

# The Effect of Photobiomodulation Therapy on the Stability of Orthodontic Mini-implants in Human and Animal Studies: A Systematic Review and Meta-analysis



Parnian Razaghi<sup>1</sup>, Janet Moradi Haghgou<sup>2</sup>, Salman Khazaei<sup>3</sup>, Nasrin Farhadian<sup>4</sup>, Reza Fekrazad<sup>5,6</sup>, Leila Gholami<sup>7\*</sup>

<sup>1</sup>Dental Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>2</sup>Department of Periodontology, School of Dentistry, Hamadan Dental Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>3</sup>Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>4</sup>Department of Orthodontics, School of Dentistry, Hamadan Dental Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>5</sup>Radiation Sciences Research Center, Laser Research Center in Medical Sciences, AJA University of Medical Sciences, Tehran, Iran

<sup>6</sup>International Network for Photo Medicine and Photo Dynamic Therapy (INPMPDT), Universal Scientific Education and Research Network (USERN), Tehran, Iran

<sup>7</sup>Department of Periodontology, School of Dentistry, Dental Implants Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

## \*Correspondence to

Leila Gholami, Shahid Fahmideh Blv. Department of Periodontics, School of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran. 654178-38741  
Tel: +988138381894;  
Email: l.gholami@hotmail.com, l.gholami@umsha.ac.ir

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## Abstract

**Introduction:** The present study aimed to systematically explore available literature on the possible impact of photobiomodulation (PBM) therapy on the stability and success of orthodontic mini-implants.

**Methods:** A comprehensive electronic search was conducted in PubMed, ISI Web of Science, Scopus, Cochrane and Embase databases for human and animal studies published until July 2021. Two independent researchers reviewed the studies based on specific eligibility criteria.

**Results:** 15 studies were included in the systematic review after a comprehensive search. Ten studies were included in the meta-analysis. Four were human RCT studies that evaluated the stability with Periotest. Three other human RCT studies and two animal studies had evaluated the Implant stability quotient (ISQ). Two human RCTs that had evaluated displacement of mini-implants were also analyzed. The analysis of Periotest stability results showed a positive effect of PBM on mini-implant stability at 30 and 60 days after implantation ( $P < 0.05$ ). In human studies using the ISQ method, a slight improvement was seen in the PBM groups; however, this was not statistically significant ( $CI = -1.92-2.70$ ,  $SMD = 0.39$ ). In studies that examined the displacement of mini-implants, no statistically significant difference was observed between irradiated and non-irradiated groups ( $CI = -1.92-2.70$ ,  $SMD = 0.03$ ). According to the results of animal studies, which had used the ISQ method, the use of laser was statistically effective in increasing the stability of mini-implants ( $SMD = 1.43$ ,  $CI = 1.00-1.85$ ).

**Conclusion:** PBM therapy can be suggested as an adjunctive clinical method to improve the stability of mini-implant treatment. Further well-designed clinical studies can help establish evidence-based dosing and irradiation protocols.

**Keywords:** Mini-implant, Stability, Photobiomodulation

## Introduction

Proper anchorage is a critical factor in achieving successful treatment outcomes in orthodontics. To that end, the application of mini-implants (mini-screws or mini-implants) as a temporary skeletal anchorage system in orthodontics has made a significant difference in traditional anchorage options.<sup>1,2</sup> Correct application of mini-implants and screws as a new and more efficient

strategy has helped reduce the anchorage instability encountered in traditional anchorage methods. Moreover, they have advantages such as the reduced need for patient cooperation, simple placement and removal, with the minimally invasive surgical procedures of a low cost and a high success rate.<sup>3,4</sup>

On the other hand, despite their high success rate and extensive use, a frequently reported drawback is implant

failure due to lack of stability. Therefore, managing the stability of mini-implants is still a challenging factor that needs to be considered.<sup>5</sup> The stability of mini-implants includes the two stages of initial stability and long-term stability. Initial stability indicates a mechanical connection, which may depend on many factors such as the size and thickness of the cortical bone around the mini-implant screws during insertion and the size and design of the screw and the insertion angle. Long-term biological stability increases during the healing process and is related to bone remodelling and aggregation.<sup>6-8</sup>

To date, many methods have been proposed to help enhance the long-term stability and success of these types of implants. In recent years, the use of low-level laser irradiation regarded as photobiomodulation (PBM) therapy has been considered a safe and non-invasive method to promote bone healing and improve the stability of mini-implants.<sup>9</sup>

PBM is a non-thermal effect of coherent or non-coherent light at cellular levels, resulting in photochemical changes that affect cells' function, proliferation, and migration. Although the underlying mechanisms involved are not yet fully revealed, a confirmed mechanism is increasing cell metabolism and synthesizing adenosine triphosphate (ATP). This form of irradiation stimulates mitochondrial photo-acceptors, causing cells, such as osteoblasts, to proliferate and differentiate. Moreover, PBM seems to modulate the inflammatory response by increasing the inflammatory cytokines to reabsorb the traumatized bone area and improve bone metabolism.<sup>3,10</sup>

Some studies on dental implants have demonstrated the effectiveness of PBM in increasing bone-to-implant contact (BIC) and implant stability, bio-stimulatory effects on the cell, as well as improving the healing and eventually anti-inflammatory and analgesic effects.<sup>1,9-14</sup>

A similar effect may be observed in mini-implants. Therefore, various studies have examined the effect of PBM on these types of implants by different methods. For this reason, the present study aimed to systematically explore previously published literature, both human and animal studies, on the possible impact of PBMT on the stability and success of orthodontic mini-implants.

## Materials and Methods

### Data Sources

This systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search was carried out on relevant documents published in major databases, including PubMed, Web of Science, Scopus, Cochrane, and Embase. The search was performed with maximum sensitivity using a combination of free text and subject heading such as MESH, without any restriction in language and up to July 2021.

### Search Strategy

The following keyword combinations were used for the search strategy:

('mini screw') OR ('mini-implant') OR ('TAD') OR (Temporary anchorage devices) OR ('mini-implant') AND ('photobiomodulation') OR ('bio-stimulatory laser') OR ('therapeutic laser') OR (Phototherapy) OR ('low-level light therapy') OR ('low energy laser therapy') OR ('Low Level Laser therapy') AND ('stability') OR ('success').

Also, to access more resources, a thorough hand search and a review of reference lists of selected articles were performed to identify any other studies. To ensure the correct selection of articles related to the study and the inclusion criteria, two researchers independently (LG, PR) performed an electronic search on the mentioned websites and evaluated the articles. Using academic translators available at the university as well as Google Translate, search for papers in other languages was considered. However, no relevant non-English article was identified.

### Eligibility Criteria

The PICOS considered for the current systematic review were subjects (patients or animals) receiving mini implant/screw anchorage systems, with an intervention of PBM therapy irradiation of any kind compared to a non-irradiated group. A primary outcome of stability and success or evaluation of any inflammatory changes or displacement as secondary outcomes was evaluated. All randomized controlled trial (RCT) studies, non-random intervention studies, quasi-experimental studies, and animal studies were reviewed. Studies were excluded if they had any of the following conditions:

1. Insufficient information about the details of the procedure and the type of laser used
2. Studies in which specimens had severe maxillofacial defects or required orthognathic surgery
3. In vitro studies, case series, case reports, review studies, letters to the editor, personal comments and articles describing the technique without sample reporting.

### Data Extraction

The search results of mentioned databases were entered in Endnote software. After deletion of all identified duplicates in the search, the title and abstracts of studies were evaluated to exclude irrelevant studies, and then the full text of the remaining studies was read entirely and reviewed by two separate researchers. Disagreements between the authors were resolved through negotiations. In order to collect the required information from the entered studies, two extraction forms were designed electronically. The first form included a table for study design information (Table S1) and the second form

covered PBM characteristics data (Table S2).

### Statistical Analysis

The pooled standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated from eligible studies using a random effect model. Subgroup analyses were conducted on data from animal and human studies. Heterogeneity of results between studies was checked using the Q value and  $I^2$  statistic.

$I^2$  statistic values of 25%, 50% and 75% were considered low, moderate, and high heterogeneity. Publication bias was assessed by Begg's and Egger's tests.<sup>15</sup> Statistical analyses were performed at a significance level of 0.05 using Stata software, version 14 (Stata Corp, College Station, TX, USA).

## Results

### Description of Studies

In our systematic search of the mentioned databases,

a total number of 576 studies were found until July 2021 (Figure 1). Duplicate papers were deleted using the options available on Endnote. After the removal of duplicate records and excluding unrelated articles to the subject of the present study by screening the titles and abstracts, 15 articles, of which 9 were human clinical trial studies and 6 were animal studies, were included in the current systematic review (Table S1). Four of the human studies meticulously evaluated the stability of mini-implants by Periotest<sup>3,16-19</sup>; three studies by implant stability quotient (ISQ)<sup>20-23</sup>; one study probed into the position of mini-implants by cone-beam computed tomography (CBCT); and a final study scrutinized inflammatory markers around mini-implants before and after laser irradiation.

Likewise, among the animal studies, several methods were employed to evaluate stability. Two studies used the ISQ,<sup>24,25</sup> one evaluated BIC,<sup>26</sup> and the others ran Periotest,<sup>27</sup> histological tests<sup>28</sup> or mechanical pullout tests.<sup>29</sup> The data

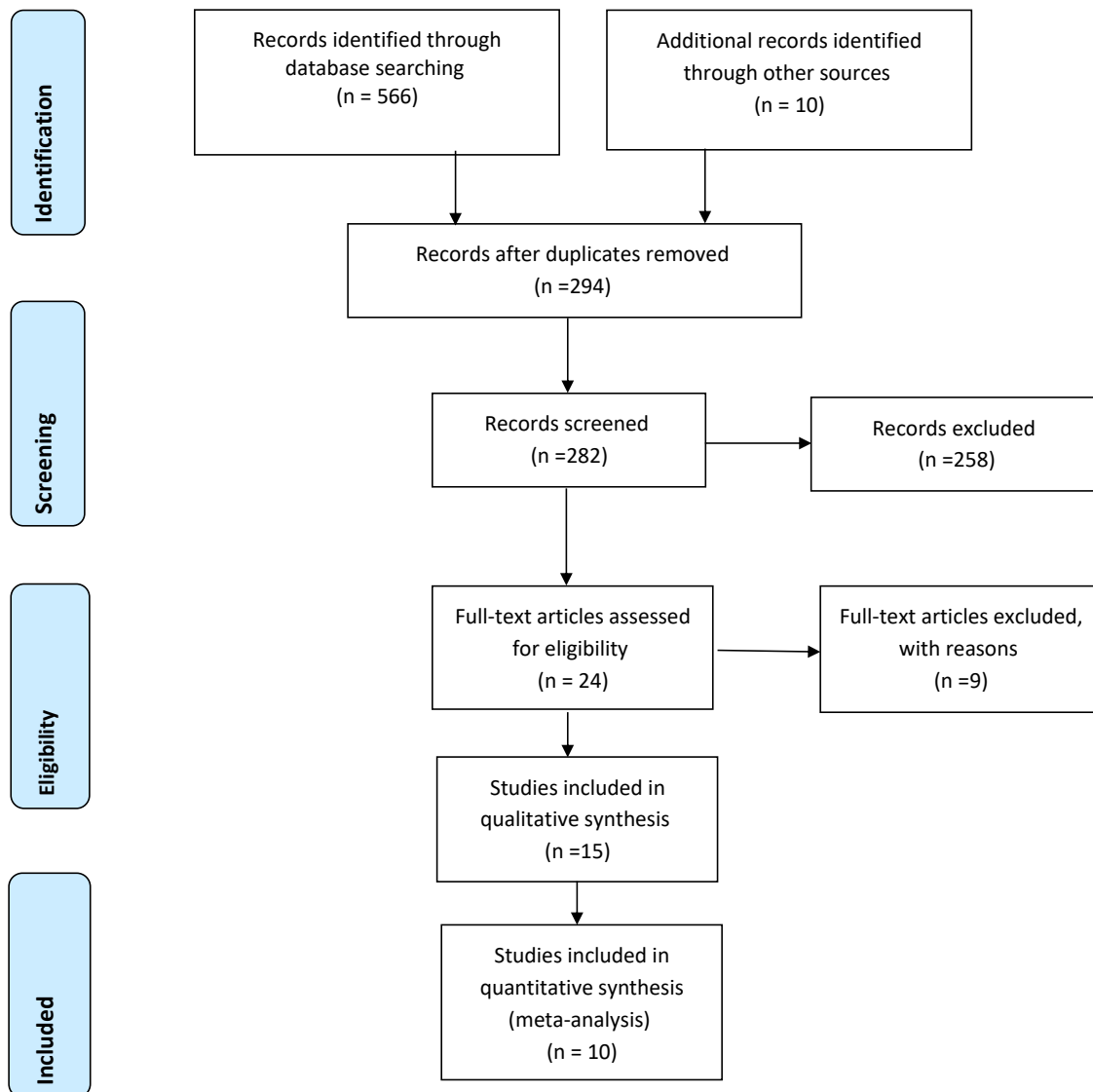


Figure 1. Diagram of the Search Strategy.

were collected after reviewing and deleting studies that lacked quantitative analysis.

Following this step, 10 studies were selected for meta-analysis, including four human RCT studies that used Periotest, three human RCT and two animal studies that assessed the stability with ISQ, and two human clinical trial studies that examined the displacement of mini-implants.

Regarding the parameters of laser irradiation used in the human studies, in general, red and near-infrared wavelengths with a radiant power of less than 200 mW and density energy of 4-37 J/cm<sup>2</sup> have been used. However, variations in irradiation parameters are observed. Similarly, there are variations in the irradiation parameters/protocol used in animal studies, although all have reported positive effects (Table S2).

### Main Analysis

According to the results of studies that used Periotest, the adjunctive laser irradiation significantly accelerated recovery and increased the stability of mini-implants. Stability results were not statistically significant between the studied groups in the early days after implantation (day 0, day 9 and day 15) ( $P$  value > 0.01). In comparison, on days 30 and 60 after the operation, results demonstrated

significantly better results in the laser-treated group than in the control group ( $P$  value < 0.01) (Table S3).

Studies were homogeneous on days 30 and 60 ( $I^2 = 0\%$ ). They showed low heterogeneity on day 0 ( $I^2 = 20\%$ ) and had moderate heterogeneity on days 9 and 15 ( $I^2 = 57.9\%$  and  $I^2 = 56\%$  respectively).

In human studies using the ISQ method, mini-implants were evaluated three months after placement. Results of the analysis were not statistically significant but exhibited that stability in the laser group was better than in the non-irradiated control group ( $CI = -1.92-2.70$ ,  $SMD = 0.39$ ). According to the values of  $I^2 = 96.6\%$  and  $P < 0.001$ , the studies were heterogeneous (Figure 2).

In human studies that used the displacement analysis method, findings showed that the application of an adjunctive laser irradiation improves the stability of mini implants; however, this was not statistically significant ( $CI = -1.92-2.70$ ,  $SMD = 0.03$ ). According to the analysis, these studies were homogeneous ( $I^2 = 0$ ,  $P = 0.549$ ) (Figure 3).

Analysis of animal studies using the ISQ method indicated that the stability of mini-implants in the laser group was significantly better than the control group. ( $SMD = 1.43$ ,  $CI = 1.00, 1.85$ ). Heterogeneity of the studies was low ( $I^2 = 39.0\%$ ,  $P = 0.2$ ) (Figure 4).

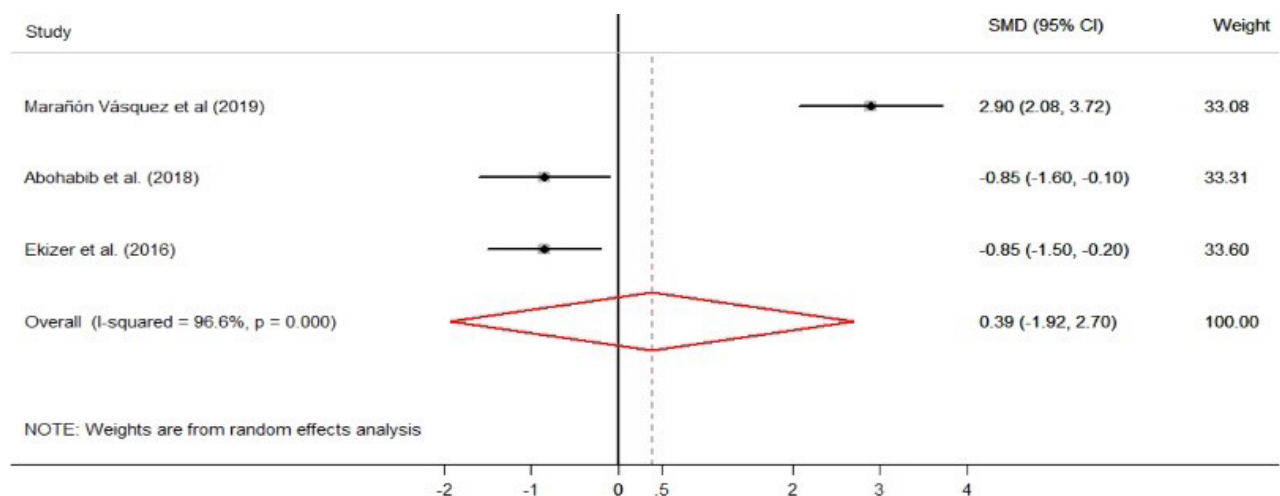


Figure 2. Forest Plot of ISQ Test Results.

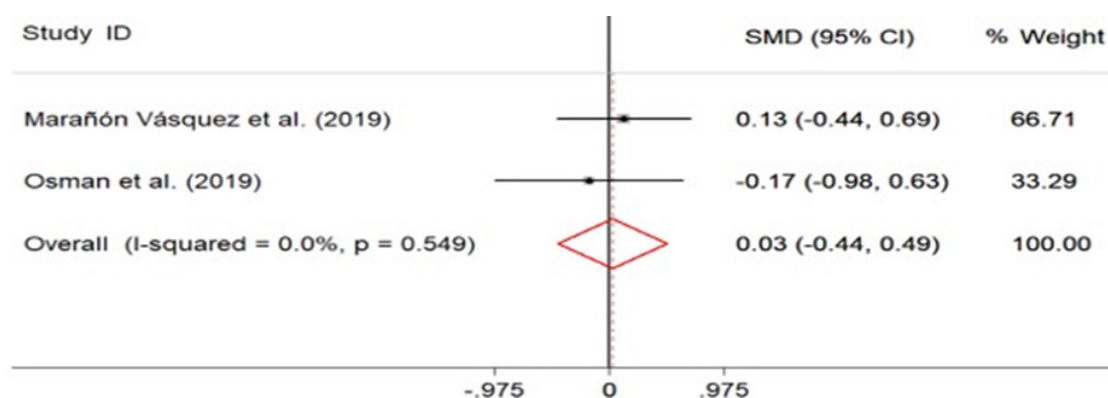


Figure 3. Forest Plot of Displacement Analysis Results.

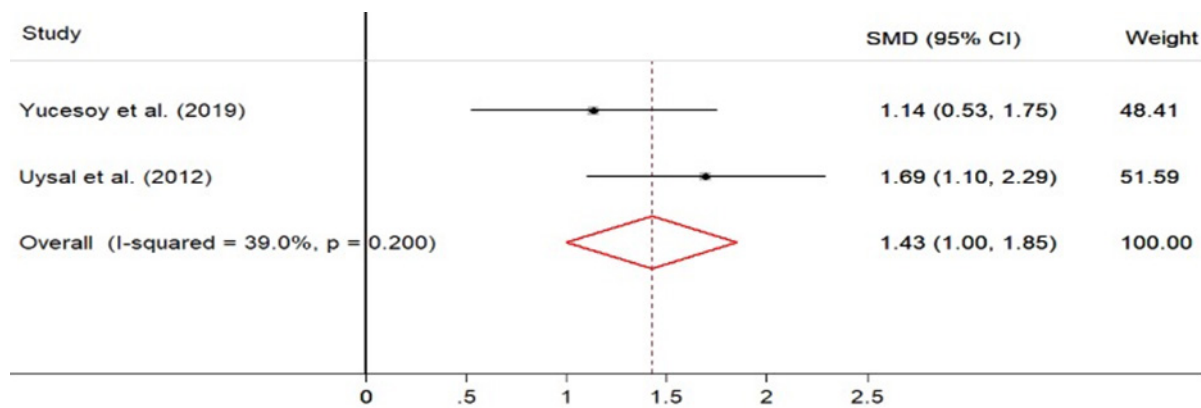


Figure 4. Forest Plot of Animal Studies With ISQ Analysis.

### Publication Bias

Egger's and Begg's tests<sup>15</sup> were used to investigate publication bias. According to the results obtained from these tests and the slope of the line, there was no significant evidence of publication bias ( $P = 0.413$ ).

### Quality Assessment

Risk of bias assessment for all human studies was performed on the modified Jadad scale.<sup>30</sup> Eight main domains were examined in the articles which included: (1) randomization of study, (2) method of randomization, (3) Blinding/masking, (4) method of blinding, (5) clear description of withdrawals, (6) clear description of the inclusion/exclusion criteria, (7) method used to assess adverse effects of study and (8) methods of statistical analysis (Table S4).

Regarding the animal studies, the risk of bias was assessed by the Systematic Review Center for Laboratory Experiment Tool (SYRCLE tool).<sup>31</sup> Ten domains covering the aspects of selection, performance, detection, attrition and reporting were considered to grade the quality of the evidence (Table S5).

### Discussion

In recent years, PBM has been considered a fascinating field for many researchers with many safe and effective potential clinical applications in dentistry, and it needs to be precisely evaluated through well-designed clinical trials and systematic reviews to establish clinical practice guidelines. In the present study, available human and animal research on PBM and its effects on the stability and displacement of mini-implants was investigated and analyzed. Moreover, the effect of a laser on inflammation around mini-implants, post-implantation pain, and mini-implant displacement has also been assessed in the available articles. To the best of our knowledge, three other systematic and meta-analysis studies have been conducted in this field.<sup>32-34</sup> The results of these studies are almost the same; however, our study is the only one that has also examined animal studies. In comparison with

these studies, the number of articles included in human meta-analysis in the present study was higher; moreover, the present study analyzed the reports of human studies on the displacement method by meta-analysis.

### Human Studies

Periotest and ISQ measurements were employed in these studies for the evaluation of the stability of the mini implants. Objective measurements, including resonance frequency analysis (RFA) or Periotest value (PTV), are often carried out to test implant stability and ossification. In the RFA technique, a Smart Peg is placed on the top of the implant, and then the implant resonances are recorded with a magnetic pulse and the frequency is recorded in Hz.<sup>24</sup> Following computer-aided data analysis, the resonant frequency in Hz becomes an ISQ indicator. Higher ISQ values, ranging from 1 to 100, indicate better implant stability and better ossification.<sup>24</sup>

Overall, the results of the present analysis did not identify any statistically significant difference in the stability results of ISQ tests. Nevertheless, Abohabib et al,<sup>20</sup> Mara  n-V  squez et al<sup>21</sup> and Ekizer et al<sup>22</sup> have reported significantly higher ISQ test and RFA results for laser-treated mini-implants over time. The discrepancy between the results in this meta-analysis and the findings of the above studies is probably due to the small number of articles included in the meta-analysis. Further similar designed studies may add to the evidence.

Analysis of Periotest results also indicated that the stability of mini-implants in the laser group is statistically better than the control group over time from day 30 onwards. This trend is observed in studies by Matys et al,<sup>16</sup> Flieger et al,<sup>3</sup> and Osman et al.<sup>17</sup> As demonstrated in Table S2, Matys et al have clearly reported a similar rising trend in mini-implant stability after 30 days with the two laser wavelengths of red and near infra-red.<sup>1,18</sup> Flieger et al<sup>3</sup> have reported that the use of lasers significantly improved the stability of mini-implants even from the third day after treatment. This phenomenon could be explained by the bio-stimulatory effect of PBM on the

inflammatory phase of the bone remodeling after the injury was evoked by placing the implants. After the first 2 hours up to the end of the third day in the peri-implant area, several changes can be observed such as blood clot and granulation tissue formation and the development of a provisional matrix rich in vessels, mesenchymal cells, and fibers. This process is described as fibroplasia and angiogenesis and lasts from the fourth to the seventh day. In the second week of the inflammation phase, a formation of new woven bone is observed. This is the first phase of the osseointegration process.<sup>25</sup> The PBM can change, ameliorate, and improve each process in the first inflammation phase.<sup>3</sup> Further, eligible studies are needed for meta-analysis in this regard.

With reference to the meta-analysis of the studies with the displacement analysis method, the results were not statistically significant, due probably to differences in the study methods such as the methods for evaluating displacement, the amount of force applied, and the follow-up time, which need to be considered in future studies.<sup>21,35</sup>

The reports of the studies indicate that PBM has a definite effect on reducing inflammation around mini-implants, which leads to increased success and reduced patient discomfort.<sup>25,28</sup> Mini-screw insertion causes initial trauma, which in turn produces an inflammatory response in gingival and bone tissues. PBM seems to modulate this inflammatory response and improve bone metabolism and turnover. Unfortunately, due to the heterogeneity of the study design, a meta-analysis of these studies was not possible.<sup>25</sup>

Three human studies have assessed the effect of PBM on pain on the first day of surgery with NRS-11. However, none have reported statistically significant results, and only one study showed that patients in the experimental group reported a shorter range of pain. These studies were also not enough to enable a quantitative meta-analysis.<sup>25,36</sup>

Desired therapeutic results of PBM are highly sensitive to the protocol of irradiation.<sup>37</sup> Consequently, improper laser treatment protocols may reduce the biological effects in the target areas.<sup>6,37</sup>

The effect of the laser may also be masked by the initial stability of the implant. When the initial stability is high enough, small changes in the stability may not be apparent during the measurements.<sup>38</sup> Another limitation as mentioned in Ekizer and colleagues<sup>22</sup> study was the difference between maintaining oral hygiene and patients' tooth brushing habit in the selection of subjects in the studies included in this systematic study, which can reduce inflammation around the mini-implants and increase success.<sup>25,38</sup> Finally, the lack of a classification of patients based on potential confounding factors and variations in follow-up sessions, insertion protocols and mini-implant designs are also the determining factors

that should be considered.

Regarding laser radiation parameters used in the studies included in the present review, although heterogeneity still exists in irradiation settings, red and near-infrared wavelengths with a radiant power below 200 mW and an energy density of 4-20 J/cm<sup>2</sup> used in several sessions with 72 hours intervals seem to have more favorable results.<sup>1,18,22</sup> Instead of a laser, Ekizer et al<sup>22</sup> used a red LED with a low-power density of 20 mW, but with long radiations of 20 minutes per session, rendering favorable results. In the study of Abohabib et al, however, a higher output power and longer radiation intervals (one week) were used, which resulted in no significant positive effects.

In general, it is recommended to use lower power and energy densities of irradiation with longer exposure time and shorter session intervals in PBM therapies. Care should be taken not to use excessive doses of irradiation that can have inhibitory effects on cell activity.<sup>39,40</sup>

### Animal Studies

In most of the animal studies reviewed in the present study, the ISQ test was used to evaluate mini-implant stability. Results revealed that after applying a laser, the stability of mini-implants was enhanced compared to the control group.

Omasa et al,<sup>27</sup> examined the stability of mini-implants by Periotest and reported that PBM improved the stability of mini-implants. They also showed that in the LLLT experimental group, the newly-formed bone around the mini-implants expanded compared to the control group. However, this study was not included in the meta-analysis because the other studies that performed stability measurement with Periotest were human studies.

In the included animal studies, increasing the stability of low-level laser therapy (LLLT) in the experimental group has been observed by various evaluation methods. For instance, Goymen et al<sup>26</sup> found that laser irradiation improved BIC, and Garcez et al<sup>28</sup> stated that the higher success of mini-implants may be due to their anti-inflammatory and bone-stimulating effects. The results of the animal studies and histological reports in the mentioned studies are in line with meta-analysis results of the present study, supporting a positive effect of PBM on the stability of mini-implants.

In the available animal studies, the results have been consistent, and the PBM shows favorable effects. Regarding irradiation protocols in the two studies by Yücesoy et al<sup>25</sup> and Uysal et al,<sup>24</sup> an LED was utilized as a PBM light source. Although a few studies have used diode lasers, there was variation in radiation parameters among these studies.

Notably, the ossification mechanism and functional activities of the tibia, femur, and jaw might vary, and differences may also exist between animal models and the

human body in complexity. This should be considered when evaluating the results of animal studies and developing clinical irradiation protocols.<sup>25,28,41</sup>

## Conclusion

### Human Studies

The results of the present study showed that the stability of mini-implants in all evaluated human studies increased over time in the laser group. These results were statistically significant based on Periotest results on days 30 and 60 after surgery ( $P < 0.05$ ). In studies using the ISQ evaluation method, further improvement was seen in the irradiated groups; however, the results of the meta-analysis were not statistically significant. (CI = -1.92-2.70, SMD = 0.39). Moreover, mini-implant displacement evaluations reported better results for the PBM groups; the meta-analysis however, did not show any statistically significant effect (CI = -1.92-2.70, SMD = 0.03).

### Animal Studies

The results of the meta-analysis performed in the current study, on ISQ stability evaluation of mini-implants, indicated that the use of PBM has positive effects on their stability (SMD = 1.43, CI = 1.00-1.85).

In general, lasers can be suggested as an adjunctive clinical method to improve clinical success with mini-implant treatment. However, long-term studies with a larger study population and similar study designs and irradiation protocols are considered necessary to further validate the results and reach evidence-based optimal clinical protocols.

### Conflict of Interests

The authors declare that they have no conflicts of interest.

### Ethical Considerations

Not applicable.

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### Supplementary files

Supplementary file 1 contains Tables S1-S5.

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