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ORIGINAL ARTICLE

Efficacy of photobiomodulation on accelerating bone healing after tooth extraction: a systematic review

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Abstract
Post-extraction healing of the socket may take up to 24 weeks to complete. This systematic review aims to evaluate whether photobiomodulation accelerates bone healing in those sockets. A search strategy was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed, Cochrane Library, and Scopus electronic databases were searched for in vivo studies with restrictions on the year (< 50 years old) and language (English). After applying the inclusion criteria, ten studies were selected for review. Test subjects included humans (3), rats (5), and rabbits (2), either healthy or with specified systemic condition(s). Laser parameters applied varied between studies significantly. Six studies measured bone density or bone trabeculae percentage, while remaining studies measured secondary outcome measures such as osteogenesis markers, patient's self-reported pain scores, and clinical epithelial regeneration. No side effects of photobiomodulation have been reported. Higher concentration of osteogenesis markers Ocn and Runx2 were consistently reported across studies, as well as higher percentage of bony trabeculae and bone density. Within the limitations of this review, improvement in bone repair can be found when using photobiomodulation in extraction sockets.

Keywords Bone repair · Photobiomodulation therapy · Low-level laser therapy · Tooth extraction · Bone density · Osteogenic markers

Introduction

After tooth extraction, there follows a well-documented series of changes, both histologically as well as clinically. Histologically, within the first 6–8 weeks after an extraction, a blood clot forms and is replaced by granulation tissue, which is then replaced by mineralised, immature, woven bone. However, in the next 16–18 weeks, bone remodelling will produce mature bone without much consistency among patients. In fact, in some patients, the process of bone remodelling may not often be completed by the end of these 24 weeks [1]. Clinically, changes occur in both the hard and soft tissues. A systematic review recently analysed the changes in height and width of the alveolar bone after extraction, and found a mean reduction of 1.67 mm in the height of the buccal wall, 2.03 mm in the height of the lingual wall, and 0.64 mm in the interproximal aspects [2]. In the gingival tissue, there was a mean reduction in height of 0.8 mm orally at the end of 12 months. Over that period, there was also a reduction in the width (bucco-lingual dimension) by 50%, of which two thirds occurred in the first 3 months [3]. The clinical consequences of these physiological hard and soft tissue changes may affect the outcome of the ensuing therapies aimed at restoring the lost dentition, either by limiting the bone availability for ideal implant placement or by compromising the aesthetic result of the prosthetic restorations. Hence, a multitude of techniques are in research to reduce the dimensional loss of the alveolar ridge, make healing more predictable, and to accelerate the bone healing [4].

An area of growing interest is photobiomodulation or low-level laser therapy (LLLT). Photobiomodulation has been applied in dentistry for many years in a variety of applications such as reducing inflammation, promoting wound healing, pain management, and tissue regeneration [5, 6]. No side effects for photobiomodulation have been reported in the in vitro and in vivo studies found [7]. There has been a significant number of in vitro and in vivo animal studies, as well as several

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systematic reviews that have evaluated photobiomodulation in bone regeneration. The effect of photobiomodulation on cells involved in bone regeneration and repair was analysed in a review, concluding enhanced osteoblastic proliferation and differentiation of cell lines used in the included in vitro studies [8]. Several other in vitro and in vivo studies have found that bone healing can be improved by increased expression of osteogenesis markers, both in the early and late phases [6, 9]. A recent systematic review evaluated whether photobiomodulation improves the bone repair in maxillofacial defects such as tooth extractions, maxillary expansion, periodontal defects, maxillary cystic defects, distraction osteogenesis, and orthodontic movement. The review concluded a possible improvement in bone density due to photobiomodulation [7]. Another systematic review published in 2016 evaluated general healing and pain reduction due to photobiomodulation after tooth extraction, finding a lack of sound quality studies and concluding lack of evidence for its effect on tissue healing [10]. Despite the association, possible causality, and contradictory results, no published systematic review has been found published thus far evaluating the effect of photobiomodulation on bone repair in the socket specifically after tooth extraction. Hence, the purpose of this systematic review is to critically review the literature and evaluate the null hypothesis that photobiomodulation does not produce any difference in bone density in the socket after extraction. The specific question to answer in this review has been structured per PICOS format as suggested in the PRISMA checklist: Does photobiomodulation therapy improve bone repair in the socket after extraction? The participants include humans or animals undergoing tooth extraction. The intervention group (photobiomodulation therapy) was compared with the control (plain light/no irradiation). The primary outcome measured was bone density, while the secondary outcome measured was osteogenic markers. The study designs should involve studies with a control, and a minimum of ten subject cases.

Methods

This systematic review has been conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, as well as previously published systematic reviews [7, 11]. The protocol for this review has also been registered on PROSPERO (International prospective register of systematic reviews: CRD42017060616) prospectively to avoid the risk of duplication, and to assist in complying with PRISMA. A comprehensive search of PubMed, Scopus, and Cochrane library was conducted with the following search strategy: ("Low Level Laser Therapy" OR "Cold Laser" OR "Low Level Laser Irradiation" OR "Laser Biostimulation" OR "Laser Therapy, Low Power" OR "Laser Therapy, Low Level" OR "Photobiomodulation Therapy" OR "Laser Biostimulation" OR "Laser Phototherapy") AND ("Healing" OR "Bone remodelling" OR "Bone repair" OR "Bone regeneration" OR "Blood clot formation" OR "Granulation" OR "Osteoblast") AND "Tooth extraction". This included studies published up until March 2017. Additional studies were identified from the references.

Articles were initially added to a citation manager EndNote X8 ® (Clarivate Analytics, New York City) and duplicates were eliminated. They were initially screened by Title and then Abstracts to sort articles into an excluded and included folder. Inclusion criteria included (1) study was published in the last 50 years in a professional or scientific English journal, (2) study involved in vivo determination of bone repair in the jaws (i.e. in vivo human and animal studies), and (3) types of laser and treatment parameters were clearly stated. Exclusion criteria included (1) in vitro studies involving cells and tissues, not whole animals and (2) studies with less than ten subjects. Articles in both the folders were then cross-checked by another researcher (G. R.). The selection process can be seen in Fig. 1.

The methodological quality of human studies has been assessed using the Jadad scale or the Oxford quality scoring system [12], where a score of 3 or higher (in range of 0 to 5) indicates a high-quality study (Table 3).

Results

Inclusion of studies, quality of studies, and test subjects

Forty-eight studies were found after the duplicates were removed. One additional study was identified through secondary sources. After eligibility criteria were applied, 12 records were selected. Two were excluded, as full-text articles were not found online. The remaining ten studies were included and a full-text review was conducted. The detailed search strategy can be seen in Fig. 1. Out of ten, five studies have utilised rats as their subjects and two have utilised rabbits.

Based on the Jadad scoring scale, Romão et al. (2015), and Mozzati et al. (2011), both scored 4, on a scale of 0–5 indicating a high quality of study, while Kucirova et al. (2000) scored a 2, indicating a lower quality of study (Table 3).

Laser characteristics of the included studies

Laser parameters used in included studies have been reported in Table 1. There is a considerable variability in the power, mode, dose, duration in one treatment sitting and total number (frequency) of sittings. Wavelength is relatively consistent in the range of 670 to 980 nm. It has been noted that wavelengths between 780 and 950 nm can penetrate the tissue beyond the surface. This is a necessary property for the studied effect, if the laser were to directly impact upon repair of the bone in the

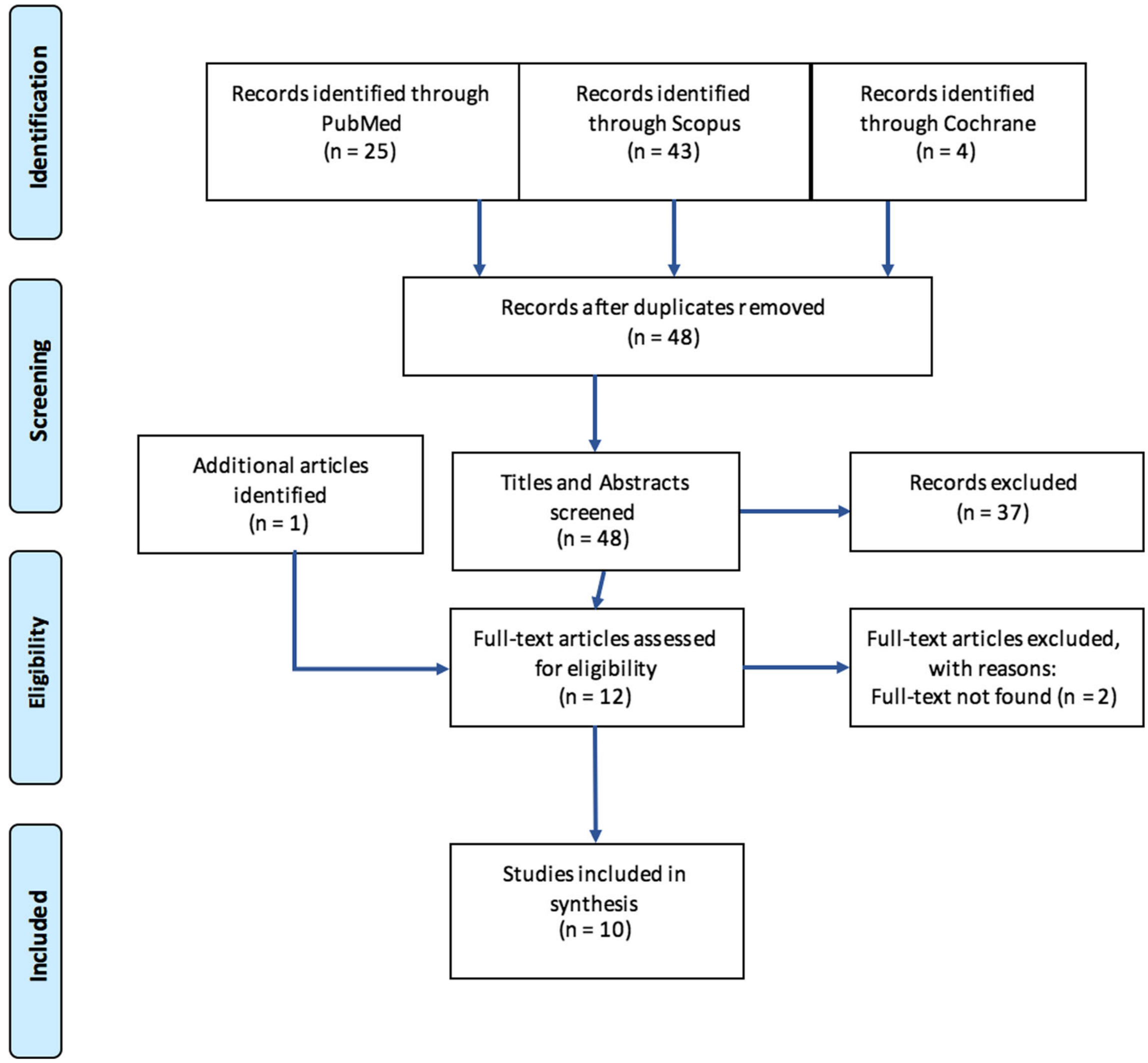

Fig. 1 Flow chart demonstrating the selection process

socket, deeper to the gingiva [13]. The majority of studies used gallium-aluminium-arsenide (GaAlAs) diode lasers, one used LED, another one used Nd:YAG, and two other used gallium-arsenide (GaAs) diode lasers. Variations in the dose, duration treatment, and the total number of sittings make it comparison between studies difficult or impossible.

Outcome measures used in the included studies

Table 2 compiles the outcome measures, as well as the characteristics of test subjects and the results of all the included studies. Six included studies measured primary outcome measure of bone density using three major methods—CT/Micro CT, histological analysis of % volume density of trabecular bone, and plain X-rays [6, 14–17, 21]. Five studies measured secondary outcome measures of expression of osteogenesis markers, most commonly being Runx2 and Ocn [6, 9, 18–20].

Discussion

A need for an exhaustive systematic review of current evidence was identified to support clinical decision making regarding the use of photobiomodulation for accelerating bone healing in dental sockets post tooth extraction. Therefore, this review systematically investigated in vivo animal studies published on the matter. The results highlighted heterogeneous data, with variations in laser protocols, animals used, and measured outcomes. This prevented a quantitative analysis (meta-analysis) of the systematic review. This also prevents direct extrapolation of results to clinical applications.

A recent systematic review conducted by Noba et al. (2018) [22] investigated the effectiveness of laser-assisted healing after oral surgery. This study looked at bone healing following a number of oral surgical events, including orthognathic surgery, tooth extraction, bony defects, and cyst removal. It is important to note that bone healing can vary, depending on the oral surgical event [23]. Therefore, having

Table 1 Laser parameters used in included studies

Author	Type of laser	Wavelength	Power	Mode	Dose	Dose Duration per appointment	No. of sittings
Comunian et al 2017 [14]	LED for group 1, Laser for group 2	830nm for LED, 780nm for Laser	Not specified	Continuous	30J/cm^2	150s with LED and 50s with Laser	9
Hamad et al 2015 [15]	GaAlAs Diode Laser	808nm	900 mW	Continuous	1459J/cm^2	5 min	5
Korany et al 2012 [16]	GaAlAs Diode Laser	830nm	75 mW	Continuous	Not specified	ns	1
Kucerova et al 2000 [17]	GaAlAs Diode Laser for group 1, He-Ne Laser for group 2	670nm for Diode laser, 632.8nm for He-Ne laser	20 mW for Diode laser, 5 mW for He-Ne laser	Pulsating with frequencies A = 292 Hz, B = 9000 Hz, C = 5 Hz for Diode laser. For He-Ne laser 5 Hz.	1.5J/cm^2	ns	4
Mergoni et al 2015 [18]	Nd:YAG laser	1064nm	1250 mW	Very short pulse mode 15 Hz	14.37J/cm^2	5 applications of 1min each in 1 sitting	4
Mozzati et al 2012 [19]	GaAs Diode Laser	904-910nm	200 mW	Superpulsed	180J/cm^2	15 min	3
Noda et al 2016 [6]	GaAs Diode Laser	904-910nm and 650nm for secondary laser beam	200 mW	High frequency pulsed 50kHz	43.8 and 17.4J/cm^2	1 min	3 and 5
Park JB et al 2013 [20]	GaAlAs Diode Laser	980nm	10 mW	Continuous	13.95J/cm^2/minute	0, 1, 2 or 5 min each sitting	3 and 7
Park JJ et al 2011 [9]	GaAlAs Diode Laser	980nm	10 mW	Continuous	13.95J/cm^2	1 min	3, 5, 7 and 14 days
Romao et al 2015 [21]	GaAlAs Diode Laser	808nm	100 mW	Continuous	75J/cm^2	150 sec	7

more specific data of the role of lasers following tooth extraction can help better assess the clinical benefits for procedures that are commonly taken up by general dentist. This current study focused on the role of photobiomodulation following tooth extraction and hence the search criteria picked up a greater number of studies than the study by Noba et al. (2018) [22].

There are two key issues in study design identified in this review. Firstly, species and subject differences have an impact on whether certain laser parameters can be recommended. Out of the ten included studies, only three studies utilised human subjects [17, 19, 21]. Two studies utilised rabbits [14, 15] and remaining five used rats [6, 9, 16, 18, 20]. With primitive bone structure and lack of harversian system in rats, healing is known to be different to humans [24]. Rabbits on the other hand, have harversian systems, but have a fast healing rate, with general consensus for bone repair being approximately 42 days [24]. Therefore, intergroup analysis between studies was not possible. Further, in the rat subgroup of studies, one study [16] subjected rats to 6 Gy gamma radiation, one study subjected them to bisphosphonate treatment [18], and one induced diabetes mellitus [9], and two other used healthy rats. This prevented direct comparison of this subgroup.

In the three human studies, two utilised healthy subjects [17, 21], while one included patients with hepatic failure waiting for liver transplantation [21]. Although specific liver disease has not been stated in the study [19], it is reported that hepatic failure, either before or after liver transplantation, causes the bone mineral density to drop substantially [25]. Therefore, the impact on bone healing post extraction is not comparable with that in healthy humans. This issue of subject selection needs to be considered for further studies.

Secondly, variation in laser parameters such as type of laser (GaAlAs, Nd:YAG, LED, or GaAs) power, energy level, wavelength, duration, energy density, and treatment frequency prevented direct comparison and establishment of optimal laser parameters for bone healing. Biomodulatory potential over a wide range of power and dosage has been demonstrated by the studies in this review. However, an ideal range is required to be established for improving cell proliferation and healing and preventing cell damage. In a recent study [26], photobiomodulation was applied at multiple energy levels (4, 8, and 16 J) with varying powers (50, 100, 200, 300, 400, and 500 mW) to fibroblasts and osteoblasts. Photobiomodulation treatment over 100 mV for 4, 8, and 16 J has been found to be the most optimum for bone repair and tissue healing process [26]. However, the study was conducted as an in vitro cell culture model and requires further animal studies to confirm the effectiveness.

Additionally, the observation intervals and period for human studies are inadequate. Romão et al. (2015) measured sockets 40 days (5–6 weeks) after the extraction [21]. This has been known to be approximately when initial stages of

Table 2 Data from included studies regarding outcome measures, subject attributes, and results

Author	Teeth extracted	Animal (n)	Systematic condition	Outcome measure	Observation period	Result
Comunian et al. 2017 [14]	Lower right first premolar	Rabbits (18)	Healthy	Clinically, hyperaemia, oedema, infection, bleeding, or any changes in the treated areas. CT was done after 90 days to assess bone density in Hounsfield Units (HU).	18 days clinically and 90 days histologically	Faster alveolar closing in both groups treated with LED and Laser. Reduced hyperaemia in both groups treated with LED and Laser. Statistically significant higher bone density in groups treated with LED compared to control.
Hamad et al. 2015 [15]	Lower right and left first premolar	Rabbits (20)	Healthy	Histology of socket specimens and Percentage volume density of trabeculae bone formation at various time intervals.	45 days	Significantly greater volume density of trabecular bone at both 14 and 30 days. At 14 days, mature regular bone trabeculae, thicker and longer than the non-irradiated sockets. At 30 days, more mature bone in irradiated sockets. At 45 days, non-irradiated sockets still contained immature bone while lasered sockets contained restored harversian system.
Korany et al. 2012 [16]	Lower right and left first molar	Rats (30)	Subjected to 6 gray Gamma radiation	Histology of socket specimen and percentage of bony trabeculae.	10 days	Statistically significant higher percentage of bony trabeculae in lasered group after 7 days but not after 10 days. There was inceased amount of deposition and accelerated maturation of bone.
Kucerova et al. 2000 [17]	Lower molar	Humans (150)	Healthy	Salivary secretary IgA and Albumin levels, Bone density via radiographs. Patient's subjective feeling of discomfort 5 days after extraction.	6 months	Greater sIgA and Albumin levels in Diode laser (Various frequency, highest with 9000Hz) compared to control. Insignificant difference in sIgA and Albumin levels between He-Ne laser and control. No significant difference in bone density found between all treatment methods and control. Patient found more comfort with laser therapy.
Mergoni et al. 2015 [18]	Upper left molar	Rats (30)	2 groups (bisphosphonate treatment and bisphosphonate treatment + laser) received zoledronate 0.1 mg/kg and dexamethasone 1 mg/kg every 2 days for 10 weeks.	Alveolar expression of osteopontin (OPN) and osteocalcin (OCN).	8 days	Significant increase in the expression of OCN in both the treatment + laser group as well as just laser group compared to treatment only and control group.
Mozzati et al. 2012 [19]	Bilateral - tooth not specified	Humans (12)	Hepatic failure patients waiting for liver transplantation	Inflammatory and Osteogenesis markers: IL-1β, IL-6, IL-10, TGF-β2, COX-2, BMP-4, BMP-7, PPAR-β, Collagen Type I and III. Clinical epithelial regeneration and patient's self-reporting of pain levels on VAS.	7 days	Patients reported less pain in laser treated sites. Examiners found rapid and complete epithelial regeneration in laser treated sites. Significant increase in Collagen Type III, IL-1β, IL-10. No difference in BMP-4, and BMP-7 was found.
Noda et al. 2016 [6]		Rats (27)	Healthy	Bone volume (BV), Bone mineral content (BMC) and	7 days	Un-epithelialised area smaller after 3 days in lasered sites compared to control. Lasered

Table 2 (continued)

Author	Teeth extracted	Animal (n)	Systematic condition	Outcome measure	Observation period	Result
	Upper right and left first molar			bone mineral density (BMD) using Micro-CT. Two blinded examiners also measured bone height from base of alveolus to the lowest point on the newly formed bone. Osteogenic marker expression: Collagen Type I, BMP-2, Ocn, Runx2, Alp and PCNA-positive cells.		sites had significantly higher BMC, BV, and BMD. Significantly higher levels of Ocn, Runx2, Alp. No change in Collagen Type I, and BMP-2. PCNA positive cells were significantly higher in laser treated sites.
Park JB et al. 2013 [20]	Upper right and left first molar	Rats (24)	Healthy	Expression of markers: Runx2, collagen type 1, osteocalcin, platelet-derived growth factor-B, and vascular endothelial growth factor.	7 days	5-minute radiation produced the most increase in all the tested markers.
Park JJ et al. 2011 [9]	Upper right and left first molar	Rats (24)	Diabetes Mellitus	Histological analysis and molecular analysis using RT-PCR	14 days	Significantly higher expression of Runx2 in groups that were lasered. Group of rats with Diabetes and no laser treatment had the lowest amount of new bone formation, while group without diabetes and with laser therapy had highest amount of new bone formation. Rats with diabetes and laser therapy had significantly higher amount of new bone formation as well as higher level of Collagen type 1, at 5 and 7 days than group with diabetes alone. Collagen type I was higher at all given points of time in group without diabetes and with laser therapy. Osteocalcin expression increased in all groups except the one with diabetes and no laser treatment.
Romao et al. 2015 [21]	Lower molar	Humans (20)	Healthy patients	Trabecular bone density using Micro-CT. Bone volume relative to total tissue volume was also measured using bone morphometric data. Bone formation in histomorphometric analysis was also measured.	40 days	Bone volume relative to total tissue volume was grater in lasered group compared to control. Significantly larger area of newly formed bone in group treated with laser compared to control group.

Table 3 Assessing methodological quality of human studies based on Jadad scoring scale (12)

	Kucerova et al. 2000 [17]	Mozzati et al. 2012 [19]	Romao et al. 2015 [21]
Is randomisation mentioned?	Yes	Yes	Yes
Is method of randomisation appropriate?	Method not mentioned	Yes	Yes
Is blinding mentioned?	Yes (Participants were blinded)	Yes (Participants were blinded)	Yes (Participants were blinded)
Is method of blinding appropriate?	Method not mentioned	Method not mentioned	No
Is fate of all participants known?	Not reported	Yes	Yes
Score	2	4	4

osteogenesis begin, but by no means complete. Mozzati et al. (2012) measured markers of healing 7 days post extraction with reduced pain and more rapid epithelial regeneration in lasered sockets, as well as increase in pro-inflammatory marker IL-Iβ, anti-inflammatory marker IL-10, and collagen type III [19] (Table 3). Kucerova et al. (2000), on the other hand, reports statistically insignificant changes in bone density, comparing data collected immediately after extraction and 6 months after extraction, therefore measuring whether an overall increase in bone density is possible with laser therapy upon completion of healing [17]. However, because no intervals between those 6 months were measured, it is inconclusive whether laser therapy produced similar bone density is a faster period of time. Hence, none of the human studies included measure the accelerating effect of photobiomodulation.

The primary outcome assessed in this systematic review was bone density. This was measured in six studies with positive results in five [6, 14–16]. Methods of measuring bone density varies from CT [14], Micro-CT [6, 21], histological determination of % volume density of trabecular bone formation [15, 16], and radiographs [17]. Only one human study [18] measured bone density using Micro-CT. Micro-CT is increasingly becoming the standard of bone density and architecture monitoring and is ideal in rodents as the trabecular thickness is 50–100 μm, and a voxel size of 10–20 μm is quite achievable [27]. The bone volume/total volume (%) was higher in laser group (88.55 ± 2.14) vs control group (67.51 ± 1.50) in the human study (p value < 0.0001) [21].

The secondary outcome measured were alveolar expression of Ocn and Runx2. There are four studies that tested for Ocn and/or Runx2 [6, 9, 18, 20]. Runx2 is a transcription factor gene, expression of which indicates osteoblastic differentiation and bone formation [28]. Osteocalcin, Ocn, is often used as a late osteogenesis marker also indicating bone formation [29]. Noda et al. found an increase in the expression of both Ocn and Runx2, consistent with an increase in bone mineral density, bone mineral content, and bone volume with photobiomodulation [6]. This trend was also consistent with other studies that were done [9, 18, 20], despite the variation in laser parameters and study designs.

As photobiomodulation is dependent on multiple parameters, it is recommended for researchers to provide a rationale for the use of certain laser parameters, use larger observation periods, utilise micro-CT for bone density measurement, and to use the same strain of healthy rabbits instead of mice in animal studies. Feasibility study may also be of benefit, specifically whether multiple visit intervention with photobiomodulation is practical, given patient compliance and cost of recall.

Conclusion

Within the limitations of this review, potential improvement in bone repair can be found when using photobiomodulation in extraction sockets. Despite the heterogeneity of data, quality of studies, as well as insufficient observation intervals and periods, positive effects reported by these studies cannot be completely neglected. The evidence suggests an increase in bone density, as well as increased expression of osteogenesis markers such as Ocn and Runx2.

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