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*Research article*

# Is LASER therapy a viable option for increasing implant stability in bone tissue?

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**Abstract:** Fractures can occur at any age, but in modern times as the worldwide population grows older, the risk increases. Many of the fractures need metallic implants for a more efficient healing process and a reduced risk of complications. An implant can be used in orthopedic surgery if it can safely interact with the bone and the surrounding tissue. The most used materials in fracture management are metal alloys (Steel, Titanium, Cobalt-Chrome) that need to be compatible with tissue, however, they do not stimulate the healing process. Physiotherapy could improve the bone/implant interaction by stimulating the local metabolism and cell proliferation while also reducing local symptoms such as pain. The advantages of using LASER therapy are: a reduced number of contraindications, the availability of the equipment in rehabilitation facilities, and the compliance of patients as there is no discomfort during the procedure. The main drawback of using LASERs in bone stimulation is that there is no consensus in protocol usage between researchers because of the multitude of parameters. Through this article, we aim to shed some light on the use of LASER therapy in implant osseointegration and bone healing.

**Keywords:** implant osseointegration, implant stability, Low-level LASER therapy, Photobiomodulation, Physiotherapy, bone

## I. INTRODUCTION

Fractures can occur at any age and in any individual, however, factors such as age, sex, and the presence of comorbidities could influence the risk. The incidence of osteoporosis is increasing proportionally with the population's life expectancy [1]. Low bone density is correlated to a higher risk of fracture and reduced stability of orthopedic implants [2]. The systemic treatment for osteoporosis increases bone density, but satisfactory results need time, complementary methods of increasing bone density in a certain area should be a priority in order to reduce the risk of complications [3]. Noninvasive therapies such as

Low-Level LASER therapy (LLLT) could prove beneficial in treating regular or pathological bone fractures [4]. Studies suggest that the biostimulation induced by LLLT accelerates the healing process and improves remodeling due to increased hydroxyapatite and collagen deposits, protein expression, and neovascular proliferation. The different energy density levels seem to produce results proportional to the level of energy [5,6].

The LASER acronym stands for Light Amplification by Stimulated Emission of Radiation, and it represents a device that produces a highly collimated beam of monochromatic light composed of photons using an active medium. When the atoms in the active medium receive energy they shift to more elevated orbits, after time varying from nanoseconds to milliseconds they tend to return to lower energy orbits that are more stable releasing energy through photons that form the LASER beam. The active medium can be a solid (neodymium-Nd: YAG), liquid (rhodamine), plasma (argon, krypton), or gaseous (He-Ne, CO2) [7]. One of the advantages of using photobiomodulation for bone tissue stimulation is that it is already available in most rehabilitation facilities for the treatment of various afflictions such as fibromyalgia, tendinopathy, osteoarthritis, neuralgia, epicondylitis, carpal tunnel syndrome [8-13].

LASERs used in musculoskeletal pathologies can be separated into 2 groups LLLT (Low-level LASER therapy) and HILT (High-intensity LASER therapy). The main differences are: wavelength, power, penetration, and tissue temperature changes. LLLT LASERs are represented as class I, IM, II, and III, with a wavelength of 600–980 nm, <1W Power with low penetration <2 cm, and temperature changes <1 °C. HILT LASERs are class IV with a wavelength of 660–1280 nm, power of 1-75W, 5-15 cm penetration, and low thermal accumulation in tissues [14].

LLLT or photobiomodulation is a noninvasive procedure that applies LASER beams emitted through a device that is used in different afflictions for symptom management and stimulatory effects. It is widely used in Rehabilitation Medicine in managing pain, inflammation, edema and tissue damage. The effects of LASER therapy have been proven in neurological, muscular, orthopedic, and rheumatological afflictions.

Some fractures require implants for stabilization and to insure proper alignment [15]. The interaction between bone tissue and implant is called osseointegration, the capacity of the bone and the surrounding tissue to accept the implant and form a stable system [16]. Superior stability can be obtained by stimulating the bone tissue or by augmenting the implants. Most bone implants nowadays are produced using titanium alloys because of their mechanical properties, corrosion resistance, and high biocompatibility [17]. Biocompatibility determines the interaction between a material and tissue. A material that is introduced into a living organism should not produce an inadequate response, it should be either inert or should promote the healing process. The biocompatibility of Ti is determined by the TiO2 film that appears on the surface in contact with Oxygen [18]. Biocompatibility and osseointegration can be improved by adding bioactive coatings (hydroxyapatite, polyether ether ketone, nano-diamonds), surface patterning for a better cell adhesion and orientation or reducing the elasticity module (Young Modulus) [19].

Studies on LLLT impact in tissue healing suggest that Adenosine triphosphate (ATP) and calcium concentration can increase, while Calcium sensitive signaling pathways become more active after stimulation [20-21]. In vitro studies show that osteoblastic differentiation and proliferation are promoted by two transcription factors, RUN-X2 and OSX. Under the influence of the transcription process, the osteoprogenitor cells differentiate into osteoblasts and osteocytes. According to research papers, the RUN-X2 transcription factor is more expressed in bone tissue that has been irradiated by LLLT and the OSX gene is more expressed after 21 days in rats exposed to a LLLT beam with a wavelength of 540 nm [22]. RUN-X2 and OSX factors also upregulate the expression of Osteocalcin, a noncollagenous protein hormone produced by osteoblasts, type 1 collagen most frequently found collagen in bone tissue, and osteopontin, an extracellular structural protein implicated in the remodeling process. Type 1 collagen, osteopontin and osteocalcin are reported to increase after LASER treatment. Photobiomodulation induces neovascularization that helps in bone healing by increasing the metabolic rate in the area. VEGF (vascular endothelial growth factor) and ANGPT-2 (angiopoietin-2) used as signaling molecules in order to assess angiogenesis are reported to also increase when irradiated with a Low-level LASER [23].

There are a series of parameters that can help guide practitioners help manage different diseases. The multitude of parameters can be overwhelming thus leading to misunderstanding of different protocols.

**LASER measurement units/parameters**

- Power (P) is measured in watts (W) and it represents the energy level of the emitted photons. There is Peak power (Pp)- the highest power level the impulse reached and Average power (Ap) – a mean of the power levels of impulses that were emitted in a certain period of time.

- The intensity or power density is measured in W/cm2 and it indicates power per surface unit (the spot size).

- Energy is measured in Joule (J) and it represents power multiplied by time (WxT) indicating the quantity of light in the time frame. As an example, in order to achieve 80 J of energy the LASER beam should have a power of 20 W over 4 sec.

- Fluency or energy density is measured in J/cm2 and it shows the amount of energy per surface unit. If 1 cm2 is irradiated with a 5W LASER in 5 seconds then the energy density would be 25J/cm2 (WxT/surface), however, if the area is 5cm then the energy density is 5 j/cm2.

- Impulse fluency is measured in J/cm and it indicates the energy density for each impulse. Considering that LASER therapy is usually administered in impulses the power or the length of time can vary during a session (low power-long exposure, high power-short exposure) [7].

- Wavelength is measured in nm and it defines the distance of consecutive crest points (the highest points) in a wave. Penetration is determined by wavelength (a higher wavelength corresponds to a better penetration). LLLT wavelength usually ranges from 600 to 1070 nm and understanding the different ranges can help the therapist treat pathology more accurately. Lower ranges of 600 to 700 nm are better for more superficial tissues while wavelengths in the range of 780-950nm are better suited for deeper tissue stimulation. The wavelengths in the 700-770 nm range are not commonly used because they seem to lack biochemical activity [24]. According to White et.al a beam with a wavelength of 808 can penetrate 20% of the tissue, but if the wavelength is 904 nm the penetration reaches 54%. A wavelength of 400 to 700 nm is not highly efficient because 50 to 90% of the energy is being absorbed by skin pigments and the penetration is lower than 1 cm (epidermis) [14].

Apart from describing the LASER beam, some parameters refer to the equipment characteristics such as the type of medium being used (Nd. Yag, CO2, GaAlAs..etc), the diameter of the optic fiber, or parameters that are suited to practical usage, such as distance to the treatment area (in contact or from a certain distance) or type of emission (continuous or in impulses). Modifying each of these parameters could lead to different results.

The multitude of LASER parameters offers the researcher the option of using different approaches in treating pathology. The number of sessions, the number of points of irradiation, or the distance between LASER and the tegument can prove to be important factors that influence the results.

Even though LASER therapy is used in bone research, there is no consensus on what protocols improve bone quality or implant stability because the parameters differ between researchers. In this study, we aim to shed some light on different study protocols that evaluated the osseointegration of Titanium implants in bone tissue. We included two types of studies: 1. Studies that evaluated the effect of LASER photobiomodulation on implant osseointegration in rodents (In vivo experiments) and 2. Studies that evaluated the effect of LASER photobiomodulation on dental implants in the human skull, as there are no studies on orthopedic implant stability after LASER therapy in any other type of bone. We excluded studies that evaluated nonmetallic implants. All studies were found by researching the PubMed and Google Scholar databases.

## II. RESULTS

### II.1 The efficacy of Low-Level Laser Therapy in implant osseointegration in rodents

Studies performed in vivo are necessary for a better understanding of photobiomodulation's role in implant stability. Most used animal models for implant research in vivo are rodents (rats and rabbits) as their size is large enough for surgical practice and LLLT treatment but the housing and feeding logistics remain favorable (Table 1).

**Table 1.** Parameters - LASER therapy on Titanium implants in rodents

| First author | Power (W) | Wavelength (nm) | Total exposure time (s) / session | Number of sessions | Number of points of irradiation | Results |
|---|---|---|---|---|---|---|
| 1. Karakaya M [24] | 0.3 | 940 | 80 | 10 consecutive | 4 | In favor of LLLT |
| 2. Campanha BP [25] | 0.01 | 840 | 202 | 7, 1 every 48h | 4 | In favor of LLLT after 15 and 30 days with no difference at 45 days |
| 3. Gomes FV [26] | 0.05 | 830 | **1.** 102<br>**2.** 202<br>**3.** 402 | 7, 1 every 48h | 2 | In favor of LLLT but only for a fluency of at least 10J/cm$^2$, 20j/cm$^2$ showed the best results |
| 4. Goymen M [27] | 0.3 | 810 | **1.** 190<br>**2.** 395 | 10 consecutive | 1 | In favor of LLLT with a fluency of 20J/cm$^2$ |
| 5. Khadra M [28] | 0.15 | 830 | 180 | 10 consecutive | 9 | In favor of LLLT |
| 6. Kim YD [29] | 0.1 | 808 | 60 | 7 consecutive | 6 | In favor of LLLT (immunohistochemical analysis Rank, Rank L, OPG) |
| 7. Kim JR [30] | 0.1 | 808 | 60 | 7 consecutive | 6 | In favor of LLLT in histological analysis and removal torque test at 12 weeks, but no statistical difference in Micro-Ct scanning or removal torque test at 6 weeks |
| 8. Massotti FP [31] | 0.05 | 830 | **1.** 102<br>**2.** 202<br>**3.** 402 | 7 consecutive | 2 | In favor of LLLT but only if the fluence was 20J/cm$^2$ (5 and 10 J/cm$^2$ similar to controls) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9. | Mayer L [32] | 0.05 | 830 | No Exposure time | 7, 1 every 48h | 2 | In favor of LLLT |
| 10. | Omasa S [33] | 0.2 | 830 | 270 | 7 consecutive | 2 | In favor of LLLT in Periotest, but inconclusive in BMP-2 gene expression and micro-CT imaging. |
| 11. | Prado RFD [34] | 0.1 | 808 | 100 | 7, 1 every 48h | 4 | In favor of LLLT, but the best results were found in groups that received a coated implant (CaP coating) |
| 12. | Primo BT [35] | 0.04 | 830 | 121 | 1 after surgery | 4 | No difference between LLLT protocol and control |
| 13. | Vasconcellos LM [36] | 0.04 | 780 | 100 | 7, 1 every 48h | 4 | In favor of LLLT after 2 weeks in both ovariectomized and non-ovariectomized rats, after that, the results were not conclusive |
| 14. | Lopes CB [37] | 0.01 | 830 | No exposure time | 7, 1 every 48h | 4 | In favor of LLLT only at 45 days, but no difference at 15 days |

As seen in table 1, the wavelength used during LASER therapy in the evaluated studies was set between 780 and 940 nm, with a higher prevalence of 830 nm. As stated before, higher wavelengths show better penetrability and the wavelengths in the aforementioned interval can reach at least 2 cm deep, which is enough considering the type of animals used (rats and rabbits) and the depth of the structure of interest (bone). The power also varied between researchers from 0.01 up to 0.3 W. The time of exposure each session varied from 60 up to 420 seconds per session, and the number of points of irradiation varied from 1 to 9. There was a difference between the number of sessions and the session timing of the irradiation with some of the stimulation being performed daily where others preferred a day off.

The LASER used in all studies was diode probably because of it's disponibility and price. In the research published by Karakaya [24] , Primo [35] and Lopes [37] the nature of the LLLT device was not specified.

There were also differences in the distance of irradiation. Karakaya et.al [24] opted for a distance of 1.5 cm between the handpiece and the tegument. Gomes et.al [26] placed the handpiece directly perpendicular to the mandible. Khadra [24] and Mayer [32] used the handpiece in direct contact with the tegument. Omasa [33] preferred using a distance of 1 mm from the skin. Prado [34] and Vasconcellos [36] used an optic fiber to directly stimulate the bone through a surgical cavity.

1.Karakaya M et.al studied the effects of photobiomodulation on implant stability in 22 ovariectomized rabbits that underwent fracture and implantation of a Ti dental implant in the right tibiae using a device with a fluency of 6J/cm2 per session and a total energy of 60J. The animals were distributed into 4 groups: OVX (ovariectomized) without other interventions, ShamOVX (non-ovariectomized) and no intervention, OVX + LASER therapy, and Sham OVX + LASER therapy. The best results were obtained in the group that received Sham OVX + LLLT, the group that received OVX + LLLT had significantly improved implant stability compared to Sham OVX no LLLT. The micro-CT scan and the removal torque tests showed a significant ($P<0.05$) increase in implant stability in irradiated osteoporotic rats compared to the controls (osteoporotic rats with no LLLT), however, the results of the PerioTest showed no difference between the 2 groups at 6 weeks after surgery [24].

2.Campanha BP et.al evaluated the effect of LASER therapy on Ti implants with poor initial stability (rotation freedom) placed in the tibiae of 30 rabbits. The fluency used was 86 J/cm2 per session with a total energy delivery of 602 J. The bone/implant contact was evaluated through removal torque. At 15 and 30 days there was a significant difference in favor of the LLLT irradiated groups, but after 45 days there was no significant difference between groups. LLLT improved bone-implant contact in the first 15 and 30 days, but the results were similar between groups at 45 days [25].

3.Gomes FV et al. assessed implant stability and bone formation in 32 rabbits that underwent extraction of the left mandibular incisor followed by implant placement. The group compared three different fluencies: 5J/cm2 (35.7 J total energy), 10J/cm2 (70.7 J total energy), and 20J/cm2 (140 J total energy) between each other and to a control group (sham LLLT). After 45 days the animals were euthanized and the stability was assessed through 3 methods Resonance Frequency Analysis, Scanning Electron Microscopy (SEM), and stereology. The parameters assessed in SEM and stereology were BIC (bone/implant contact) and BA (ratio between newly formed bone area and total area of possible bone formation). SEM results showed significantly improved BIC values in 10 and 20 J/cm2 groups compared to the rest, but no difference between 5J/cm2 and sham LLLT. BA values were significantly higher only in the 20J/cm2 group compared to the control. The stereological BIC analysis showed statistically significant differences in all three LASER treated groups (5,10,20J/cm2) compared to the control group, and BA results showed an increase in stability (statistically significant) only for 10 and 20 J/cm2 fluencies. RFA also showed an increase in stability only in the 20J/cm2 compared to the sham group. Although 10J/cm2 was more efficient in most tests than the control group, 20J/cm2 fluency was the most effective dose. 5J/cm2 proved to be a dose insufficient for bone stimulation [26].

4.Goymen M et al researched the cumulative effect of photobiomodulation and force in implant stability on 17 rabbits that received two orthodontic self-drilling mini screw implants in each fibula. The two implants (screws) were connected via a nickel-titanium coil that permitted an applied force of 150 g. There were 2 fluencies used in the irradiated (LLLT) groups 10 (585 J total energy) and 20J/cm2 (1170 J total energy). The animals were divided into 6 groups, and each possible combination was assessed: LLLT (20J/cm2)+150 g force, LLLT (10J/cm2) + 150 g force, LLLT (20J/cm2) no force, LLLT (10J/cm 2) no force, noLLLT+150g force, no LLLT no force. The method of assessment was histomorphometry, BIC (bone/implant contact), and CBT (cortical bone thickness) ratio. BIC evaluation showed a significantly increased contact in all groups, however, the group that received 20J/cm2 LLLT and 150g force presented the best results and the group that received no LLLT and no force was the poorest. All groups that received 20J/cm2 with or without applied force scored higher, but 150g force (no LLLT) was superior to LLLT 10J/cm2 (no force). CBT evaluation showed that the highest score was in group 20J/cm 2 with no force applied, but there was no significant statistical difference to the other groups. There was also no statistical correlation between BIC and CBT [27].

5. Khadra M et al evaluated the osseointegration of coin-shaped Titanium implants in 12 rabbits that received 2 implants in each tibia. In the irradiation protocol used, the fluency was 23J/cm2 with a total energy tissue absorption of 270 J. The assessment methods used were tensile strength test, histomorphometry, and energy dispersive x-ray microanalysis evaluation. Tensile strength evaluation showed a statistically significant difference in the LASER stimulated group. The histomorphometric evaluation showed a 10% higher bone/implant contact in the irradiated group and the x-ray microanalysis showed a statistically significant difference in phosphorous and calcium percentage in the LLLT stimulated group [28].

6. Kim YD et al used immunohistochemical analysis (RANK, RANKL, OPG) to evaluate the effect of LASER therapy on bone formation and implant osseointegration in 20 rats that received Ti implants installed in the tibia. The total energy delivered was 40.32 J, with a power density of 830 mW/cm2. In the group that received LASER therapy, RANKL was more expressed than in the control group starting from day 1 to day 21. OPG was expressed from day 1 in both groups, but in the group that received LLLT the increase in expression was faster and more uniform compared to the control group where it increased slowly. RANK was observed in bone cells from the first day in the LASER irradiated group and it became more expressed during the following days, but in the control group, it was only expressed after 21 days [29].

7. KIM JR et al used histomorphometry analysis, removal torque testing, and resonance frequency analysis (RFA) to evaluate the effects of LLLT on Ti implant attachment in both femurs of 13 rabbits. The power density used was 830 mW/cm2, but the fluency and total energy could not be calculated due to a lack of parameters. Histological findings showed a more pronounced bone matrix and collagen at 6 and 12 weeks (H&E stain and Masson's Trichrome stain) in the stimulated groups. BIC evaluation showed higher contact at 6 and 12 weeks in the LLLT groups but with no statistical significance. Removal torque tests showed no significant difference between groups at 6 weeks, but with a statistically significant difference at 12 weeks in favor of the LLLT group [30].

8.Massotti FP et al. studied the effect of LLLT on the peri-implant bone healing process in 24 rabbits that received Ti implants (with thread) after extraction of the left mandibular incisor through histomorphometry. The animals were placed into 3 groups with different LASER beam fluencies 5, 10, and 20J/cm2 per session and total energy absorption of 35.5, 70.7, 141.4J, and a control group. The higher fluency was acquired through a longer time of exposure as seen in Table 1. BAR% (total area of bone from the 5th to 7th thread on the implant) and BA% (amount of bone within each thread from the 5th to 7th thread) values were the highest in the group that received 20J/cm2 per session, but there were no statistically significant differences between groups, however, BIC (bone-implant contact) and CF(collagen fiber) values showed a statistically significant difference in group 20J/cm2 compared to the rest. BIC and CF showed similar values in the groups that received fluencies of 5 or10J/cm2 and control [31].

9. Mayer L et al evaluated the effects of LLLT on the integration of 14 titanium dental implants that were placed after the removal of the left incisor in 14 rabbits. The total LASER energy absorbed in the tissue at the end of the irradiation period was 140 J with a power density of 17.85 W/cm2 per session. The methods used for assessment were RFA in synergy with a micro-CT scan after euthanasia. RFA results showed significantly higher osseointegration in all groups after 30 days, but with a highly statistically significant difference in favor of the experimental group. Micro-CT scan also showed a higher percentage of newly formed bone in the experimental group (statistically significant) [32].

10. Omasa S et al. studied the biostimulation effects of LLLT on mini-implant osteointegration in the tibial bone of 39 rabbits with a device that used a fluency of 195 J/cm2 and a total energy of 378J. The stability was evaluated at 7 and 35 days after implantation using the following methods: micro-CT scan, PerioTest and BMP-2 gene expression. The PerioTest showed better stability (statistically significant) in the LLLT groups at both times of euthanasia (7 and 35 days). The micro-CT scan showed newly formed bone tissue surrounding the implant 5 days after surgery with a seemingly better result in the experiment group, but no statistical significance. The expression of the BMP-2 gene was significantly higher in the LLLT group 1 day after LLLT, but 3,5, and 7 days after photobiomodulation the expression was similar between groups [33].

11. Prado RFD et al. compared the osseointegration of dental implants with or without Cap (calcium phosphate) coating alone or in association with LLLT stimulation. The LASER beam was directed through the skin with a fluency of 16J/cm2 per session and total energy of 70J. The histological analysis showed no bone formation after the 1st week in any of the groups, but all groups apart from the control displayed higher amounts of trabecular bone. After 6 weeks, all groups displayed similar quantities of bone at the apposition between bone and implant. Histomorphometry after 1 week showed a statistically significant difference in the group that received CaP coating + LASER compared to the control (Ti implants with no additions or LLLT), but no differences compared to the groups that received either just the CaP coating or just LLLT. At 2 weeks the group that received either CaP or LLLT had significantly higher stability compared to the control group, but the group that received both CaP and LLLT had similar stability to the control group. After 6 weeks all groups were similar during histomorphometric testing. The torque test that was performed after 6 weeks showed that the groups that received either CaP coating or CaP + LLLT had significantly higher stability compared to the control. The control group presented the least stable implants and the combination of LLLT and CaP coating seems to be effective in the first 2-3 weeks [34].

12. Primo BT et al. evaluated the effects of surface roughness and LLLT on 24 titanium implants placed in both femurs of 12 rats. They divided the animals in 3 groups: smooth titanium, acid-etched titanium, and smooth Titanium + LLLT (4.8 J/cm2 fluency, 4.84 J total energy). The assessment method was the removal torque test. The only group with higher removal torque values was acid etched one with surface roughness. LLLT did not influence osseointegration, but the irradiation was only done once with a small dose [35].

13. Vasconcellos LM et al. investigated the effect of LLLT (fluency 16J/cm2, 27J total energy) on bone healing in 84 rats with a normal or low bone density that received a titanium implant in their left femur. At first, the rats were split into 2 groups and half were ovariectomized. After the sterilization, all rats were separated again, some received LLLT, and others received sham. Histomorphometry was used for evaluation. At 2 weeks the groups that received LLLT showed a greater quantity of mature bone compared to the other groups. The cumulative bone formation differed over time, at 2 weeks the group that was not ovariectomized but received LLLT showed the best results and the group that was ovariectomized but did not receive LLLT showed the poorest. At 4 weeks the cumulative bone formation did not differ. At 6 weeks the best results could be seen in the group with sham ovariectomy and LLLT. In the ovariectomized group a significant difference could be observed only at 2 weeks in favor of LLLT. In the non-ovariectomized groups, there was a difference in favor of the LLLT group at 2 and 6 weeks [36].

14. Lopes CB et al evaluated the bone quality and healing in 14 rabbits that received a dental titanium implant on 1 tibia and LLLT through Raman spectroscopy. The device used a fluency of 85J/cm2 per session and a total energy of 602J. At 15 days there was no significant difference between groups but up to the 45th day the irradiated group showed a statistically significant difference compared to the controls [37].

### II.2 The efficacy of Low-Level Laser Therapy in dental implant osseointegration in patients

The effect of Low-level LASER therapy has been researched in peri-implantitis, peri-mucositis, and the osseointegration of implants in the human alveolar bone. Compared to in Vivo tests performed on rodents, protocols used in Dental Medicine have even more differences and there is no consensus on parameter usage (Table 2).

**Table 2** Parameters – LASER therapy on Titanium stomatological implants in patients

| First author | Power (W) | Wavelength (nm) | Total exposure time (s) / session | Number of sessions | Number of points of irradiation | Results |
|---|---|---|---|---|---|---|
| 1. Arakeeb MAA [38] | - | 808 | 60 | 6, 1 every 48h | 2 | LASER proved a negative effect on L-PRF screws, resulting in poor osseointegration |
| 2. Flieger R [39] | 0.1 | - | 200 | 7, Immediately and on days 3,6,9,12,15,30 | 2 | In favor of LLLT |
| 3. Gulati P [40] | 0.1 | 980 | 60 | 4- immediately and on days 3,7,14 | 6 | In favor of LLLT, but only at 6 months and 1 year (no difference at 6 weeks) |
| 4. Matys J 2019 [41] | 0.1 | 635 | 80 | 7- 1 before surgery, 2 immediately after and on days 2,4,6,14 | 2 | In favor of LLLT using the Periotest device, but no difference in CBT testing |
| 5. Mikhail FF [42] | 0.2 | 904 | 30 | 9- 3 sessions per day on days 3,6,9 | - | In favor of LLLT |
| 6. Lobato RPB [43] | 0.05 | 808 | 498 | 2- 1 before surgery, 1 after | 6 | No statistical difference between LLLT and control |
| 7. Matys J 2020 [44] | 0.1 | 808 | 80 | 7- in the days 1,3,6,9,12, 15,30 | 2 | In favor of LLLT but only after 30 and 60 days, no difference before |
| 8. Mehdyiev I [45] | 0.025 | 630-660 | 360 | 4, 1 every 48 h | 3 | In favor of LLLT |
| 9. Garcia-Morales JM [46] | 0.086 | 830 | 60 | 7 every 48 h | 20 | No statistical difference between LLLT and control |
| 10. Osman A [47] | 0.7 | 910 | 60 | - | 1 | No statistical difference between LLLT and control |
| 11. Torkzaban P [48] | 0.1 | 940 | 80 | 7, 1 every 48 h | 2 | No statistical difference between LLLT and control |

As seen in table 2, the wavelength used in the irradiation protocols varied from 630 nm to 980 nm. Power varied between 0.025 and 0.1 W. There were important differences in time of exposure per session ranging from 30 to 498 seconds. In dental research, the authors used very different protocols compared to the in vivo studies performed on rodents where there were fewer variations in the number of irradiation sessions. Some of the authors used standard physiotherapy protocols (consecutive sessions 1 every other day or 1 every 48 hours) [38, 45, 48] while others decided to change the time in between sessions (no reason was given). In some of the protocols the LASER stimulation was performed before the surgery and others increased the number of sessions carried out in a single day. The number of irradiation points varied from 1 to 20, but most authors preferred using 2. The authors did not specify the distance of irradiation.

1. Arakeeb MAA et al. measured the level of osseointegration of 40 dental Ti implants placed in 40 male patients with missing teeth. The exact location of the implant was not specified. The patients were randomly allocated to 4 groups: Titanium with no augmentation, Ti + LLLT, Ti + leukocyte and platelet-rich fibrin (L-PRF), Ti + LPRF + LLLT. The device used a LASER with a beam fluency of 20J/cm2 per session, but the total energy delivered to the tissue could not be calculated due to the lack of parameters listed. Relative bone density (RBD) was measured through cone beam computed tomography at 1, 6, and 12 weeks after insertion. The only significant difference was at 6 and 12 weeks in group Ti+L-PRF compared to the rest. There was no significant difference between the other groups, even though the groups that received LASER (either alone or in addition to L-PRF) showed better results, but with no statistical significance. The LLLT had an inhibitory effect on L-PRF because of the activation of osteoclasts [38].

2. Flieger R et al used photobiomodulation on 20 patients that received 40 Mini-implants placed between the second premolar and first molar teeth, 2 mm below the mucogingival junction on both sides of the maxilla. The bone was stimulated on one of the implants in each patient with a power density of 199.04 mW/cm2 and a total energy of 140J. The implant stability was measured through a Periotest device immediately and at and 3, 6, 9, 12, 15, 30, and 60 days after the insertion. There was significantly higher stability in the LLLT group at 3, 30, and 60 days, but no difference in pain reduction [39].
3. A pilot study elaborated by Gulati P et al evaluated the level of crestal bone resorption in 20 patients that received 20 implants in place of the first mandibular molar through digital intraoral periapical radiographs (IOPA) cone beam computed tomography (CBT). Half of the subjects received LASER therapy with a beam fluency of 24 J/cm2 and a total energy of 24J. The results of IOPA reveal a significant difference in crestal bone loss at 6 months and a year, the irradiated group proving better stability than the control, but no difference at 6 weeks. There were no significant differences between the implant osseointegration in the same group. The CBT examination showed significantly better results in the LLLT group at 6 months, and 1 year [40].
4. The study conducted by Matys J et al in 2019 aimed to evaluate the stability(primary and secondary) and bone density in the peri-implant zone of 40 titanium implants placed in the posterior region of the mandible in 24 patients. Half of the patients received LLLT with a beam power density of 199.04mW/cm2 and a total energy of 56J. The implant stability was assessed through a Periotest device and the bone density was measured through CBT. The Periotest evaluation revealed no difference in the first 2 weeks, but after that, at 4 and 8 weeks, the irradiated group was proven to have significantly increased stability. However, after 12 weeks there was again no difference between groups. CBT measured in 3 points (cervical, middle, and apical) showed no difference after 4 weeks. Significantly higher values in bone density were observed in the LLLT group only after 12 weeks [41].
5. Mikhail FF et al evaluated the effect of LLLT used in synergy with oral supplementation of Vitamin C (500 mg)+ Calcium (500)+ Omega 3 (1000 mg) on the osseointegration of Ti implants placed in the mandibular first molar region of 20 patients. Only half of the patients received LASER therapy, but both received supplements. The LASER used a device with a fluency of 4.7 J/cm2 and a total energy of 42.3 J. The method of assessment chosen was radiographic panoramic imaging (greyscale) taken right after implant and at 1.5 and 6 months. Results showed that both groups had statistically significant changes for the better at 1.5 and 6 months compared to implantation, however, the LLLT group exhibited better bone density values in all 3 points of interest (apical, distal, and mesial at 1.5 and 6 months) with a statistical significance. Dietary supplementation with vitamin C, Omega 3, and Ca improves bone quality, but the association with LASER therapy further improves osseointegration [42].
6. Lobato RFB et al. Measured the stability of 50 titanium Implants placed in 44 patients (the region is not specified). Half of the patients received LASER therapy with a fluency of 62.25 J/cm2 and total energy of 132 J. The method of assessment was the Ostell device with ISQ (implant stability coefficient) and digital periapical radiographs at 2 different times T0 (implant time) and Ta (time of abutment- time of crown placement on the Ti implant). There was no statistical difference between the controls and the groups that received photobiomodulation at the abutment installation time on ISQ or radiography [43].
7. Matys J et al used LASER therapy to improve implant stability of 44 patients implants placed in 22 patients. Each patient received LLLT with a fluency of 16J/cm2 and a total energy of 56 J on one of the implants, the other was used as a control. The method of assessment was Periotest and the implant stability was measured right after surgery and 3, 6, 9, 12, 15, 30, and 60 days after implant placement. The only statistically significant difference was at 30 and 60 days in favor of LLLT. There was no difference in pain management between the control and therapy groups [44].

8. Mehdyiev I et al observed the effects of LLLT on bone formation in 12 patients that required bilateral sinus floor augmentation for implant prosthetic rehabilitation. All patients required bilateral sinus augmentation with simultaneous implant placement (24 augmentations). The LASER beam fluency was 72 J/cm2, but the total energy was not specified and it can not be measured due to a lack of parameters (surface of irradiation). The method of assessment was panoramic radiographic imaging. 4 panoramic radiographs, one preoperative and three postoperative (1st, 3rd, and 6th month), were taken for each patient. There was a significant increase in bone density at 1, 3, and 6 months in the therapy group. However, the increase in bone tissue increased in the first month, then it decreased slightly at 3 months, and then at 6 months, it increased again [45].
9. A double-blinded study conducted by Garcia-Morales JM on 30 Ti implants placed in the posterior region of the maxilla of 8 patients (16 LASER- 14 control) evaluated the effect of LLLT photobiomodulation on stability. The method of assessment used was Resonance Frequency Analysis (RFA- Ostell Device). Each patient had at least a control and an implant with LLLT. The measurements were performed after 10 days, 3, 6, 9, and 12 weeks. The LASER beam fluency was 92,1 J/cm2 but the total energy was not specified. No statistically significant difference between the ISQ means between the 2 groups at any time interval. In the control group, the stability gradually increased over time, but the LASER irradiated group experienced fluctuations in stability with a peak after 10 days, followed by a decrease at 6 weeks and an increase after 12 weeks [46].
10. Osman A et al evaluated the effect of LLLT on osseointegration in 12 patients that received 24 orthodontic mini-screws inserted into the buccal alveolar bone between the second premolar and first molar on the right and left sides. Each patient received LASER treatment on one side but the fluency and total energy were absent in the protocol study and they could not be calculated because of a lack of parameters. 14 days after implantation a150 g force retraction force was placed on the implants. The measurements were done via Periotest on days 7, 14, 21, 30, and 60 and the soft tissue was assessed using a gingival index that ranged from 0 to 3 (3 represents high inflammatory levels). The test showed no significant difference between the 2 groups. The gingival index showed light inflammation in 4 patients belonging to the control group, and no inflammation in the LASER group [47].
11. Torkzaban P et al evaluated the effect of LASER therapy on implant stability in 19 patients that received 80 dental implants. The LASER device used a fluency of 28 J/cm2 and a total energy of 56 J. Implant stability was measured using an OSTELL device in implant stability quotient (ISQ) value immediately after surgery and at 10 days and 3, 6,12 weeks later. Both groups had increased stability over time (statistically significant), but there was no significant difference between LLLT and control [48].

## III. Discussion

The articles presented above show many differences between LASER protocols in studies performed either in vivo on rodents or human alveolar bone, but photobiomodulation seems to be beneficial as an osteointegration tool. The effects of LASER therapy were evaluated through various methods of assessment ranging from histology, micro-Ct scans, Scanning Electron Microscopy, and tensile strength tests (in vivo) to Cone Beam Computed Tomography, Resonance Frequency Analysis, and different implant stability devices performed on implants placed in living human subjects. The results performed in vivo on rodents seem to show better results than the research conducted in Stomatology.

Some of the studies performed on the osteointegration of Titanium implants in rodent bone have shown improvement only in the first few weeks after irradiation, but no significant differences later on, while others showed significant differences only after 3 to 4 months. The studies that compared different fluencies showed that higher fluencies yielded better results, and 20 J/cm2 was proven to be superior to lower values. The number of sessions seems to influence the results, the protocols that used 1 or 2 treatment sessions observed no difference between stimulated and control groups. Most studies showed significant osteointegration between 5 and 10 sessions, indicating that the concentration of LASER energy in the stimulated tissue is important. The structures stimulated via LASER photobiomodulation were mostly superficial <2 cm (human alveolar bone, rodent femur, or tibiae), and the wavelength differences ranged from 630 to 940 nm did not make a difference because deep penetration was not required. A study on bone formation in rabbits that received osteotomies evaluated the differences between infrared (790–830 nm) and red LASERS (660–690 nm) with identical parameters and showed that there was no significant difference between the two [49]. However, if the structure of interest is situated more than 2 cm deep, a higher wavelength is required, and the equipment needed is HILT (High-Intensity Laser Therapy) with better penetrability. A study of HILT performed on rabbits suggests that a single session 5 days before implant placement can improve osseointegration [50]. Studies that evaluated implant surface modifications combined with LASER therapy yielded positive results in the case of CaP coatings [34], but the LASER had an inhibitory effect on L-PRF implants and it reduced bone/implant contact, thus implant surface augmentation could lead to better results, but there is also the risk of unwanted interactions [38]. Osseointegration could also improve by using oral ingestion of different supplements (Ca, Vitamin D, Omega3) in synergy with LLLT, as seen in a study by Mikhail et al. [42]. Photobiomodulation through LASERs can also improve bone quality and regeneration in induced defects. In studies performed in vivo on rodents by Guzzardella [51] and Kazem [52], LASER therapy increased callus formation in rodents that received bone defects. Photobiomodulation can also improve bone quality in systemic diseases such as osteoporosis. Karakaya [24] showed better osteointegration of implants in osteoporotic rats that received LASER therapy, and Scalize [53] showed that bone defects induced in the calvaria bone of osteoporotic rats were healing faster after being irradiated at least 3 sessions of LASER therapy with a fluency of at least 20J/cm2. In a study performed by Akyo [54] on diabetic rats with femoral-induced defects, LLLT therapy increased bone mass compared to normal and diabetic non-irradiated specimens.

LASER therapy is not the only form of physiotherapy that has been researched in bone healing. Several studies compared Ultrasound therapy to Low-Level LASER therapy in bone formation after osteotomy. In vivo studies on animals show that even though Ultrasound improves bone healing, but LLLT is superior [55,56].

## IV. CONCLUSIONS

LASER photobiomodulation could help increase patient functionality by establishing a more stable bone-implant contact after a fracture and reducing the risk of further damage to the nearby structures through tissue stimulation. The effects of analgesia, edema and inflammation reduction observed through studies could increase patient comfort and could reduce the need for drug treatment.

Even though LASER therapy seems to be beneficial in bone healing and implant osseointegration, there is no consensus on protocol choice, mainly because the equipment used differs. The multitude of parameters could dissuade physicians from using photobiomodulation on bone formation, but the protocols could be simplified by focusing on fluency (J/cm2), energy (J), number of sessions, and wavelength (nm) because other variables (surface, time of exposure..etc) can be changed accordingly for each piece of equipment to achieve a similar protocol.

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