Lack of clinical evidence on low-level laser therapy (LLLT) on dental titanium implant: a systematic review

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Received: 7 October 2015 / Accepted: 28 December 2015
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Abstract Low-level laser therapy (LLLT) has proved to have biostimulating effects on tissues over which they are applied, therefore accelerating the healing process. Most studies in implantology were focused on a reduction of the duration of osseointegration. There exist few articles analyzing the potential effects of these therapies on the osseointegration of titanium dental implants. The aim of this study was to assess the effect of LLLT on the interaction between the bone and the titanium dental implant and the methodological quality of the studies. We conducted an electronic search in PubMed, ISI Web, and Cochrane Library. From 37 references obtained, only 14 articles met the inclusion criteria. The analysis of the studies shows that most of the experiments were performed in animals, which have a high risk of bias from the methodological point of view. Only two studies were conducted in human bone under different conditions. Several protocols for the use of low-power laser and different types of laser for all studies analyzed were used. Although animal studies have shown a positive effect on osseointegration of titanium implants, it can be concluded that it is necessary to improve and define a unique protocol to offer a more conclusive result by meta-analysis.

Keywords Low-level laser therapy · Dental implants · Osseointegration · Regeneration · Bone remodeling · Biological processes

Introduction

Early scientific research with laser in dentistry was carried out at the beginning of the 1960s and went on until the 1980s. However, it was not until the 1990s that the Food and Drug Administration (FDA, USA) approved for the first time the use of laser, Nd-YAG in this particular case, for the surgery of soft tissues in the oral cavity. Numerous advances have been made since then, and they have led to the generalization of the use of laser, either high- or low-power ones, in the different fields of dentistry for treatment such as of oral mucositis [1], tooth sensitivity [2], osteonecrosis [3], or alveolar osteitis [4] pain in orthodontic treatment [5]. Low-power laser has proved to have biostimulating effects on tissues over which it is applied, therefore accelerating the healing process. In implantology, most studies were focused on a reduction of the duration of osseointegration [6, 7].

Technical background

Lasers may be classified in multiple ways, regarding their active medium, their wavelength, their emission patterns, or other criteria. It is usual to classify them taking into account the power at which they are going to be used. Therefore, two main groups of lasers can be considered: high-power lasers and low-power lasers [8].

Low-level lasers are those that emit within the red spectrum or the near-infrared region with an average...
power from 50 mW to 1 W. Since their action is mainly based on photochemical effects, they have the distinctive property of not raising tissue temperature.

The most common kinds of low-power lasers are (1) gallium arsenide (GaAs) laser (pulsed laser with a wavelength of 904 nm), (2) fiber optic-transmissible gallium and aluminum arsenide (GaAlAs) laser (with a wavelength of 830 nm), and (3) helium–neon (HeNe) laser (with a wavelength of 632.8 nm), the latter emitting within the visible spectrum, specifically the red one.

Since they lack thermal effect, low-energy lasers are not generally used in surgery. Indeed, their power is lower and the area of effect is larger than that in the high-energy ones. Therefore, the heat is dispersed and may not result in alterations of the bone tissue. Nevertheless, they are mainly used because of their cell bio-stimulating, analgesic, and anti-inflammatory actions. Currently, they are mainly applied to accelerate tissue regeneration and wound healing while reducing inflammation and pain [9]. Also, they are frequently used to treat dentin hyperesthesia and to act as an antibacterial disinfecting method in endodontic and periodontal treatments [10].

Biostimulating effects of low-level laser therapy

Early works regarding the use of low-level laser therapy (LLLT), which describe its biostimulating effects, were carried out at the end of the 1960s and the beginning of the 1970s, and their main goal was to observe an acceleration of the healing process in the treatment of chronic ulcers. Their results showed the efficiency of this new kind of therapy, which could generate a possible biostimulating effect on wound healing. Despite the lack of knowledge about LLLT-specific mechanisms, the authors thought that these good results were due to an increase in both epithelial and fibroblast proliferation and stimulation of collagen synthesis and phagocytic activity, as well as of endorphin induction [11].

The proposed theories invoked a possible increase in cell proliferation due to the influence of photoreceptors in the cellular respiration chain and stimulation of the immune response.

The mechanisms through which the photobiostimulation generated by LLLT is produced still remain unclear [12]. It has been suggested that laser radiation promotes cellular redox activity, which plays a vital role in cell regulation since its modification participates in the modulation of many biological processes.

Through angiogenesis stimulation, LLLT has proven its ability to improve bone mineral density of the regenerated bone in distraction osteogenesis cases. This constitutes the phenomenon of photobiomodulation [13], a mechanism that has also been invoked in the case of treatment with allogenic bone graft for bone deficit clinical situations previously to implant treatment [14].

Also, and by the same mechanism, de Souza et al. [15] and Barbosa et al. [16] showed the positive effect of LLLT on bone repair. This effect, which depends on the duration of application and the wavelength, led to a significant decrease in the time required to achieve bone remodeling.

The effects of low-level laser therapy on the osseointegration of dental implants

An objective of dental implant therapy is to achieve an appropriate union between the patient’s alveolar bone and the implant, which is known as osseointegration [17]. This step is likely to occur in the shortest time possible.

Many treatments have been proposed aiming to improve and accelerate bone formation around the dental implant surface. As in the other disciplines of dentistry, LLLT has also been applied on the field of implantology [18].

There exist few articles analyzing the potential effects of these new therapies, especially those of LLLT on the osseointegration of implants. Hence, the aim of this systematic review was to update this topic from the results obtained after the review of scientific literature, in order to understand in a more detailed way the effects of LLLT on the interaction between the bone and the implant, as well as to evaluate its possible influence in the duration of osseointegration and any other relevant circumstances regarding implantology.

Material and methods

We prepared this systematic review by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [19].

Inclusion and exclusion criteria

We included articles that were published from January 2000 to 2015, were published in any language, and were in vitro and in vivo studies (with any animal model) that evaluate the effect of LLLT on the osseointegration of titanium implants. The articles that were not included were observational studies, systematic reviews, and literature reviews.
Search strategy

A computerized literature search was performed by two investigators (JR and RR) using PubMed/MEDLINE, Cochrane Library, and ISI Web. Table 1 shows the search strategy.

Article selection

Two authors (RR and JR) performed all searches and selected articles fulfilling the inclusion criteria independently and in duplicate. Any article that does not clearly meet the criteria after review of the full text was decided by a third author (JC-PF) (Fig. 1). The level of agreement between the reviewers regarding study inclusion was calculated using Cohen’s kappa statistic.

Assessment of risk of bias and methodological quality

The assessment of risk of bias from clinical studies in humans was evaluated by JR and RR following the Cochrane Handbook [20]. The assessment of risk of bias in clinical studies in animal models was evaluated by JR and RR based on the study of Krauth et al. [21] and with the following list of criteria:

Fig. 1  Flow chart
<table>
<thead>
<tr>
<th>Author</th>
<th>Model of study</th>
<th>Size sample</th>
<th>Study intervals</th>
<th>Laser type</th>
<th>Dose, points of application number</th>
<th>Days of laser application</th>
<th>Type of implant and surface</th>
<th>Performed analysis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>García-Morales et al.</td>
<td>Humans</td>
<td>$n = 8$</td>
<td>12 weeks</td>
<td>GaAlAs</td>
<td>Wavelength = 830 nm and 86 mW; 20 points (3 s/point of application) × 0.25 J; total energy density = 92.1 J/cm$^2$</td>
<td>Every 48 h for 14 days</td>
<td>Cylindrical XIVE-S (Dentsply Friadent®)</td>
<td>Resonance frequency analysis</td>
<td>(1) Stability values increased in the irradiated group from day 10, but with no statistical significance (2) Stability values in the irradiated group decreased from day 10 until week 6</td>
</tr>
<tr>
<td>Mandić et al.</td>
<td>Humans</td>
<td>$n = 12$</td>
<td>6 weeks</td>
<td>GaAlAs</td>
<td>Wavelength = 637 nm and 40 mW; total energy density = 6.26 J/cm$^2$</td>
<td>Every 24 h for 7 days</td>
<td>BlueSky® (Bredent, Germany) Implant ø 4 mm and height 10 mm</td>
<td>Resonance frequency analysis</td>
<td>(1) Irradiated implants achieved a higher stability compared with controls during the entire follow-up and the difference reached significance in the 5th postoperative week (2) The difference in ALP activity between the groups was insignificant</td>
</tr>
<tr>
<td>Dörtbudak et al. [7]</td>
<td>Baboons</td>
<td>$n = 5$</td>
<td>5 days</td>
<td>Diode laser</td>
<td>Wavelength of 690 nm and 100 mW; 1 point (1 min/point of application); dose = 6 J</td>
<td>1 day</td>
<td>Implant ø = 5.5 mm; height = 10 mm; acid-etched, sandblasted surface</td>
<td>Histological study</td>
<td>(1) Higher osteocyte viability in the laser-treated group$^a$ (2) Similar resorption area in the laser and control groups</td>
</tr>
<tr>
<td>Khadra et al. [25]</td>
<td>Rabbits</td>
<td>$n = 12$</td>
<td>8 weeks</td>
<td>GaAlAs</td>
<td>Wavelength = 830 nm and 150 mW; 9 points × 3 J/session (20 s/point of application); energy density per point of application = 23 J/cm$^2$</td>
<td>10 consecutive days</td>
<td>Cylindrical ø = 6.25 mm; height = 1.95 mm TiO$_2$-blasted surface</td>
<td>(1) Tensile test (2) Histomorphometric evaluation (3) Energy-dispersive X-ray microanalysis</td>
<td>(1) Higher bone anchorage in the laser-treated group$^a$ (2) Higher BIC % in the laser-treated group$^a$ (3) Higher calcium and phosphorus % in the laser-treated group$^a$</td>
</tr>
<tr>
<td>Lopes et al. [26]</td>
<td>Rabbits</td>
<td>$n = 14$</td>
<td>15, 30, and 45 days</td>
<td>Diode laser</td>
<td>Wavelength = 830 nm and 10 mW; 4 points × 21 J/cm$^2$; total energy density = 85 J/cm$^2$</td>
<td>Every 48 h for 15 days</td>
<td>Cylindrical ø = 2.6 mm; height = 6 mm</td>
<td>Raman spectroscopy</td>
<td>(1) No difference in HA concentration between the laser-treated group and the control group after 15 days (2) Higher amount of HA in the laser-treated group after 30 and 45 days$^a$</td>
</tr>
<tr>
<td>Kim et al. [27]</td>
<td>Rats</td>
<td>$n = 20$</td>
<td>1, 3, 7, 14, and 21 days</td>
<td>GaAlAs</td>
<td>Wavelength = 808 nm and 96 mW; 6 points of application (10 s/point of application); total energy per session = 6.72 J</td>
<td>Every 24 h for 7 days</td>
<td>Implant ø = 2 mm; height = 3.5 mm; thread size of 0.4 mm</td>
<td>(1) Immunohistochemical analysis (2) Histomorphometric analysis</td>
<td>(1) RANKL: higher expression in the laser-treated group than in the control group from day 1, being its expression in bone more evident on days 14 and 21 (2) OPG: higher expression in the laser-treated group than in the control group</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Model of study</td>
<td>Size sample</td>
<td>Study intervals</td>
<td>Laser type</td>
<td>Dose, points of application</td>
<td>Days of laser application</td>
<td>Type of implant and surface</td>
<td>Performed analysis</td>
<td>Results</td>
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</tr>
<tr>
<td>Lopes et al. [28] (2007)</td>
<td>Rabbits</td>
<td>n = 14</td>
<td>15, 30, and 45 days</td>
<td>Laser photobiomodulation</td>
<td>Wavelength = 830 nm and 10 mW; 4 points × 21.5 J/cm²; total energy density = 86 J/cm²</td>
<td>Every 48 h for 15 days</td>
<td>Cylindrical titanium implants (2.6 mm, 6 mm long; DentFix®; Cambuí, Brazil)</td>
<td>Raman spectroscopy and SEM</td>
<td>(1) Difference in HA concentration between the laser-treated group and the control group after 30 and 45 days. (2) Higher bone density in the laser-treated group than in the control group.</td>
</tr>
<tr>
<td>Jakse et al. [29] (2007)</td>
<td>Sheep</td>
<td>n = 12</td>
<td>16 weeks</td>
<td>Diode laser</td>
<td>Wavelength = 680 nm and 75 mW (1) Sinus lift: 1 point (1 min/point of application) with an energy density of 3–4 J/cm² (2) Second surgical phase (implants): 1 point (1 min/point of application) with an energy density of 3–4 J/cm²</td>
<td>Unknown</td>
<td>Histomorphometric evaluation</td>
<td>(1) Sinus lift: no differences in bone regeneration between the laser-treated and control groups after 4 and 12 weeks post surgery. (2) Second surgical phase implants: higher BIC % in the laser-treated group after 4 and 12 weeks.</td>
<td></td>
</tr>
<tr>
<td>Pereira et al. [30] (2009)</td>
<td>Rabbits</td>
<td>n = 12</td>
<td>3 and 6 weeks</td>
<td>GaAlAs</td>
<td>Wavelength = 780 nm; 4 points (10 s/point of application); 7.5 J/cm²</td>
<td>Every 48 h for 14 days</td>
<td>Cylindrical and self-tapping ø = 3.3 mm and height = 6 mm</td>
<td>Histomorphometric evaluation</td>
<td>(1) Higher BIC % in the laser-treated group.</td>
</tr>
<tr>
<td>Maluf et al. [31] (2010)</td>
<td>Rats</td>
<td>n = 24</td>
<td>14 days</td>
<td>GaAlAs</td>
<td>Wavelength = 795 nm; 4 points (2.0 J/cm² by point); totaling a dose of 8 J/cm²/day</td>
<td>Every 48 h for 12 days</td>
<td>2 mm of diameter for 3.5 mm of length (Conexão Sistemas de Próteses, Anujá, São Paulo, Brazil)</td>
<td>Digital torque machine</td>
<td>(1) The experimental group presented larger difficulty for breaking up the implant interface with the bone block than the control group.</td>
</tr>
<tr>
<td>Boldrini et al. [6] (2013)</td>
<td>Rats</td>
<td>n = 64</td>
<td>7, 15, 30, and 45 days</td>
<td>GaAlAs</td>
<td>Wavelength = 808 nm and 50 mW; 2 points of application (1.23 min/point of application); energy density = 11 J/cm²</td>
<td>Two applications for 1 day</td>
<td>Titanium micro-implant (Titanium Fix A.S. Technology, São José dos Campos, São Paulo, Brazil) 4.0 mm in length and 2.2 mm in diameter</td>
<td>Torquimeter</td>
<td>(1) At 30- and 45-day periods, torque values tended to increase which were statistically higher for the LLLT group.</td>
</tr>
</tbody>
</table>

The control group in every day of the study. (3) RANK: similar expression in both groups, though the control group recorded lower values on day 21. (4) Higher bone density in the laser-treated group than in the control group.
Table 2 (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Model of study</th>
<th>Size sample</th>
<th>Study intervals</th>
<th>Laser type</th>
<th>Dose, points of application number</th>
<th>Days of laser application</th>
<th>Type of implant and surface</th>
<th>Performed analysis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primo et al. [32] (2013)</td>
<td>Rats</td>
<td>$n=12$</td>
<td>45 days</td>
<td>Diode laser</td>
<td>Wavelength = 830 nm; 4.8 J/cm² in 4 different sites (121 s)</td>
<td>1 day</td>
<td>1.4 mm in diameter and 3.3 mm in length (Promm Industria de Materiais Cirurgicos Ltda., Porto Alegre, Brazil)</td>
<td>Removal torque test</td>
<td>(1) Implants with a rough surface seem to add resistance to the bone–implant interface compared with smooth titanium implants or implants treated with LLLT ( ^a )</td>
</tr>
<tr>
<td>Massotti et al. [33] (2015)</td>
<td>Rabbits</td>
<td>$n=24$</td>
<td>30 days</td>
<td>GaAlAs</td>
<td>Wavelength = 830 nm and 50 mW at 3 different energy densities per treatment session (E-5, 5 J/cm²; E-10, 10 J/cm²; and E-20, 20 J/cm²)</td>
<td>Every 48 h for 13 days</td>
<td>Conical, self-tapping osseointegrated implant (3.25ø × 11.5 mm, NNT3211; NanoTite; BIOMET3i, Palm Beach Gardens, FL, USA)</td>
<td>Histomorphometric evaluation</td>
<td>(1) Significantly higher BIC and significantly more collagen fibers in group E-20 ( ^a )</td>
</tr>
<tr>
<td>Gomes et al. [34] (2015)</td>
<td>Rabbits</td>
<td>$n=32$</td>
<td>43 days</td>
<td>GaAlAs</td>
<td>830 nm, 50 mW; 5, 10, and 20 J/cm²</td>
<td>Every 48 h for 13 days</td>
<td>3.25 mm in diameter, 11.5 mm (NanoTite; BIOMET3i, FL, USA)</td>
<td>ISQ and SEM</td>
<td>(1) The results showed better ISQ for the 20 J/cm² group ( ^a ) (2) BIC values were significantly higher ( ^a ) in the 20 J/cm² group, on both SEM and stereology (3) Bone area values were better in the 10 J/cm² ( ^a ) and 20 J/cm² ( ^a ) groups compared to the control group</td>
</tr>
</tbody>
</table>

\( ^a \) Statistically significant results
Treatment allocation/randomization It describes whether or not treatment was randomly allocated to animal subjects so that each subject has an equal likelihood of receiving the intervention.

Concealment of allocation It describes whether or not procedures were used to protect against selection bias by ensuring that the treatment to be allocated is not known by the investigator before the subject enters the study.

Blinding It relates to whether or not the investigator involved with performing the experiment, collecting data, and/or assessing the outcome of the experiment was unaware of which subjects received the treatment and which did not.

Inclusion/exclusion criteria It describes the process used for including or excluding subjects.

Sample size calculation It describes how the total number of animals used in the study was determined.

Compliance with animal welfare requirements It describes whether or not the research investigators complied with animal welfare regulations.

Financial conflict of interest It describes if the investigator(s) disclosed whether or not he/she has a financial conflict of interest.

Statistical model explained It describes whether the statistical methods used and the unit of analysis are stated and whether the statistical methods are appropriate to address the research question.

Use of animals with comorbidity It describes whether or not the animals used in the study have one or more preexisting conditions that place them at greater risk of developing the health outcome of interest or responding differently to the intervention relative to animals without that condition.

Test animal descriptions It describes the test animal characteristics including animal species, strain, sub-strain, genetic background, age, supplier, sex, and weight. At least one of these characteristics must be present for this criterion to be met.

Dose–response model It describes whether or not an appropriate dose–response model was used given the research question and disease being modeled.

All animals accounted for It describes whether or not the investigator accounts for attrition bias by providing details about when animals were removed from the study and for what reason they were removed.

Optimal time window investigated It describes whether or not the investigator allowed sufficient time to pass before assessing the outcome. The optimal time window used in animal research should reflect the time needed to see the outcome and depends on the hypothesis being tested. The optimal time window investigated should not be confused with the “therapeutic time window of treatment,” which is defined as the time interval after exposure or onset of disease during which an intervention can still be effectively administered.

Data extraction

Two authors (RR and JR) extracted all data from the selected papers.

Statistical analysis

Given the heterogeneity of the dose, type of laser, and number of applications, it was not possible to perform a meta-analysis and data were analyzed from a descriptive point of view. A Cohen’s kappa statistic was used to evaluate interexaminer agreement on study eligibility and quality using R version 3.1.3 (R Core Development
Results

All search strategies yielded 37 papers. Two investigators (JR and RR) independently identified 18 eligible papers. Interexaminer agreement on study eligibility was high ($k = 0.855, p = 0.042$). One author (JR) extracted all data from the selected papers. Table 2 shows the characteristics of the studies. One study was excluded after contacting the author because it was a book [22]. Two studies were clinical trials on humans, and 12 were clinical trials on animals.

Results of methodological quality assessment

Studies in humans by Mandić et al. [24] do not describe that patients have been randomly selected and allocated through self-selection being a method that provides a high risk of bias. Using the predetermined seven domains for risk of bias assessment, we determined the study of Mandić et al. [24] and García-Morales et al. [23] with a

![Fig. 3 Assessment of methodological quality of studies in animals](image-url)
high risk of bias. Figures 2 and 3 show the assessment of risk of bias and methodological quality.

In animal studies, some authors describe the method of treatment allocation/randomization chosen [25, 30–34]. Only two of the studies were blinded [25, 29]. None of them were concealment allocation and were not described as criteria for inclusion and exclusion and the sample size that provides a high risk of bias.

None of the studies described the dose–response data of each effective animal model or optimal time window for research that provides an unclear risk of bias.

All studies [6, 7, 25–34] report and use minimal morbidity and describe the animal test that provides a low risk of bias. All studies [6, 7, 25, 26, 28–34] explain the statistical method used least such as the study by Kim et al. [27] that provides a low risk of bias. In some studies, it is unclear if there is any conflict of interest [6, 7, 25, 27, 30–32] that provides an unclear risk of bias and other studies [26, 28, 29, 33] may have a possible conflict of interest that provides a high risk of bias. Only in the study of Gomes et al. [34] did there appear to be no conflict of interest that provides a low risk of bias.

In some studies [6, 27, 30, 31], there is unclear compliance with animal welfare requirements that provides an unclear risk of bias and, in studies of Lopes et al. [26, 28] and Primo et al. [32], there is a high risk. The rest of the studies have a low risk of bias [7, 25, 29, 33, 34].

Discussion

In recent years, there has been a great development in research on low-level laser therapies for the dentistry field and a specialized use in areas such as implantology [35–37].

In animal studies, the results in the group irradiated with low-power laser on titanium implants reported beneficial results from the microscopic point of view such as increased bone–implant contact [25, 29–31, 34]; better connection between bone–implant [6]; greater percentage of calcium and phosphorus [25]; greater percentage of calcium hydroxyapatite [26, 28]; increases in the production of OPG, RANKL, and RANK [34]; and no effect on bone resorption [7].

Khadra et al. suggest that in the irradiated group, faster bone maturation [25] helps improve bone healing [26] and increases the cellular activity of tissues [34], with increased activity of ATP \( p < 0.05 \) and a greater increase and viability of the osteocytes compared to the control group (non-irradiated) [7].

In the recommendations by Krauth et al. [21], there is no classification based on the 13 categories or proposed domains. However, the evaluation of each of the items generally reveals that there may be a high risk of bias in animal studies.

Human studies reported no statistically significant results from the macroscopic point of view [23, 24]. This was used in both GaAlAs lasers, but under different bone densities: great [23] and poor [24] as well as different types of implant: no self-tapping [23] and self-tapping [24].

These very poor results in humans can be caused by the implant surface used and applied with the laser dose. Primo et al. [32] revealed that the implant surface may influence the results in addition to the strength of bone–implant interface rough surfaces compared to smooth surfaces or treated with low-power laser. Studies of Massotti et al. [33] and Gomes et al. [34] show that the dose of low-power laser influences the integration of the implant with the bone, agreeing that the dose of 20 J/cm\(^2\) is the most effective. Some authors [23, 25] agree that there is no standard protocol, although laser irradiation has been defined to the field of implantology.

In the studies included in this systematic review, a wide variation in the election of the energy density, the number of applications, and the wavelengths of low-power laser used in implant therapy is observed. The assessment of methodological quality in animal and human studies suggests that it is necessary to determine a specific protocol using a low-power laser that would allow for more conclusive studies with meta-analysis.

Conclusion

As a general conclusion, it should be observed that despite the fact that LLLT has proved to provide multiple benefits regarding tissue regeneration, there are not enough clinical studies which analyze the effects of this treatment on implant osseointegration. It can be drawn from this update that, according to experimental research results, LLLT might be a useful help to the osseointegration process, although in the current state of knowledge, there is a lack of human clinical studies.

References


