteocyte count per unit 2—osteocyte viability 3—total resorption area (eroded surface)	Osteocyte viability was significantly higher in the samples that were subjected to laser irradiation immediately after implant site drilling and implant insertion, in comparison to control sites. The bone resorption rate, in contrast, was not affected by laser irradiation.
Guzzardella et al. (2003)[13]	780 nm	300 J/cm^2, 1 W, 300 Hz, pulsating emission, 10 min from postoperative day 1 and for 5 consecutive days	Cylindrical implants of HA	Distal femurs of 12 rabbits	Histomorphometric and microhardness in 3 and 6 weeks after implantation	A higher affinity index was observed at the HA–bone interface in the LPL group at 3 ($p < 0.0005$) and 6 weeks ($p < 0.001$); a significant difference in bone microhardness was seen in the LPL group vs. the control group ($p < 0.01$).
Khadra et al. (2004)[14]	GaAlAs 830 nm	Every day for 10 days 150 mW spot size: 0.13 cm^2 9 × 3 J in each tibia per session 23 J/cm^2	2 Coin-shaped Ti implants (6.25 mm × 1.95 mm)	Cortical bone in each proximal tibia of 12 New Zealand white female rabbits	Tensile pullout test Histomorphometric analysis Energy-dispersive X-ray microanalysis (for calcium and phosphorus on the implant test surface)	Positive effect on the functional attachment of Ti implants to bone. The irradiated implants showed a better bone bonding than nontreated controls. Mineral analysis suggests that calcium and phosphorus contents on the implant surface also increase when the implants are irradiated with LLL. Bone maturation processed faster in irradiated bone.
Lopes et al. (2005)[15]	830 nm laser	7 Sessions at 48-h intervals, 21.5 J/cm^2 per session, 10 mW, phi ~0.0028 cm^2, 85 J/cm^2 treatment dose	Ti implant	Ti implant rabbit tibia bone	Raman spectroscopy Concentration of CHA	Significant differences in the concentration of CHA on irradiated and control specimens at both 30 and 45 days after surgery. LLLT does improve bone healing.

(*continued*)

Table 2. (Continued)

Author (year)[Ref.]	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Kim et al. (2007)[16]	808 nm	96 mW 830 mW/cm^2 For 7 days Total irradiated energies were as follows; energy per point: 960 mJ, total dose per session: 6.72 J, and total dose during complete schedule: 40.32 J	Ti implants (commercial pure Ti—grade 3) diameter 2.0 mm, length 3.5 mm	Tibia of 10 rats	Expression of RANKL, OPG, and RANK on the days 1, 3, 7, 14, and 21	The application of the LLL influenced the expression of OPG, RANKL, and RANK; resulted in the expansion of metabolic bone activity; and increased the activity of bone tissue cells.
Jakse et al. (2007)[17]	680 nm	During surgery and 3 times during the 1st postoperative week 75 mW 3–4 J/cm^2 1 min	2 Ti nails	12 Sheep with bilateral sinus floor elevation procedure with cancellous bone from the iliac crest	Histomorphometric analysis 16 weeks after the second-stage surgery	No positive LLLT effect on bone regeneration within a cancellous sinus graft. Overall, LLLT possibly has a positive effect on osseointegration of dental implants inserted after sinus augmentation.
Lopes et al. (2007)[18]	830 nm	7 Sessions at 48-h intervals, 21.5 J/cm^2 per point, 10 mW, ~ 0.0028 cm^2, 86 J per session	Cylindrical Ti implants (2.6 mm, 6 mm long)	Tibia of New Zealand rabbits killed in 5, 30, and 45 days after the surgery	Raman spectroscopy and SEM	Significant differences on the concentration of calcium hydroxyapatite on irradiated and control specimens at both 30 and 45 days after surgery ($p < 0.001$). It is concluded that infrared laser photobiomodulation does improve bone healing.
Pereira et al. (2009)[19]	Diode (GaAlAs)	Low-intensity laser every 48 h for 14 days postoperatively	Ti implants	Tibia of 12 rabbits	BIC and bone area within the implant threads	Low-intensity laser therapy did not affect the area of bone formed within the threads, but BIC was significantly increased in the laser-treated group at both 3 and 6 weeks.
Fan et al. (2012)[20]	He-Ne laser	Low-level He-Ne laser irradiation	36 Implants	Tibia of Beagle dogs	Histomorphometry BIC ratio	Gradually increased in a time-depend manner; at the same time points, the BIC ratio was highest in the 2-week irradiation group, and followed by the 1-week irradiation group. The results revealed that the locally low-level He-Ne laser irradiation could promote the healing of bone tissue around the implant and increase the degree of osseointegration.

(*continued*)

TABLE 2. (CONTINUED)

Author (year)$^{\text{Ref.}}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Soares et al. (2013)[21]	780 nm	The laser parameters in the groups AG/L and XG/L were $\lambda = 780$ nm, 70 mW, CW, 21.5 J/cm^2, wherease in the groups AG/I/L and XG/I/L the parameters were used: $\lambda = 780$ nm, 70 mW, 0.5 cm^2 (spot), 4 J/cm^2 per point 16 J/cm^2 per session, 48-h interval × 12 sessions, CW, contact mode. LLLT was repeated every other day during 2 weeks	Ti implants	24 Adult rabbits were divided into 8 groups: AG; XG; AG/L; XG/L; AG/I; XG/I; AG/I/L; and XG/I/L	BV and BIC interface	A significant ($p = 0.02$) increase of the BIC in autografts. The same was seen when xenografts were used, without significant difference. LLLT is effective for enhancing new bone formation with a consequent increase of bone-implant interface in both autologous grafts and xenografts.
de Vasconcellos et al. (2014)[22]	780 nm	40 mW, CW 0.69 cm^2 $t = 1$ min 40 sec perpendicularly to the bone before and after placing the implant, for 7 times	Ti Implants	Femur bone of osteopenic and normal rats The groups were: (a) NSh group: control, no laser+Sham; (b) LSh group: laser+Sham; (c) NOv group: no laser+ ovariectomy; (d) LOv group: laser+ ovariectomy	Histological analysis evaluated bone tissue formation and quality, whereas histomorphometric analysis evaluated the bone neoformation rate	Laser may improve the osseointegration process in osteopenic and normal bone, particularly based on its effects in the initial phase of bone formation.
Gomes et al. (2015)[23]	830 nm	50 mW was applied every 48 h for 13 days, starting immediately after surgery At 3 different doses per session: 5, 10, and 20 J/cm^2	Ti implant	32 Rabbits had their mandibular left incisors removed, followed by immediate insertion of a dental implant	ISQ SEM and stereology. Variables measured were BIC and bone neoformation within implant threads at 3 different sites	Better ISQ for the 20 J/cm^2 group. BIC values were significantly higher in the 20 J/cm^2 group, on both SEM and stereology. Bone area values were better in the 10 and 20 J/cm^2 groups compared with the control group. Under these conditions, LLLT enhanced peri-implant bone repair, improving stability, BIC, and bone neoformation.

(*continued*)

TABLE 2. (CONTINUED)

Author (year)[Ref.]	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Massotti et al. (2015)[24]	830 nm	50 mW 3 Different energy densities per treatment session (E-5, 5 J/cm^2; E-10, 10 J/cm^2; and E-20, 20 J/cm^2). Irradiation was performed every 48 h for 13 days	Ti scaffolds	Immediate implantation of left mandibular incisor of 24 New Zealand rabbits	Histomorphometric evaluation. BIC, bone formation area, and collagen fiber area	Significantly higher BIC and significantly more collagen fibers in group E-20. Photobiostimulation with LLLT at an energy density of 20 J/cm^2 per session had a significant positive effect on new bone formation.
de Vasconcellos et al. (2016)[25]	780 nm	40 mW, CW, 0.69 cm 1 min 40 sec Transcutaneous LLLT, at regular 48-h intervals. A dose of 4 J/cm^2 was applied to 4 points around the cavity, making a total of 16 J/cm^2 per session and a total treatment dose of 112 J/cm^2	Ti scaffolds	Femurs of healthy and osteoporotic rats 4 Groups 1—SHAM animals 2—SHAM+LL 3—OV: ovariectomized 4—OV+L	Histomorphometric examination of bone formation	Greater new bone formation within Ti scaffolds in the animals submitted to LLLT after 2 and 6 weeks. LLLT improves and accelerates bone repair within Ti scaffolds in both ovariectomized and healthy rats.
Mayer et al. (2016)[26]	Diode 830 nm	50 mW, CW, 0.0028 cm^2 10 J per spot, 2 spots per session, 7 sessions	Ti implants	Immediate implantation of left mandibular incisor of 14 New Zealand rabbits	Resonance frequency analysis Micro-CT to evaluate the amount of newly formed bone around the implants	Higher ISQs at 30 days and greater percentage of newly formed bone around the implants was observed in irradiated animals. Laser therapy could provide greater implant stability and increase the volume of peri-implant newly formed bone.
Mikhail, et al. (2018)[27]	904 nm	20 mW, CW spot diameter 4 mm 30 sec 4.7 J/cm^2 9 sessions during the 1st week postoperatively (on 2nd, 4th, and 6th days), 3 sessions per day with (1-h) rest period in between each session.	Ti implants	20 Patients (mandibular first molar region) immediately loaded dental implants in patients on vitamin C, omega-3, and calcium therapy	Radio-densitometric evaluation of changes in bone density along the bone-implant interface at the mesial, distal, and apical 1.5 and 6 months postoperatively	Rate of increase and mean differences were significantly higher in the laser group. The low-intensity laser irradiation significantly promoted bone healing and speeded up the osseointegration process.

AG, autograft; AG/I, AG+Ti implant; AG/I/L, AG+Ti implant+laser; AG/L, autograft+laser; BIC, bone implant contact; BV, bone volume; CHA, calcium hydroxyapatite; CT, computed tomography; HA, hydroxyapatite; ISQ, implant stability quotient; LLL, low level laser; LPL, low-power laser; OPG, osteoprotegrin; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; SEM, scanning electron microscopy; Ti, titanium; XG, xenograft; XG/I, XG+Ti implant; XG/I, XG+Ti implant; XG/I/L, XG+Ti implant+laser; XG/L, XG+laser.

"osseointegration," "stability" and key words used for low-level light therapy in the four electronic databases previously mentioned. Forty-nine abstracts were chosen and after full text evaluation, 16 in vivo articles that met the selection criteria for this review question were included. Any animal or human studies evaluating Ti, implant stability, or osseointegration with the adjunctive use of low-intensity light were considered eligible. There were also a few reports on mini-implants or miniscrews used for temporary purposes that were excluded here and are discussed separately in the following question.

Evidence-based recommendations and conclusion. Decreasing the duration of osseointegration has been a topic of interest for laser implant research for many years. Since it is proposed that low-level light therapy can influence osteoblast cells and the osseointegration process, it seems possible that it can also be effective at increasing the stability of Ti implants. We were able to find 16 articles until April 2019 focusing on this subject. Seven were clinical studies performed on human subjects and 9 were animal studies. In these studies, implant stability was measured by using different methods such as removal torque tests, tensile pullout test, resonance frequency analysis (RFA) devices, or measuring implant stability quotient (ISQ). The animal studies have all reported that photo therapy with low levels of light can provide greater bone-implant interface strength and also improve the osseointegration process (Table 3).[14,23,26,28–41] Removal torque values increased significantly along with time even after a single laser irradiation compared with a nonirradiated control group in the study by Boldrini et al.[32] Gomes et al. have interestingly shown that higher energy levels (10 or 20 J/cm^2) promote more implant-bone contact compared with a lower energy (5 J/cm^2). Better ISQ values were also observed in the 20 J/cm^2 group (this article was published in the Quintessense journal in the same year with the Mayer et al. bibliography).[23,34]

In the human studies, implant stability values (ISQ measurements) were shown to be increased in low level laser therapy (LLLT) groups.[33,38,39,41] However, Torkzaban et al. found no significant effect of adjunctive 940-nm low laser therapy on implant stability. In another randomized clinical trial, García-Morales (2012) reported that LLL was not able to significantly increase implant stability when assessed by resonance frequency analysis (RFA).[30,36]

Implant surface roughness is one of the factors that may also influence osseointegration and stability. In the animal study by Primo et al., three groups of smooth Ti implants, rough surface (acid etched) implants and smooth implants irradiated with LLLT were compared. The BIC of rough surface implants was greater than with smooth implants. However, there was no statistically significant difference between rough surface implants and smooth implants irradiated with LLLT.

Overall, the results should be interpreted with caution since many factors such as implant types, various irradiation parameters, and implant stability measurement methods had a wide variation in the studies and may possibly influence the results obtained. Further well-designed studies can help better elucidate this potential application of photo biomodulation in implant dentistry.

Clinical Question 3

Does photobiomodulation irradiation influence mini-Ti implant (un osteo- integrated miniscrew) stability and success?

Evidence search strategy. To find relevant research focusing on adjunctive low-level light therapy used for improving non osteo-integrated miniscrew or mini-implant stability or success, PubMed, Google Scholar, Scopus, and Cochrane databases were searched by using the key words we had selected for photobiomodulation and key words of "mini implant" OR "mini screw" AND "stability" OR "success." In vivo animal or human studies evaluating the stability and success of mini-implants or miniscrews were considered eligible. Eight studies were identified based on our inclusion criteria (Table 4).[42–47]

Evidence-based conclusion and recommendation. Improving orthodontic anchorage can be achieved by placing mini-implants or miniscrews in the alveolar bone. Enhancing the stability and therefore the success of these implants by low-level light photo biomodulation has attracted the attention of many researchers in this field in recent years. We were able to find five animal studies and three studies on human subjects. In most of the animal studies, it has been concluded that LLLT may be useful in enhancement of the stability of mini-implants based on measuring implant stability with different methods.[42–45,48] Interestingly, in the Uysal et al. study, a significant increase was found in ISQ values when photobiomodulation therapy was used on miniscrews in all three different force groups (0, 150, and 300 cN). However, as force levels increased, ISQ values decreased in non-irradiated control miniscrews.[43] In a histological study by Garcez et al. in the irradiated group, the number of inflammatory cells was less than the control group and a more intense new bone formation was observed around the irradiated miniscrews.[45]

The results of the three clinical studies have also shown improved stability and reduced inflammation around miniscrews or implants placed in human subjects. However, the improved stability results (measured by Periotest) reported in Osman et al.'s study were not statistically significant.[46,47,49] They have also evaluated the inflammatory markers in the peri-implant crevicular fluid (PGF) and concluded that since LLLT modulates the initial inflammation after the insertion of mini-implants, it seems that it is possible to increase the mini-implant success prognosis and decrease patient discomfort with adjunctive photobiomodulation.

The evidence seems to be in favor of the use of adjunctive photobiomodulation with mini-implant/miniscrew placement to improve their success and stability. To reach better evidence-based conclusions, future randomized clinical trials studies with similar study designs seem to be necessary.

Clinical Question 4

Does photobiomodulation influence proliferation and viability of non-osseous periodontal cells around Ti implants?

Evidence search strategy. The terms "cells" OR "gingival fibroblast" OR "periodontal ligament" AND "titanium"

TABLE 3. CHARACTERISTICS OF INCLUDED STUDIES: EFFECT OF PHOTOBIOMODULATION ON TITANIUM IMPLANT STABILITY

Author (year)$^{\text{Ref.}}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/groups*	*Evaluations*	*Main results*
Khadra et al. (2004)[14]	GaAlAs 830 nm	150 mW Spot size: 0.13 cm^2 9 × 3 J in each tibia per session Every day for 10 days 23 J/cm^2	2 Coin-shaped Ti implants (6.25 mm × 1.95 mm)	Cortical bone in each proximal tibia of 12 New Zealand white female rabbits ($n=48$)	Tensile pullout test Histomorphometric analysis Energy-dispersive X-ray microanalysis (for calcium and phosphorus on the implant test surface)	Positive effect on the functional attachment of Ti implants to bone. The irradiated implants showed a better bone bonding than nontreated controls. Mineral analysis suggests that calcium and phosphorus contents on the implant surface also increase when the implants are irradiated with LLL.
Maluf et al. (2010)[28]	795 nm	120 mW 2 lateral and 2 longitudinal, 6 times 8 J/cm^2 with an interval of 2 days, totaling the dose of 48 J/cm^2	Ti implants 2 mm × 3.5 mm	Shinbone of mice	Removal torque value	Stronger implant interface than the control group
Campanha et al. (2010)[29]	830 nm	21.5 J/cm^2 4 points around the implant for 51 sec. Power was 10 mW CW Fiber area of 0.02827 cm^2 total dose of 86 J per application per day. Repeated 7 sessions every 48 h	Machined implants with poor initial stability	Tiba bone 30 male white New Zealand rabbits	Removal torque values	The mean removal torque value found in the laser group was statistically higher than in the control group in the initial stages of bone healing (15 and 30 days). After 45 days, no significant difference was observed.
García-Morales et al. (2012)[30]	GaAlAs (830-nm)	830 nm, 86 mW, 92.1 J/cm^2, 0.25 J, 3 sec/point, at 20 points Spot size: 0.0028 cm^2 The irradiations were repeated strictly every 48 h for the first 14 days (7 irradiations)	Implants of 3.8 × 11 mm	In 19 human patients	Stability by means of RFA	No evidence was found of any effect of LLLT on the stability of the implants when measured by RFA. Since high primary stability and good bone quality are of major relevance for a rigid bone–implant interface, additional LLLT may have little impact macroscopically.
Primo et al. (2013)[31]	830 nm	40 mW, 0.60-mm spot diameter 4.8 J/cm^2 in 4 different sites around the implant 121 sec	Machined implants, acid-etched implants, or machined implants irradiated around the implant area with infrared low-level laser	24 Implants were placed in the femurs of 12 Wistar rats Group A (control) ¼ smooth Ti; Group B ¼ acid etching (rough); Group C ¼ smooth Ti+LLLT immediately after surgery	Removal torque and bone-implant interface resistance	A rough surface significantly improved BIC compared with smooth implants, No differences were observed in the comparison of rough surface implants with smooth implants irradiated with LLLT.

(*continued*)

Table 3. (Continued)

Author (year)$^{Ref.}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/groups*	*Evaluations*	*Main results*
Boldrini et al. (2013)[32]	808 nm	50 mW, to emit radiation in collimated beams (0.4 cm^2), for 1 min and 23 sec, and an energy density of 11 J/cm^2. 2 Applications (22 J/cm^2) were performed immediately after bed preparation for implant installation.	Ti implant (2.2 × 4 mm)	Tibia of 64 Wistar rats	Torquimeter after removing of implants after 7, 15, 30, and 45 days installation	In both groups, torque values tended to increase over time; and at 30- and 45-day periods, values were statistically higher for the LLL group in comparison to control (ANOVA test, $p < 0.0001$). Thus, it could be suggested that a single session of irradiation with LLL was beneficial to improve bone-implant interface strength, contributing to the osseointegration process.
Mandić et al. (2015)[33]	637 nm	40 mW, CW, repeated every day in the next 7 days The total irradiation dose per treatment was 6.26 J/cm^2 per implant	Self-tapping implants ($n = 44$) were inserted (4 × 10 mm) Follow-up took 6 weeks	Posterior maxilla of 12 patients (split-mouth)	ISQ, ALP activity Early implant success rate	Irradiated implants achieved a higher stability compared with controls during the entire follow-up, and the difference reached significance in the 5th postoperative week. The difference in ALP activity between the groups was insignificant at any observation point. The early implant success rate was 100%, regardless of LLLT usage.
Gomes et al. (2015); Mayer et al. (2015)[23,34]	830 nm	Three 5 J/cm^2, 10 J/cm^2, and 20 J/cm^2 Power: 50 mW applied every 48 h for 13 days, starting immediately after surgery	Dental implant (3.25 mm diameter 11.5 mm, Nano-Tite; BIOMET 3i)	Fresh socket implantation of mandibular incisor of 32 male New Zealand rabbits Control group (nonirradiated animals) and 3 experimental groups that received LLLT (group E5 = 5 J per session; group E10 = 10 J per session; group E20 = 20 J per session)	ISQ, BIC, SEM, and stereology	Better ISQ for the 20 J/cm^2 group ($p = 0.003$) BIC values were significantly higher ($p < 0.05$) in the 20 J/cm^2 group, on both SEM and stereology. Bone area values were better in the 10 and 20 J/cm^2 groups compared with the control group. Under these conditions, LLLT enhanced peri-implant bone repair, improved stability, BIC, and bone neoformation.

(*continued*)

Table 3. (Continued)

Author (year)$^{Ref.}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/groups*	*Evaluations*	*Main results*
Mayer et al. (2016)[26]	830 nm	50 mW, CW, 0.0028 cm^2 10 J per spot, 2 spots per session, 7 sessions	Ti implants Nanoparticle-treated-surface	Immediate implantation of left Mandibular incisor of 14 New Zealand rabbits	Resonance frequency analysis Micro-CT to evaluate the amount of newly formed bone around the implants	Higher ISQs at 30 days and greater percentage of newly formed bone around the implants was observed in irradiated animals. Laser therapy could provide greater implant stability and increase the volume of peri-implant newly formed bone.
Blay et al. (2016)[35]	680 and 830 nm	Noncontact CW 680 nm laser spot size: 4 mm 830 nm laser spot size: 400 μm 4 J/cm^2 per point 40 sec in 2 points on each side of the tibias 10 sessions every 48 h	Ti implants	60 Implants in 30 rabbit proximal metaphysis of the tibia 3 groups Control 680 L 830 L	Resonance frequency and removal torque values	RFA values were significantly different between baseline and the values obtained after 3 and 6 weeks. Removal torque values of all groups increased after 6 weeks; both laser groups presented greater mean values compared with control. Acceleration of the bone integration process in laser groups
Torkzaban et al. (2018)[36]	940 nm	100 mW, CW Spot area 0.2826 cm^2, and average power density (irradiance) of 354.6 mW/cm^2 Irradiated for 40 sec (14.18 J/cm^2 energy density) from each side Laser irradiation was repeated at 2, 4, 6, 8, 10, and 12 days postoperatively, and the final dose was 56 J (accumulated energy of all 7 sessions)	4 or 4.5 mm diameter and 10- or 11.5-mm length	Maxilla of 19 patients	ISQ	Statistical test revealed no significant difference in the mean values of implant stability between the test and control groups over time ($p = 0.557$). However, the mean values of implant stability changed significantly in both groups over time ($p < 0.05$). Although the trend of reduction in stability was slower in the laser group in the 1st weeks and increased from the 6th to 12th week, LLLT had no significant effect on dental implant stability.
Do Prado et al. (2018)[37]	808 nm	CW, 100 mW; 0.69 cm; 40 sec first session directly on bone, then transcutaneously at 48-h intervals, for 7 days 4 J/cm^2—4 points total of 16 J/cm^2 per session, total treatment dose of 122 J/cm^2	80 Rough threaded dental implants with and without calcium phosphate (CaP) coating	Tibia of 20 male New Zealand rabbits G1: implant G2: implant+CaP coating G3: implant+LLLT G4: implant+CaP coating+LLLT	BIC Reverse torque	In short evaluation periods (1, 2 weeks), G2, G3, and G4 showed significantly greater BIC than G1—no difference after 6 weeks. Removal torque test at 6 weeks was higher in G2 and G4. Both CaP coating alone and using LLLT induce cellular stimulation and improve BIC in short-term healing, resulting in higher implant fixation.

(*continued*)

TABLE 3. (CONTINUED)

Author (year)$^{Ref.}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/groups*	*Evaluations*	*Main results*
Gileva et al. (2018)[38]	808 nm	250 mW, 14 kHz, a defocused beam of 4.5 × 1.0 cm, a power flux density of 14.4 J/min at peak (3.2 J/cm^2 per min) at the stages of preoperative preparation and postoperative follow-up 2 times a day (16 min total), 7–10 days, and 3–5 sessions after implant uncovery 8 min each session	Ti implants (NanoTec surface; Alpha-Bio Tech)	30 Patients 136 Implants (79 case 56 control)	Secondary stability indicators (ISQ2) Osstell, determined by the frequency-resonance method (Osstell ISQ)	Primary implant stability in patients of both groups was normal. Intragroup, as well as individual indicators of secondary stability of implants when complex of dental implantation included the laser therapy in preventive and therapeuticrehabilitation regimes met the criterion of excellent and exceeded the indicators of primary stability by 14.6% compared with a significant but lower 5.9% increase in the ISQ value of the control group.
Karaca et al. (2018)[39]	Diode	86 ± 2 mW Laser spot size: 0.0028 cm^2, energy density: 92.1 J/cm^2, and an energy of 0.25 J per point 3 sec per point, in contact Total delivered energy was 5 J, equally divided by 20 irradiation points The first irradiation was performed in the immediate postoperative period at 20 points: 9 points at the vestibular region, 9 at the lingual, 1 at the distal, and 1 at the mesial region of the implant. Repeated every 2 days for 2 weeks	Ti implants DTI implant systems	25 Patients 100 immediately loaded implants Group 1: LLLT group, Group 2: ozone therapy 80% 3 min group Group 3: ozone therapy 80% 6 min group, and Group 4: control group	VAS ISQ values (Osstell) 3, 6 months	Overall implant survival rate was 92% after 6 months ISQ values were found to be significantly higher in Group 1 (LLLT group) and Group 3 of ozone therapy. At 6 months, G2 control had no sig difference. Both LLLT and ozone therapy with prolonged application time are promising methods to enhance bone healing around immediately loaded implants and increase implant stability.

(*continued*)

Table 3. (Continued)

Author (year)$^{\mathrm{Ref.}}$	*Wave length*	*Irradiation parameters*	*Implant type*	*Study population/groups*	*Evaluations*	*Main results*
Memarian et al. (2018)[40]	626 nm LED 810 nm, Diode	50 mW, 20 J/cm^2 400 sec for each implant, laser diameter: 1 cm^2 (fiber 400) LED: 20 mW/cm^2 array area: 4.80 cm^2, average intensity: 38.5 mW/cm^2, total power: 185 mW, total energy: 222 J, and average density: 46.2 J/cm^2 LED device had 8 emitters with a power of 23.125 mW Irradiation was from outside the mouth; other important parts were coved by aluminum foil Implants were irradiated on the day of surgery (zero), 3, 7, 10, and 14 days from buccal mucosa	Ti implants DIO implants (invasive fungal infections-tissue level)	3 Implants in areas of midline and canine of 12 patients 1 in the midline and the other 2 at the left and right canine teeth positions Using coin drawing, 1 implant was considered as control and the other 2 were exposed to LED or laser radiation (LED, control, LLLT)	Implant stability (Periotest) 3, 4, and 8 weeks GCF IL-1β and PGE2 4, 8 weeks	The use of LLL or LED has a positive effect on the stability of the implants 3 weeks after surgery. Laser and LED had no effect on the level of IL-1β and PGE2 in 4 and 8 weeks.
Mohajerani et al. (2019)[41]	830 nm laser 632 nm LED	Laser: 10 mW, 0.0015 cm^2 LED: 10 mW/cm^2 for 20 min every day for 10 days 4 Points around the implants	Ti implants (Zimmer, USA)	58 Patients G1, patients received LLL and LED 20 min/day for 10 days after implant insertion. Patients in G2 (controls): no irradiation	The ISQ was measured at 0 (time 0), 10 (time 1), 21 (time 2), 42 (time 3), and 63 days (time 4) after implant placement.	Results demonstrated an increase in the amount of ISQ in group 1 (intervention) at times 1, 2, 3, and 4. In the control group, the amount of ISQ decreased on days 10 and 21 after implant insertion, but increased afterward on days 42 and 63. LLL and LED increased the stability of the implants after 9 weeks of follow-up.

ALP, alkaline-phosphatase; ANOVA, analysis of variance; GCF, gingival crevicular fluid; IL, interleukin; LED, light-emitting diode; RFA, resonance frequency analysis.

Table 4. Characteristics of Included Studies: Effect of Photobiomodulation on Mini-Titanium Implants/Miniscrew Stability and Success

Author (year)$^{\text{Ref.}}$	*Wave length*	*Type of irradiation*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Omasa et al. (2012)[42]	830 nm	200 mW, CW 195 J/cm^2, 135 sec 2 points Spot size 4.2 mm diameter noncontact Total energy corresponding to 270 sec of exposure was 54.0 J The mesial and distal sides of the mini-implant, 54 J per session Once a day during 7 sessions	78 Ti mini-implants	6-week-old male rats	Stability (Periotest) New BV around the mini-implants Gene expression of BMP-2	Periotest values were significantly lower (0.79- to 0.65-fold). Volume of newly formed bone was significantly higher (1.53-fold) in the LLLT group. LLLT also stimulated significant BMP-2 gene expression in peri-implant bone (1.92-fold). LLLT enhanced the stability of mini-implants placed in rat tibiae and accelerated peri-implant bone formation.
Uysal et al. (2012)[43]	LED 618 nm	20 mW/cm^2 output power irradiation (20 min/day) was applied to the miniscrews for 10 days,	60 Ti mini-implants	Tibia of 15 New Zealand white adult male rabbits Irradiated and control groups under different force levels (0, 150, and 300 cN)	ISQ	Significant increase was found in ISQ values of LPT applied miniscrews in all force groups. By the increase of force levels, it was determined that ISQ values decreased in nonirradiated control miniscrews.
Pinto et al. (2013)[44]	DMC Equipment, Whitening Laser Model II	For 21 days, starting after surgery, with an interval of 48 h between each laser application, totaling 10 sessions at the end of the experiment Irradiation was performed in 2 points: externally and internally to the tibia, at a fluence of 90 J/cm^2 for 25 sec, resulting in energy of 2.5 J	Orthodontic mini-implants: 16 were self-threading (Titanium Fix) and 16 were self-perforating (INP)	Tibia of 16 male New Zealand breed rabbits	Stability (mechanical pullout tests)	Statistically significant difference only between group self-threading submitted to laser and all the other groups Low-intensity laser was capable of increasing stability of self-threading in orthodontic mini-implants
Garcez et al. (2015)[45]	780 nm	70 mW for 1 min/spot size of 0.04 cm^2/(dose = 34 J/cm^2)	Miniscrews	5 Landrace's pigs Split-mouth: contralateral side as the control group 50 miniscrews on the buccal side of the mandible and on the palate of the maxilla (immediately loaded with 250 g)	Histological analysis and fluorescent microscopy	Success rate of 60% for the control group and 80% for the laser-treated group. Laser group had less inflammatory cells than the control group, and the bone neoformation around the miniscrew was more intense.

(*continued*)

Table 4. (Continued)

Author (year)^Ref.^	*Wave length*	*Type of irradiation*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Goymen et al. (2015)[48]	810 nm	0.3 W, spot size: 5.85 cm^2, Treatment was initiated immediately after surgery and performed daily for 10 consecutive days 195 per point or 390 sec, releasing an energy density of 10 or 20 J/cm^2	Cylindrical, self-drilling orthodontic miniscrews	68 Self-drilling miniscrews Fibula of 17 New Zealand white rabbits 6 Groups; force application was not performed in the first 3 groups; whereas 150 g of force was applied to others	BIC Cortical bone thickness was histomorphometrically analyzed after 4 weeks	In the 150 g force plus 20 J/cm^2 dosage group, the highest BIC values were observed. There were no statistically significant correlations between cortical bone thickness and BIC values; on the other hand, no significant difference was found among the same groups in terms of cortical bone thickness values. LLLT may be a supplementary treatment method to increase the stability of the orthodontic mini screw.
Ekizer et al. (2016)[46]	LED 618 nm	20 mW/cm^2 over a period of 21 successive days (20 min/day)	Ti orthodontic miniscrews	20 Patients with bilateral canine distalization	Tooth movement measurements (mm) Stability of miniscrews ISQ values IL-1β levels in gingival and peri-implant crevicular fluid	Miniscrew stability was similar between control and LPT groups at baseline (T0) and the 1st month (T1). However, miniscrew stability was significantly increased in the LPT group in 2nd (T2) and 3rd (T3) months. Comparison of tooth movement during 3 different time intervals (T1–T0, T2–T1, and T3–T2) revealed that statistically significantly increased at every time interval after LPT. No statistically significant change was detected in the IL-1β levels between groups positive effect on miniscrew stability.

(*continued*)

Table 4. (Continued)

Author (year)$^{\text{Ref.}}$	*Wave length*	*Type of irradiation*	*Implant type*	*Study population/ groups*	*Evaluations*	*Main results*
Yanaguizawa et al. (2017)[49]	Diode laser (660 nm)	40 mW for 60 sec (total energy of 2.4 J) Light intensity of 0.07 W/cm^2 on the gingival surface and an energy density of 4 J/cm^2 per irradiation (12 J/cm^2 total treatment)	Mini-implants (1.6 mm 7 mm), self-drilling, self-tapping	Inflammation around miniscrews in maxilla of 10 human volunteers	Peri-implant crevicular fluid (PGF) for IL-6 and IL-8	PGF around nonirradiated mini-implants showed higher levels of IL-8. Levels of IL-6 24 h after mini-implant insertion. LLLT modulates the initial inflammation after the insertion of mini-implant, possibly increasing the mini-implant success prognostic and decreasing patient discomfort.
Osman et al. (2017)[47]	Diode laser (910 nm)	0.7 W for 60 sec repeated throughout the duration of 14 days with an interval of 72 h between each application (4 applications)	Miniscrews (loaded 2 weeks later)	Split-mouth design maxilla of 12 patients, 6 males and 6 females	Periotest for miniscrew mobility (before and after loading: 7, 14, 21, 30, and 60 days) Gingival index for peri-implant gingival inflammation	Improve stability of orthodontic miniscrews (not statistically significant) Reducing gingival inflammation around miniscrews

BMP, bone morphogenetic protein; LPT, light-emitting diode-mediated-photobiomodulation therapy.

Table 5. Characteristics of Included Studies: Effect of Photobiomodulation on Proliferation and Viability of Non-osseous Periodontal Cells Around Titanium Implants

Author (year)$^{Ref.}$	*Wave length*	*Type of irradiation*	*Implant type*	*Type of cells/study groups*	*Criteria*	*Main results*
Khadra et al. (2005)[50]	GaAlAs (830 nm)	84 mW 1.5 or 3 J/cm^2	Pure Ti discs	HGF	CFE and CGR after 1, 3, and 24 h, using SEM and an automatic image analyzer Cell viability	Fibroblasts exposed to laser irradiation had significantly higher percentages of cell attachment than the nonexposed cells. CFE and CGR were also enhanced for the irradiated cells ($p < 0.05$). Cell viability was high (490%) in the irradiated and control groups, without significant differences.
Khadra et al. (2005)[51]	830 nm	84 mW 0.75, 1.5 or 3 J/cm^2 distance from the probe to the cell layer was 9 cm	Ti disks	HGF Group I served as a control, group II was exposed to a single laser dose of 3 J/cm^2, and the 3 subgroups in group III were exposed to laser doses of 0.75, 1.5, and 3 J/cm^2	Attachment and proliferation of HGF cultured on Ti implant material	No increase of temperature of the cell cultures occurred before or during laser exposure at any of the doses tested. Both single and multiple doses of LLLT significantly enhanced cellular attachment ($p < 0.05$). The proliferation assays showed higher cell proliferation ($p < 0.05$) in group III at doses of 1.5 and 3 J/cm^2 after 72 h and 7 days, with agreement between staining and enzyme-linked immunosorbent assay in this cellular model, the attachment and proliferation of HGF are enhanced by LLLT in a dose-dependent manner.

CFE, colony-forming efficiency; CGR, clonal growth rates; HGF, human gingival fibroblasts.

were used in conjunction with the keywords previously mentioned for photobiomolulation to find studies on proliferation and viability of non-osseous cells on Ti surfaces after LLLT. After title screening, 25 articles remained, out of which only two studies matched our criteria for this question and they were in vitro studies conducted on non-osseous cells (Table 5).[50,51]

Evidence-based conclusion and recommendation. The effect of low-level light therapy on osteogenic cells has been well studied and there are a great number of studies on this topic. However, we were only able to find two studies by Khadra that had evaluated the effect of 830-nm low-level laser irradiation on pure Ti disks and the response of non-osseous cells (fibroblast cells). The results showed that laser irradiation significantly improved cell attachment, colony-forming efficiency, and clonal growth rates. However, cell viability did not exhibit a significant difference between the laser and control groups.[50,51]

In the second study, different doses of laser irradiation were evaluated. Both single and multiple doses of LLLT were able to enhance the attachment of cells. There was an agreement in the proliferation assay and staining and enzyme-linked immunosorbent assay indicating significantly better results for the group receiving 1.5 and 3 J/cm^2 laser therapy after 72 h and 7 days.[51]

It may be concluded that according to these in vitro studies, the attachment and proliferation of human gingival fibroblasts on Ti may be enhanced by LLLT in a dose-dependent manner and could be beneficial in clinical practice.

Future Recommendations

Laser technology has definitely brought dentistry into a new era. Many new applications based on the fascinating effect of light on oral and dental tissues has become the topic of a great and growing number of researches conducted in this field.

Photobiomodulation is a sensitive procedure and small changes in irradiation or tissue-related factors may lead to major changes in the results and outcomes. Thus, finding out the appropriate settings for reaching favorable and practical results for clinical applications needs to be determined by conducting well-designed in vitro and in vivo studies. Although there are a lot of potential applications for this kind of photo therapy in periodontology and implant dentistry and many researchers have reported positive effects, however, we are still not able to reach evidence-based conclusions for many of its applications or recommend a specific treatment protocol. This is mainly due to the great variation observed in the irradiation parameters used and different study designs of the available literature.

Effective comparison of clinical studies necessitates designing precise randomized clinical trials with longer follow-up periods and similar inclusion criteria for periodontal patients and situations. Since periodontal disease is multifactorial in nature, confounding factors that might affect the progression of disease should also be carefully considered in study designs. Other methodological factors such as sample size calculations, allocation, randomization, and blinding methods should also be considered to reduce the risk of bias of studies. Finally, as mentioned in many systematic reviews and studies in this field, finding the optimal irradiation parameters to reach favorable inhibitory or biostimulatory effects is of great importance; therefore, it is recommended that laser parameters should now be selected based on the current available evidence and comprehensively reported in a standardized manner. In addition, different laser settings need to be comparatively evaluated to reach suitable parameters and evidenced-based protocols and guidelines for clinical application covered within Part I.[52]

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