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Review

Photobiomodulation therapy (PBMT) in bone repair: A systematic review

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ABSTRACT

Background: Photobiomodulation therapy (PBMT) using low-level laser influences the release of several growth factors involved in the formation of epithelial cells, fibroblasts, collagen and vascular proliferation, besides accelerating the synthesis of bone matrix due to the increased vascularization and lower inflammatory response, with significant increase of osteocytes in the irradiated bone. Considering its properties, beneficial effects and clinical relevance, the aim of this review was to analyze the scientific literature regarding the use of PBMT in the process of bone defect repair.
Methods: Electronic search was carried out in PubMed/MEDLINE® and Web of Science databases with combination of the descriptors low-level laser therapy AND bone repair, considering the period of publication until the year 2018.
Results: The literature search identified 254 references in PubMed/MEDLINE and 204 in Web of Science, of which 33 and 4 were selected, respectively, in accordance with the eligibility requirements. The analysis of researches showed articles using PBMT in several places of experimentation in the subjects, different types of associated biomaterials, stimulatory effects on cell proliferation, besides variations in the parameters of use of laser therapy, mainly in relation to the wavelength and density of energy. Only four articles reported that the laser did not improve the osteogenic properties of a biomaterial.
Conclusions: Many studies have shown that PBMT has positive photobiostimulatory effects on bone regeneration, accelerating its process regardless of parameters and the use of biomaterials. However, standardization of its use is still imperfect and should be better studied to allow correct application concerning the utilization protocols.

Introduction

Low-level laser therapy (LLLT) is based on the application of light from a low energy laser, whose record derives from the year 1967, with the study of Endre Mester who described the biostimulatory effects that improve the tissue response during the repair process [1,2]. From the 1980s, laser therapy became widely used in the medical field, and numerous scientific studies have evaluated its effects on various cellular elements [3].

The LLLT, currently called photobiomodulation therapy (PBMT) due to its photochemical effect, in which light is absorbed, promotes a chemical change known as photobiostimulation, which influences the release of several growth factors involved in the formation of epithelial cells, fibroblasts, collagen and vascular proliferation [4], making it a therapy that promotes wound healing and pain reduction [5], besides stimulating the synthesis of enzymes that act on lysosomes and mitochondria [6]. Infrared laser radiation has photo-physical effects that change intracellular behavior, influencing the respiratory chain, with increased ATP production in the mitochondrial membrane that raises the cell metabolism, facilitating angiogenesis and collagen synthesis [7]. It is important to use this term to differentiate the PBMT, which does not produce heat, from other light-based devices that cause heating, e.g.

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the use of near-infrared (NIR) lamps or other uses of energy light whose mechanism of action is dependent on its thermal effects [8].

In order to evaluate the laser properties in the field of medical areas, scientific studies have shown positive results in several treatments such as osteoarthritis [7], tendinopathies [9], venous ulcers [10], buccal lesions [11,12], musculoskeletal pain [13], muscle fatigue [14], peripheral nerve injuries [15] and stroke [16,17].

The process of correction of bone defects can be improved with the use of PBMT, which accelerates the bone matrix synthesis due to an increase in vascularization and lower inflammatory response [18], with significant increase of osteocytes in the irradiated bone [19] and increased fibroblast growth factors (bFGF), stimulating the proliferation of all cell types involved in healing, both *in vitro* and *in vivo* [20].

Several isolated or combined treatments have been proposed to improve the quality of the new bone, such as the use of grafts, biomaterials [21–23], physical methods (low-intensity pulsed ultrasound - LIPUS) [24], with the purpose to accelerate osteogenesis [25–28]. PBMT is an effective technique for the improvement of bone quality [28] and has been used in repairing fractures or bone perforations in order to reduce the repair time [29].

With the evolution and evidence of PBMT in recent years, its use has been improved with the development of new therapies, such as antimicrobial photodynamic therapy (aPDT), based on the use of light associated with a photosensitizer that, after absorbing the light energy and beginning a series of chemical reactions, will produce reactive oxygen species, causing cell death by oxidative stress, to be used as adjuvant, for example, in periodontal treatments [30].

Along with the concepts recommended since the beginning of its use, the PBMT provides another treatment option within the therapeutic arsenal, with safe and easy utilization and favorable timely results. It should always respect the safety margins, because most faults in its application are related with errors in the technique (inadequate doses of energy, excess irradiation, insufficient irradiation on the pathology area), which can inhibit the repair process [29].

Considering its properties, beneficial effects and clinical relevance, the aim of this review was to analyze the scientific literature published until the year 2018 regarding the use of PBMT in the bone defect repair process.

Materials and methods

The initial electronic search was performed in the PubMed/MEDLINE® and Web of Science databases, accessed on 1/14/2019, with the combination of descriptors low-level laser therapy AND bone repair, considering the period of publication until the year 2018. Subsequently, articles available in full text, using non-human species (other animals) as study subjects (*in vivo*) and published in English were restricted.

Research and identification strategies were used, looking for titles and abstracts related to the study purpose, with results compatible with the methodology and relevance in its practical application. In addition, only papers with full text available were included, either as open access.

Results

Search results

The initial search in the PubMed/MEDLINE® database located 254 articles, among which 221 were excluded because they did not meet the eligibility criteria. The Web of Science database retrieved 204 papers, among which 200 were excluded. After analysis of titles and abstracts, 33 articles (Pubmed) and 4 (Web of Science) were selected for the systematic review (Fig. 1). Table 1 summarizes the data presented in the 37 articles selected for this research.

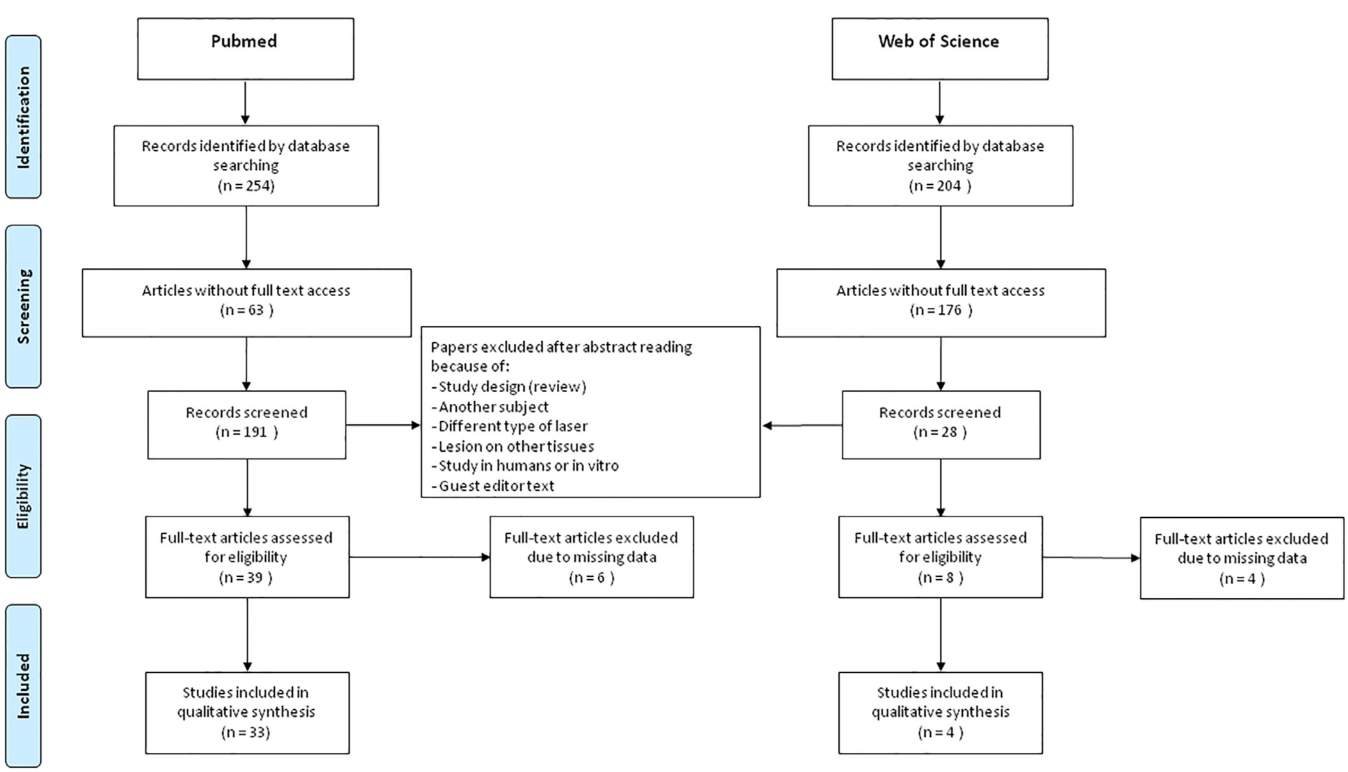

Fig. 1. Prisma flow diagram. Summary of selection of articles for the review.

Table 1
Summary of the main LLLT parameters used in the selected articles.

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Pinto et al. [21]	GaAlAs (Teralaser, DMC São Carlos-SP, Brazil)	830/0.028 cm^2	100	120	34 s every 48 h, depending on euthanasia (8, 15 and 23 sessions)	Biosilicate	Rat tibia	15, 30 and 45 days post-surgery	The biosilicate and biosilicate + LLLT groups demonstrated a decrease in the biomechanical properties compared to the control at 30 and 45 days. LLLT did not improve the osteogenic properties of biosilicate.
Soares et al. [22]	Non-specified diode laser (TwinFlex Evolution®, MMOptics, São Carlos, São Paulo, Brazil)	780/~0.4 cm^2	70	20 (Total 140)	Every 48 h, in 7 applications	Synthetic microgranular biphasic hydroxyapatite + Beta-Calcium Triphosphate	Right tibial area of rats	15 and 30 days post-surgery	Using the biomaterials, the most positive result was observed with LLLT, with better bone healing and higher deposition of hydroxyapatite.
Akyol et al. [23]	GaAlAs (Lambda Laser Products, Vicenza, Italy)	808/1-cm^2	100	10	20 s every 48 h in 5 applications	Alendronate (ALN)	Femur of rats with osteoporosis	10 and 20 days post-surgery	The combination of LLLT with ALN had a beneficial effect on bone repair, potentializing the curative effects of ALN.
Nagata et al. [26]	InGaAlP) (TheraLase®, DMC Equipamentos Ltda., São Carlos, SP, Brazil)	660/0.0283 cm^2	35	4.9 (Total 39.2)	4 s; 8 points	Bone marrow aspirate (BMA) of rat iliac crest	Calvaria of rats	30 days post-surgery	The combination of BMA/LLLT produced significantly greater bone formation in bone defects in the calvaria of rats as compared to the control, or any of the treatments alone.
Babuccu et al. [27]	GaAlAs (Doris Duo CTL 1106MX, CTL, Warsaw, Poland)	820/1 cm^2	500	16	14 days and 21 days. Without specifying time or number of points	LLLT LIPUS LLLT + LIPUS	Rat tibia	14 and 21 days post-surgery	The LLLT + LIPUS combination improved bone healing mechanically and histologically, shortening the treatment period compared to LLLT or LIPUS alone.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
de Almeida et al. [28]	GaAlAs (TheraLase DMC®, São Carlos, Brazil)	780/—-	100	6 (Total 210)	60 s at 4 different points for 7 days	Autogenous bone graft + LLLT	Calvaria of rats	30 days post-surgery	LLLT assisted the bone repair process, the amount of new bone formed and the production of osteoid matrix. In some specimens there was complete closure in the extension of the surgical defect.
Ribeiro et al. [31]	GaAs (DMC, São Carlos, Brazil)	735/3 mm	30	16	24 h after surgery and every 48 h for 15 days until euthanasia	Celecoxib	Rat tibia	15 days post-surgery	Immunoreactivity was more intense in the LLLT + celecoxib group, improving bone repair.
Nascimento et al. [32]	GaAlAs (Thera Laser, D. M. C. Equipamentos Ltda., São Carlos, SP, Brazil)	830/0.1 cm^2	10	20	3 min and 33 s, alternating days and area 0.1 cm^2	Salmon calcitonin (Ca)	Rat femur	7,14 and 21 days post-surgery	In the calcitonin + LLLT group, there was greater bone regeneration with high mineral tissue density at 14 and 21 days post-surgery, in relation to the control, calcitonin or LLLT groups.
Fangel et al. [33]	GaAlAs (Teralaser, DMC®, São Carlos, Brazil)	830/0.028 cm^2	100	60	Applications at 2, 4, 6, 8, 10 and 12 postoperative days	Biosilicate, LLLT Biosilicate+LLLT	Rat tibia	14 days post-surgery	The combination of biosilicate + LLLT improves the bone repair process.
Fazilat et al. [34]	GaAlAs (THOR Photomedicine Ltd)	810/0.8 mm	200	3	7.5 s every 2 days for 14 days	Customized distraction devices	Mandibular body of rabbits	10, 20, 40 days post-surgery	LLLT increases osteoblast proliferation, collagen deposition, and new bone formation over periods of 10, 20 days, with no significant effects in later phases of 40 days.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Maman Fracher Abramoff et al. [35]	GaAlAs (DMC, São Carlos, Brazil)	808/0.028 cm^2	100	71.4	3 applications, 20 s each	Ionizing radiation (IR)	Bone defects of the femur in rats	7, 14 and 21 days post-surgery	Exposure to IR reduces osteogenesis, and the combination with LLLT speeds up the bone repair process especially during the initial phases of 7 and 14 days.
Gomes et al. [36]	GaAlAs (Thera Lase; DMC Equipamentos, São Carlos, SP, Brazil)	830/—-	50	a) 5 b) 10 c) 20	a) 2 points - 2,5 J/cm^2 and 51 s per point; b) 2 points - 5 J/cm^2 and 101 s per point; c) 2 points - 10 J/cm^2 and 201 s per point; 48 h interval, 17 applications.	NanoTite titanium implant; BIOMET 3i	Rabbit jaw	30 days after the last LLLT application	Better results in the groups that received application of 20 J/cm^2 and 10 J/cm^2. There was no significant difference between groups receiving 5 J/cm^2 and the CG.
Soares et al. [37]	Non-specified diode laser (TwinFlex Evolution®, MMOptics, São Carlos, São Paulo, Brazil) LED (FisioLED®, MMOptics, São Carlos, São Paulo, Brazil)	780/0.4 cm^2 850 ± 10 nm/ ~0.5 cm^2	70 150	20 (Total 140) 20 (Total 140)	48 h interval, 7 applications	Synthetic Microgranular Hydroxyapatite + Beta-Tricalcium Phosphate (70%/30%, respectively).	Bone defects of the femur in rats	15 and 30 days post-surgery	LLLT + biomaterial improved bone repair, with increasing mineralization characterized by the deposition of hydroxyapatite. Formation of mature bone was observed at 30 days.
Batista et al. [38]	GaAlAs (Flash lase III, DMC Equipamentos/São Carlos, SP, Brazil)	830/0.028-cm^2	100	6 (Total 210)	Application of 2 min in surgery, and in the post-operative period every 48 h for 7 days	One session of radiotherapy (Varian Clinac® 600C S/N 0310) with a total dose of 30 Gy) 4 weeks before surgery	Left femoral area of rats	7 days post-surgery	Bone formation in all animals of the control group and the LLLT group, being greater in LLLT. This did not happen with the groups that received radiotherapy and radiotherapy combined with LLLT.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Tim et al. [39]	GaAlAs (Teralaser, DMC®, São Carlos, SP, Brazil)	830/0.028 cm^2	100	3.4	Applications every 48 h for 8, 15 and 23 days.	No material was used in the study	Right and left tibia of rats	At 8, 15 and 23 days post-surgery	Laser therapy improved the bone repair process, accelerating the deposition and organization of new bone.
Briteño-Vázquez et al. [40]	ArGa (KLD, São Paulo, Brazil)	850/0.04 cm^2	100	8	Applications of 64 s, being a daily dose for 10 days	No material was used in the study	Medial region of the crest of the right tibia of rats	10 days post-surgery	When LLLT was applied greater bone consolidation occurred, in addition to promoting greater proliferation of fibroblasts.
Massotti et al. [41]	AlGaAs (TheraLase; DMC Equipamentos, São Carlos, SP, Brazil)	830/0.002827 cm^2	50	3 groups: a) 5 b) 10 c) 20	7 sessions of application in total (1 every 48 h for 7 days)	No material was used in the study	Left side of rabbit's jaw	30 days post-surgery	The LLLT group with higher energy density presented better results in bone formation around the implant, in addition to an increase in the formation of collagen fibers.
Sella et al. [42]	GaAlAs (model Magnus Plus, DMC Equipment)	808/0.02 mm^2	200	37	1 application daily for 8 days	No material was used in the study	Femoral area of rats	8, 13 and 18 days post-surgery	From the 13-day period with LLLT, there was less inflammatory infiltrate, present until day 18. The group that received laser therapy presented trabecular new bone formation.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Park et al. [43]	GaAlAs (Diobeauty-30®; Diotech, Busan, Korea)	980/(optical fiber 300 μm in diameter)	10	13.95	3 groups: a) 1 min/day b)2 min/day c)5 min/day	No material was used in the study	Extraction sockets of first maxillary molars in rats	3 to 7 days post-surgery	LLLT increased bone healing in the early stages, increased expression of genes and proteins such as Runx2, type 1 collagen, osteocalcin, platelet derivative, B-growth factor and vascular endothelial growth factor (5-minute samples of radiation).
de Oliveira Gonçalves et al. [44]	GaAlAs (Laserpulse IBRAMED, Amparo, SP, Brazil)	830/0.116 cm^2	30	6	3 times/week, 24 s in 4 different sites around the bone graft (total of 96 s)	Autogenous bone graft. Heterologous fibrin sealant.	Frontoparietal region of rats	At 10, 20, 30 and 40 days post-surgery	LLLT promoted greater integration of the graft into the recipient bed in relation to the group that did not receive the therapy.
de Vasconcellos et al. [45]	GaAlAs (Easy Laser, Clean Line®, Taubaté, SP, Brazil)	780/0.69 cm^2	40	4 (Total 112)	1 min and 40 s, with 48-hour interval	Implants of titanium	Femur of rats with and without osteopenia	2, 4 and 6 weeks post-surgery	LLLT improved osteointegration at the initial 2-week stage, showing a greater amount of mature bone tissue. The area between existing bone and implant was filled with newly formed bone tissue at 6 weeks.
de Vasconcellos et al. [46]	GaAlAs (Easy Laser, Clean Line®, Taubaté, SP, Brazil)	780/0.69 cm^2	40	4 (Total 112)	1 min and 40 s, 48-hour interval	Implants of titanium	Rat femur with and without osteoporosis	2 and 6 weeks post-surgery	LLLT accelerated new bone formation, inducing an increase in osteogenesis.
Acar et al. [47]	GaAlAs (CHEESE Dental Laser System, DEN4A)	810/–-	100	4	1 point, 3 times/week, 2 weeks (every other day), 120 s	LLLT LIPUS LLLT+LIPUS	Rabbits calvaria	3 weeks	LIPUS and LLLT improves new bone formation without additive effect in combination.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Tim et al. [48]	Thera laser, DMC®, São Carlos, Brazil	830/0.6 mm	30	2.8	1 point, 94 s, each 24 h, for 36 h, 3 days and 7 days	No material was used in the study	Rat tibia	36 h, 3 days and 7 days	LLLT modulated the inflammation, increased new bone formation and expression of genes related to inflammation and angiogenesis.
Rajaei Jafarabadi et al. [49]	GaAlAs (PMS1252, INLC, Tehran, Iran)	830/0.35 cm	40	4	1 point, 38 s, each 48 h, 21 or 42 days	Fixed fixation fracture with stainless steel plate and implant. Low-amplitude high-frequency whole body vibration (WBV)	Rat femur	3 and 6 weeks	LLLT had positive effects on early osteogenesis and biomechanics, the WBV had greater impact on the mechanical properties of healed bone, the association of methods had no constructive results.
Atasoy et al. [50]	GaAlAs (EzLase 940, Biolase Technology, Inc. 4 Cromwell Irvine, USA)	904/30 mm	1500 3000 6000	5 10 20	1 point, 10 s, Immediately postoperative and 2, 4, 6, 8, 10 and 12.	No material was used in the study	Right tibia of rats	4 or 8 weeks post-surgery	LLLT in early and late stages may not accelerate the bone repair process.
de Lima et al. [51]	GaAlAs diode laser (MMOptics, Brazil)	780/—-	50	120	4 points, 10 s. After surgery and at intervals of 48 and 96 h, 21 and 30 days	Use of collagen sponge.	Rat calvaria	21 and 30 days	LLLT for 30 days associated with the collagen sponge obtained greater presence of secondary bone, immature bone (osteoid) and newly formed connective tissue (periosteum).

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Fernandes et al. [52]	GaAlAs (Photon lase III, DMC Equipment, São Carlos, SP, Brazil)	808/ 0.028 cm^2	30	10	1 point, 28 s, 3 times a week on non-consecutive days	Biosilicate (BS); BS + LLLT; BS/PLGA; BS/ PLGA + LLLT. BS and PLGA associated with osteoblast and fibroblast *in vitro*, irradiated or not, the same parameters of the LLLT postoperative, but in the time of 9 s.	Rat tibia	2 and 6 weeks	The use of LLLT in BS / PLGA improved the degradation of material and increased the amount of granulation tissue and newly formed bone.
Hamad et al. [53]	GaAlAs (A.R.C. laser GmbH, Germany)	808/—-	900	1459	1 point, 5 min, immediately after extraction and every 72 h for the next 12 days.	Extraction of the right and left first premolars of rabbits.	Alveolus of extraction of left premolar of rabbits	Applications immediately after extraction and every 72 h for the next 12 days. Euthanasia 7, 41, 30 and 45 days	LLLT accelerated at the beginning and end of the healing process. Increased number of mature trabeculae, dense collagen fibers and numerous blood vessels.
Ribeiro et al. [54].	Thera Laser, D. M. C. Equipamentos Ltda., São Carlos, SP, Brazil	830/—-	10	20	1 point, 3 min 33 s	Defect of 2.8 mm in the right femur. Ca and LaCa groups: Intramuscular injection of 2 UI/kg synthetic salmon calcitonin after surgery and then every other day until euthanasia.	Rat femur.	7, 14, and 21 days	Bone densitometry demonstrated that LLLT (830 nm) associated with calcitonin improved bone repair.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Vasconcelos et al. [55]	Ga-Al-As (Whitening Laser II – DMC, São Carlos, SP, Brazil)	808/the optic fiber diameter 0.6mm	100	25 580	High dose: 2 min 43 s per point (6 points) Low dose: 7 s per point (3 points)	Left first molar of rats was moved by helical elastic apparatus.	The first left maxillary molar of rats	3 times with 48-hour intervals. 7 and 10 days	LLLT at the dose used did not prevent or reduce inflammatory root resorption or reduced any change in root surface.
Garcia et al. [56]	InGaAlP (Theralase, DMC Equipments Ltd., São Carlos, SP, Brazil)	660/0.0283 cm^2	35	49 (Total 24.7)	5 points, 4 s per point	Autogenous bone	Rat calvaria	30 days post-surgery	The new bone formation was higher in the group that used autogenous bone + LLLT. The group that only used LLLT presented better results in relation to the control group and the group in which the defect was filled with blood only.
de Almeida et al. [57]	InGaAlP Thera Laser (DMC Equipamentos Ltda, Sao Carlos, São Paulo, Brazil)	660/1 mm	35	4	8 points, 3 s each and also a scan of 3 s, irradiation only before suturing.	Autologous graft in the mandible of mice modified by nicotine.	Mandibular angle	7, 14, 28 days	LLLT assisted in enhancing bone formation in conjunction with control groups.
Bayat et al. [58]	He-Ne (Iranian Atomic Energy Organization; Bonab, Iran)	632.8/0.0314 cm^2	10	148.4	2 points, 3 times/ week, Total of 466 s.	Circular defect of 5 × 10 mm in the articular cartilage of the subchondral bone distally in the right patellar sulcus. Anesthetized rabbits.	Right and left femoral condyle of the right knee of rabbits. Control group placebo	After surgery and followed for 2, 4, 8 or 16 weeks.	LLLT laser He-Ne cannot significantly accelerate the healing of a large osteochondral defect.
Barbosa et al. [59]	InGaAIP AsGaAl (Flash Lase III -DMC Equipment Ltda, São Carlos, SP, Brazil)	660–690/1 cm^2 790–830/ 1 cm^2	100 100	4 4	1 application after osteotomy and then every 48 h for 7, 14 and 21 days.	No material was used in the study.	Right femoral area of rats	7, 14, 21 days post-surgery	The group that received 830 nm presented greater bone deposition than the control group.

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Table 1 (*continued*)

Authors	Type of laser (manufacturer)	Wavelength (nm)/Spot beam	Output power (mW)	Energy density (J/cm^2)	Quantity of radiation	Therapeutic variables	Irradiation site	Evaluation time	Principal results
Khadra et al. [60]	GaAlAs (Ronvig Dental, Daugaard, Denmark)	830/18 mm	150	23	6 points lateral of the implants and 3 points below it. The treatment time per point was 20 s.	10 mm cylindrical bars of grade 2 titanium (ASTM B 348).	By placing the probe in light contact with the area to be treated (implants).	Treatment was initiated immediately after surgery and carried out daily for ten consecutive days.	LLLT had a positive effect on the functional attachment of titanium implants to bone.
Pretel at al. [61]	GaAlAs (Laser Beam Multi Laser DR. 500 device; Laser Beam Indústria e Tecnologia Ltda., Niterói, RJ, Brazil)	780/1.0 mm	50	178	40 s directly on the defect area	No material was used in the study	In direct contact with the bone defect área.	15, 45, and 60 postoperative days.	LLLT showed a biostimulating effect on bone remodeling by stimulating the modulation of the initial inflammatory response.

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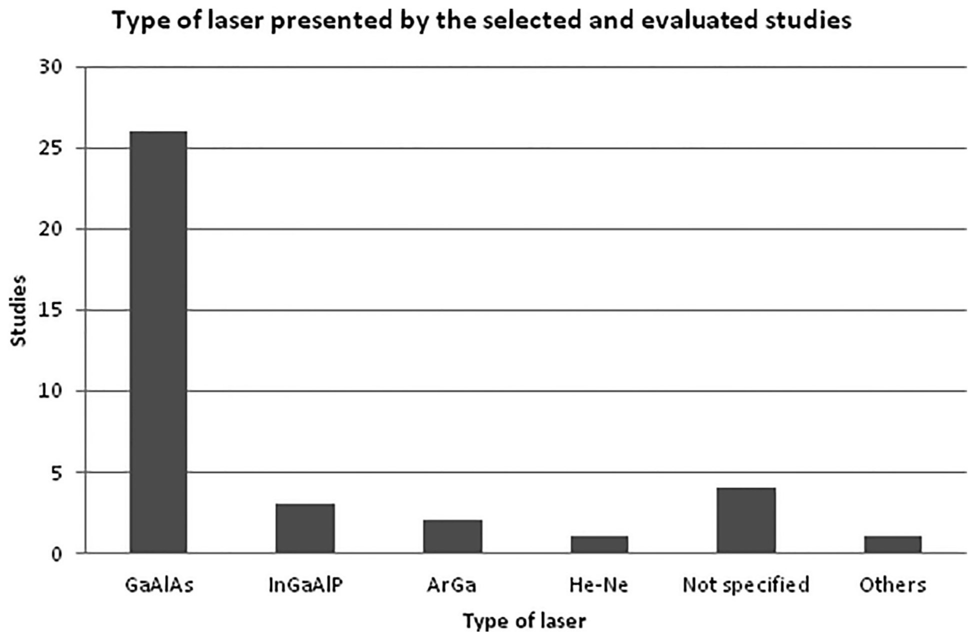

Fig. 2. Type of Laser presented by the selected and evaluated studies. Gallium aluminum arsenide (GaAlAs) that presented greater use in the selected studies in bone repair (26 studies). Four studies did not specify the type of laser used. One of the studies compared two types of laser (others).

Studies excluded after complete analysis

The reasons for the exclusion of papers in the present investigation included the use of other types of laser, tissue, review papers, studies conducted in humans, lack of data such as output power, or unspecified number of sessions of laser application.

Description of studies

Preliminarily, there were variations in the parameters of low-level laser use, mainly in relation to the wavelength, in which the invisible infrared light spectra were the most frequently used, adding up to 32 studies [21–23,27,28,31–55,60,61], and the visible red light spectrum was used in 4 studies [26,56–58]. Only one of the studies selected for analysis aimed to compare the performance of low-level laser of two distinct wavelengths (red and infrared) and its effects on cell proliferation in bone repair [59].

The most commonly used type of laser among studies was gallium aluminum arsenide (GaAlAs) in twenty six studies [21,23,27,28,32-36,38,39,41-47,49-53,55,60,61], followed by indium-gallium-aluminum phosphide (InGaAlP) in three studies [26,56,57]; two studies used arsenide-gallium (ArGa) [31,40], one study used helium-neon (He-Ne) [58], and in four other studies the type of laser used was not specified [22,37,48,54]. However, the study of Barbosa et al. [59] made a comparison between InGaIP and GaAlAs (Fig. 2).

Regarding the comparison of PMBT and other physical methods, the study by Soares et al. [37] compared LED and a non-specific diode laser, and two studies compared laser GaAlAs and LIPUS [27,47].

The wavelengths observed showed a great variation, including studies with 632.5 nm [58], 660 nm [26,56,57], 735 nm [31], 780 nm [22,28,37,45,46,51,61], 808 nm [23,35,42,52,53,55], 810 nm [34,47], 820 nm [27], 830 nm [21,32,33,36,38,39,41,44,48,49,54,60], 850 nm [40], 904 nm [50] or 980 nm [43]. Barbosa et al. [59] compared 660–690 nm and 790–830 nm (Fig. 3).

As well as wavelength, the energy density used in the selected studies showed great variability, presenting a range of 2.8 [48] to 1459 J/cm^2 [53], with 4 J/cm^2 being the most used [45–47,49,57,59] (Fig. 4).

Discussion

According to the growing interest in the scientific community, mainly medical, dental and physiotherapeutic specialties in the use of low-level laser therapy in procedures for the recovery of bone lesions, this systematic review aimed to evaluate the advantages, disadvantages and clinical applicability of PBMT. It was noted that, due to its properties, PBMT aids the process of new bone formation, shortening the recovery time of lesions.

It is described that the PBMT in the irradiated tissue accelerates the processes of bone regeneration and remodeling [31,33–35,37,43,45–49,51–54,57,60,61], mainly due to events of increased deposition of hydroxyapatite and collagen in the osteoid matrix, improving the biomechanical properties of bone, increasing the expression of genes and bone proteins, favoring vascular proliferation [27,44,45,48,53] which leads to a decrease in treatment time. These factors also depend on the utilization protocol. In the low-level laser test in which three different energy densities were used, it was concluded that the lower energy density laser obtained a lower photobiomodulatory effect, referring to the lack of bone formation at the initial moments of osseointegration [36].

In order to increase the repair and bone remodeling process, biomaterials can be used, which combined with PBMT [23,32,33,37,44,51,52] potentiate its effects by improving the mineralization process by increasing the deposition of calcium hydroxyapatite [22]. However, Pinto et al. [21] evaluated that low-level laser therapy did not improve the bioactive properties of biosilicate and produced a decrease in the biomechanical properties of the bone defect. Previous studies have reported that exposure to insults, trauma or diseases such as osteoporosis [45], osteopenia [46] and ionizing radiation [35], PBMT power isolated or associated with biomaterial produces remarkable improvement, even with good or poor health [23,35,39,45,46,49,51–54,57].

As an exception, a study revealed that radiation exposure can clearly disrupt the repair process [38]. Also, Acar et al. [47] associated PBMT to LIPUS and did not observe additional effects on bone

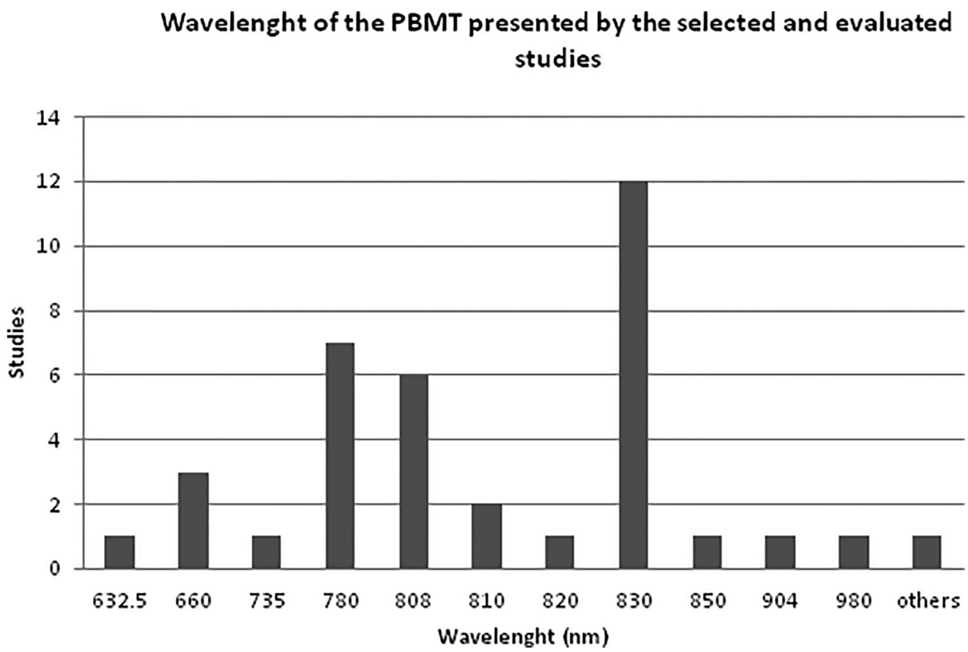

Fig. 3. Protocols of PBMT. Wavelenght (nm) presented by the selected and evaluated studies. 830 nm that presented greater use in the selected studies in bone repair (12 studies). One of the studies compared different wavelenghts (others).

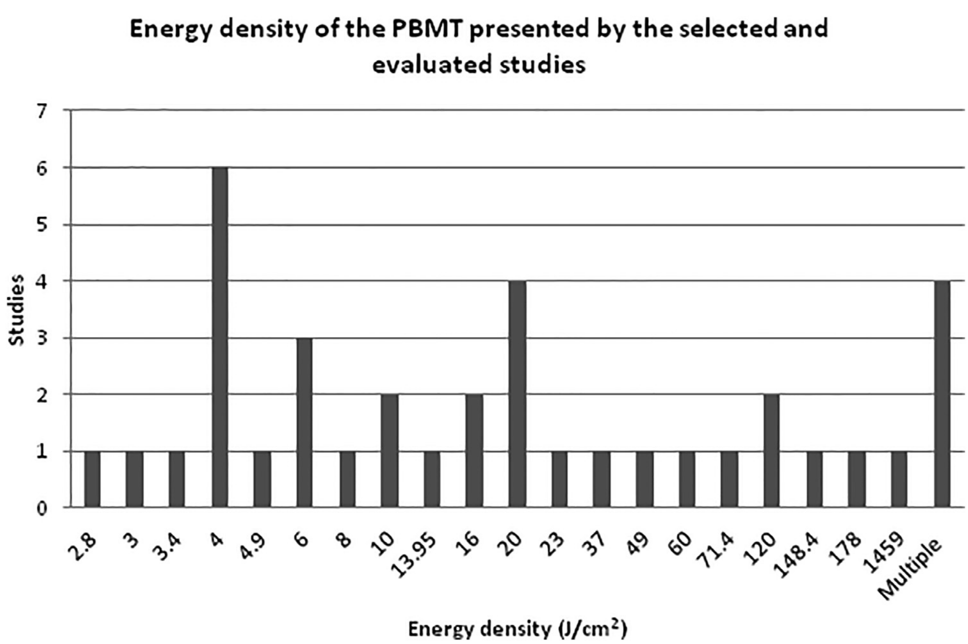

Fig. 4. Protocols of PBMT. Energy density (J/cm^2) presented by the selected and evaluated studies. 4 J/cm^2 that presented greater use in the selected studies in bone repair (6 studies). Four studies used multiple energy density (multiple).

regeneration, and Vasconcelos et al. [55] did not observe reduction of inflammation or other changes.

PBMT is a radiation with wavelengths in the red or infrared light spectrum [2], being the most used infrared invisible light to have better effects in the early stages of bone repair, showing higher bone density as measured by densitometry caused by faster bone deposition [59]. The parameters of PBMT are not yet standardized, but most studies analyzed used energy densities ranging from 1.5 J/cm^2 to 1459 J/cm^2, with the most commonly used dose being 6 J/cm^2 [38,44,57]. Studies that employ different energy densities have agreed that higher doses produce better results in the bone repair process [36,41], while Bayat et al. [58] presents divergent results, reporting that LLLT He-Ne at 148.4 J/cm^2 did not accelerate the bone repair.

In general, PBMT has a power of 1 mW–500 mW [2]. In the studies evaluated, the lowest optical power output was 10 mW [32,43] and the highest 6000 mW [50]. The PBMT exposure time also plays a very important role in the results, being proportional to the increased expression of genes and proteins that aid the process of bone repair and regeneration [43]. Most investigations of this compilation, except for some studies [21,50,55,58], agree that low-level laser therapy has positive photobiostimulatory effects on bone regeneration, accelerating its process regardless of its parameters, which need to be standardized to allow a pattern of results.

Some studies have failed to describe important information such as the type of laser [22,37,48,54], the spot beam [28,36,47,51,53,54] and number of points and time of application [27], which were important data for analysis of the present research. Widely variable energy densities, wavelengths, and amount of applied radiation were found, data that contribute to the correct interpretation of the results from the laser application protocol. Therefore, the interpretations and conclusions of the studies should be careful.

Analyzing the data in Table 1, as well as the histograms shown in Figs. 2–4, it was possible to observe that the protocol of LLLT based on the use of Gallium Aluminum Arsenide (GaAlAs), with a wavelength of 830 nm and energy density of 4 J/cm^2, presented positive results in the repair of several types of bone defects. Because the literature demonstrates a large discrepancy in the parameters used for PBMT, it becomes difficult to discuss the effects of therapy and which protocol will be most adequate to achieve the desired therapeutic effects.

Several experimental sites in the study subjects (alveolus tooth, mandible, tibia, calvaria, femur or maxilla) have provided a more global perspective of the effects of repair in different bodily areas. It was not possible to perform the meta-analysis due to the diversity of parameters found in the studies included in this review, and this can be considered a limitation of the present study. The recommendation of the positive effects of PBMT and its photobiostimulatory effects indicate that the use of this therapy tends to increase over the years and the search for standardization in the varied techniques and their uses would make the success even greater.

Conclusion

In the present study, an article database was obtained which allows us to develop a more solid criterion about the laser and its positive photobiomodulatory effects in the process of bone repair and regeneration, being that the studies demonstrated that PBMT improves the processes of repair of bone defects, regardless of the parameters and the use of biomaterials. However, standardization is still flawed, and it should be better studied to allow more specific conclusions in relation to PBMT use protocols.

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Declaration of Competing Interest

There was no conflict of interest.

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