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EDITED BY

Maurizio Delvecchio,
University of L'Aquila, Italy

REVIEWED BY

Yuzhen Wang,
People's Liberation Army General Hospital,
China
María Guadalupe Moreno Treviño,
University of Monterrey, Mexico

*CORRESPONDENCE

Quentin Perrier

✉ qperrier@chu-grenoble.fr

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Diabetes in spotlight: current knowledge and perspectives of photobiomodulation utilization

Quentin Perrier^{1*}, Cécile Moro² and Sandrine Lablanche³

¹Univ. Grenoble Alpes, INSERM U1055, Pharmacy Department, Grenoble Alpes University Hospital, Laboratory of Fundamental and Applied Bioenergetics, Grenoble, France, ²Univ. Grenoble Alpes, CEA-Leti, Clnatec, Grenoble, France, ³Univ. Grenoble Alpes, INSERM U1055, Diabetology and Endocrinology Department, Grenoble Alpes University Hospital, Laboratory of Fundamental and Applied Bioenergetics, Grenoble, France

Introduction: Diabetes is a global health concern characterized by chronic hyperglycemia resulting from insulinopenia and/or insulin resistance. The rising prevalence of diabetes and its associated complications (ulcers, periodontitis, healing of bone defect, neuropathy, retinopathy, cardiopathy and nephropathy) necessitate innovative therapeutic approaches. Photobiomodulation (PBM), involves exposing tissues and cells to low-energy light radiation, leading to biological effects, largely via mitochondrial activation.

Methods: This review evaluates preclinical and clinical studies exploring the potential of PBM in diabetes and its complications, as well all clinical trials, both planned and completed, available on ClinicalTrials database.

Results: This review highlights the variability in PBM parameters across studies, hindering consensus on optimal protocols. Standardization of treatment parameters and rigorous clinical trials are needed to unlock PBM's full therapeutic potential. 87 clinical trials were identified that investigated PBM in diabetes mellitus (with 5,837 patients planned to be treated with PBM). Clinical trials assessing PBM effects on diabetic neuropathy revealed pain reduction and potential quality of life improvement. Studies focusing on wound healing indicated encouraging results, with PBM enhancing angiogenesis, fibroblast proliferation, and collagen density. PBM's impact on diabetic retinopathy remains inconclusive however, requiring further investigation. In glycemic control, PBM exhibits positive effects on metabolic parameters, including glucose tolerance and insulin resistance.

Conclusion: Clinical studies have reported PBM-induced reductions in fasting and postprandial glycemia without an increased hypoglycemic risk. This impact of PBM may be related to its effects on the beta cells and islets in the pancreas. Notwithstanding challenges, PBM emerges as a promising adjunctive therapy for managing diabetic neuropathy, wound healing, and glycemic control. Further investigation into its impact on diabetic retinopathy and muscle recovery is warranted.

KEYWORDS

photobiomodulation, diabetes, neuropathy, wound healing, periodontitis, retinopathy, glycemic control

1 Introduction

Diabetes is characterized by chronic hyperglycemia due to insulinopenia [type 1 diabetes (T1D)] and/or insulin resistance [type 2 diabetes (T2D)]. The International Diabetes Federation reported 537 million of potential cases of diabetes across the world in 2021 with an increment planned for 2045 at 783 million of potential cases (1). As a result, diabetes caused 6.7 million of death in 2021 (1) and led to USD 966 billion health expenditures (1) partially due to numerous complications related to diabetes disease (2) such as macrovascular complication (ischemic cardiomyopathy, stroke and arteriopathy) (2–5) and microvascular complications: 1) retinopathy, diabetes is the first cause of non-traumatic blindness (6), 2) nephropathy, diabetes is the first cause of dialysis, 3) amputation and 4) neuropathy (7, 8) leading to foot ulceration and exposing patient to a risk of lower limb amputation [diabetes is the first cause of non-traumatic amputation (9)]. Finally, patients living with diabetes are also exposed to a risk of periodontitis (10). Altogether, diabetic complications alter quality of life (11, 12). These complications can be prevented through optimal glycemic control and could be managed with some medicines (13, 14). However, despite optimal medical management, prevention of diabetic complications remains a challenge and additional treatment remains mandatory.

Light was used as potential of treatment since the ancient Egypt. The biological reaction to light and its therapeutic applications are not new. For example, the beneficial effect of light on neonatal jaundice, discovered in the 1950s, made phototherapy (with blue light with a wavelength between 420–490 nm) the main modality for its treatment (15). Another example, the effects of light on mood, demonstrated in the 80s, made it possible to propose light therapy as a treatment for seasonal affective disorders, and it has recently been shown to have an effect comparable to antidepressants in episodes major depression (16).

Photobiomodulation therapy (PBM), formerly called “Low level laser therapy”, is a phototherapy based on the exposure of tissues and cells to non-ionizing and very weak light radiation with a wavelength generally ranging from red (between 600–700 nm) to the near infrared (between 700–1400 nm) and resulting in biological effects following its absorption by endogenous chromophores. Historically, PBM was first described by Endre Mester in 1968 who observed faster hair regrowth in rodents exposed to a low-energy laser with a wavelength of 694 nm (17, 18). In the same years, it was also developed by the National Aeronautics and Spatial Administration (NASA) to accelerate the healing and regeneration of muscle cells in astronauts (19). For the past decades, biomedical research relating to PBM has been constantly increasing, indicating a growing interest in its therapeutic potential. Interest in PBM has also been linked to technical developments in illumination technology, with the improvement of LEDs, which are cheaper, safer and give off less heat than lasers (20). Depending on the targeted use, and the illumination device, PBM can be brought along white light, to have the full spectrum of wavelength as a natural light, or along LED to obtain mainly a light targeted around a wavelength, or a laser to deliver only a define wavelength. At the

beginning of the 2000s, the use of PBM in aesthetics (hair regrowth, wrinkle reduction) and sports recovery helped to democratize its use. Photobiomodulation is now used to help heal damaged tissues, improve immune response, reduce inflammation, and was recommended to prevent or treat certain side effects of treatments such as chemotherapy and radiotherapy (mucositis and radiodermatitis). In 2010, the first clinical authorization was reached as therapeutics for pain in conditions such as osteoarthritis. Since the 2020s, based on successful preclinical researches, various clinical trials have been initiated to evaluate PBM as a treatment to slow down neurodegenerative diseases, such as Alzheimer’s or Parkinson’s diseases (21, 22). Over the past three years (2020–2022), approximately 850 articles per year have been published and referenced in MEDLINE.

The main mechanism of action involves the mitochondria (23), possessing photo-acceptors sensitive to the lengths used with PBM. Briefly, PBM has been reported to activate non-mitochondrial cellular functions (light/heat-gated ion channels) and restore mitochondrial function (through interfacial water and/or activation of cytochrome C oxidase), resulting in a short-term increase adenosine triphosphate (ATP) energy production in body cells and increased production of NO. This process leads to long-term effects, with the expression of various stimulatory and protective genes. The main biological effects highlighted in preclinical and clinical studies are an anti-inflammatory, analgesic action, an increase in blood circulation, angiogenesis, and a healing/regeneration and tissue proliferation action (24–26). Given these effects, the potential therapeutic applications are numerous. PBM is already used in certain medical disciplines. It is part, for example, of the recommendations for the prevention of mucositis in patients treated by radiotherapy.

The use of PBM in the context of neurodegenerative diseases, and in particular Parkinson’s disease, is currently being studied and is the subject of clinical trials. PBM could represent an innovative therapeutic solution, to slow down the neurodegenerative process. The preclinical results in this direction are very encouraging, and clinical data should be published soon due to ongoing clinical trials. The metabolic syndrome in neurodegenerative diseases, and in particular Parkinson’s disease, are well established (21, 22). The observed effect of PBM on cellular metabolism, inflammatory and scarring processes is a lead that may indicate an interest of PBM in the regulation of phenomena related to metabolic syndromes, such as diabetes.

In the present work, the purpose is to review the clinical studies using PBM and conducted in the field of the treatment of diabetes and diabetic complications.

2 Materials and methods

Identification was made regarding:

- Pre-clinical (animal study) and clinical data available until 23 May 2023
- Clinical trials available on clinicaltrials.gov (27) until 23 May 2023

2.1 Searching strategy and selection criteria of papers

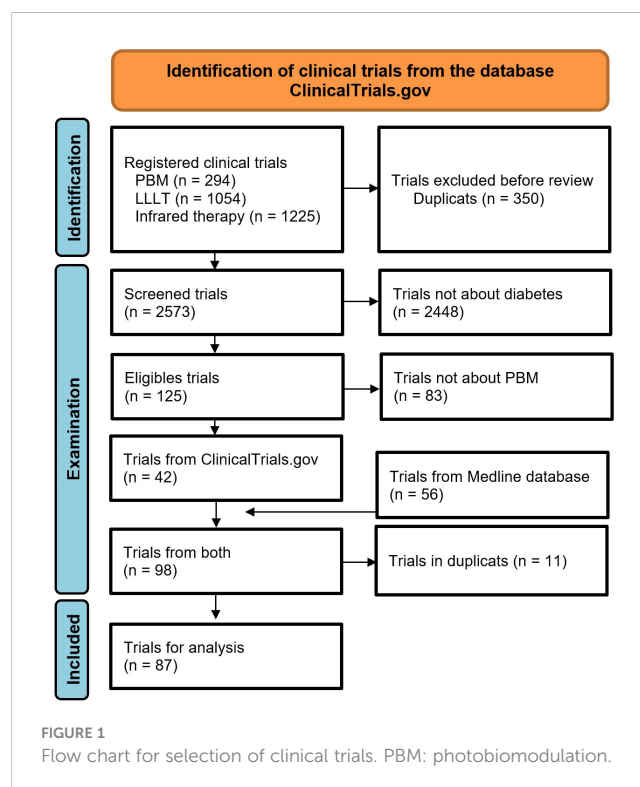
A MEDLINE research was conducted via PubMed using the search terms: [(Photobiomodulation) or (Low-level laser therapy) or (Near-infrared therapy)] AND (diabetes or diabetic or T1D or T2D) AND (1900/01/01:2023/05/23[edat]). In addition, references from cited papers were investigated. For each paper, the following parameters were recorded: 1st author, year of publication, model used (including the number of patients in clinical trials), wavelength, light source (LED or laser), mode of administration (continuous or pulsed), PBM parameters (power density in mW/cm², time per exposure, energy density in J/cm², frequency, sites), and the study's conclusion. The data were analyzed both collectively and individually, considering different diabetes conditions such as retinopathy, ulcers, and periodontitis. In the case of clinical trial papers, it was specified whether they were randomized clinical trials (RCTs), pre-post interventional trials (Pre-Post ITV) or observational studies.

2.2 Searching strategy for clinical trials and classification

The screening of the ClinicalTrials database (27) was conducted using three terms: photobiomodulation, low-level laser therapy and near-infrared therapy. Only trials related to diabetes were considered eligible, and studies employing methods other than PBM were excluded (Figure 1). For each included trial, the following parameters were recorded: starting date, country of the sponsor, expected number of enrolled patients, and enrolment status (not yet recruiting, recruiting, enrolling by invitation, active, suspended, terminated, completed, withdrawn, or unknown). Regarding clinical trials published in the Medline database, the following parameters were recorded: country of the sponsor and number of enrolled patients. All these trials were classified as completed.

3 Results

Following Medline research, 124 articles met the search criteria. 170 different exposure times were studied and varied widely, with 35% of the studies (60/168) having exposure times (for one session) of less than a minute and 35% (59/168) exceeding 5 min (Figure 2). Laser was the predominant light source investigated in 80% of the studies (Figure 2), and continuous exposure was the primary mode of administration (84% of studies, Figure 2). The power density values ranged from 1 mW/cm² to 8.32 W/cm², whereas the energy density ranged from 0.03 to 420 J/cm². These studies investigated various wavelengths ranging from 425 to 1064 nm, with 82% of studies between 600 and 900 nm, and six studies exploring multiple wavelengths applying simultaneously (Figure 2). It should be noted that



these parameters were not fully described or available in 37 studies (29%).

3.1 Clinical trials in humans

42 trials were identified in ClinicalTrials database (27), and 56 articles were found in Medline. After removing duplicate trials, 87 were conducted or planned (Figure 2). These trials included 5,837 patients (see Table 1 for details). The top three countries planning to conduct trials on PBM and diabetes were the United States (n = 19), Brazil (n = 18), and India (n = 10, Figure 3). 50% of publications were by completely independent teams (n = 21 articles). Regarding diabetic neuropathies, two teams each published three studies: Burke et al. (28–30), and Arun G et al. (31–33). Regarding diabetes chronic periodontitis, three teams each published 2–3 studies: Chava et al. (34, 35), Haaki et al. (36, 37), and Obradovic et al. (38–40). Regarding performance and functionality during or after exercise in patient with diabetes Ferraresi et al. (41–43). published three studies. Finally, two teams have published on neuropathic pain and diabetic ulcers: Arisawa et al. (44, 45), and Schindl et al. (46–48).

3.2 Impact of PBM on diabetic neuropathy

A total of 23 studies were conducted, including 5 on preclinical models- (49–53) and 18 in humans (28–33, 46, 54–63) (Table 2).

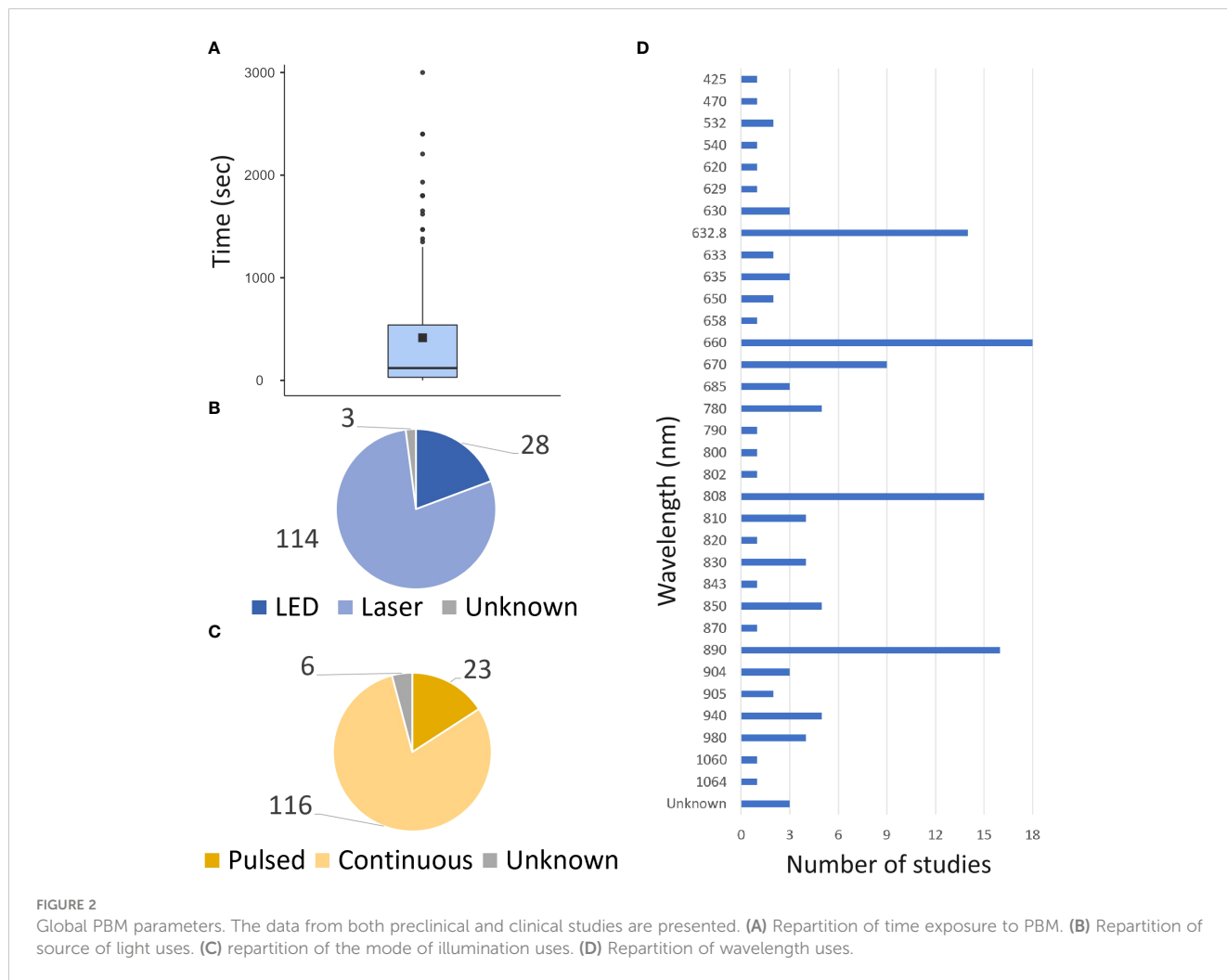


TABLE 1 Number of patients treated in clinical trials with PBM for diabetes condition.

Status of studies	Number of studies	Expected number of participants
Active, not recruiting	1	80
Completed	66	4954
Not yet recruiting	2	160
Recruiting	5	300
Suspended	1	60
Terminated	4	75
Unknown status	6	208
Withdrawn	2	0
Total	87	5837

These numbers of participant represent the expected enrolment for trial not already completed.

3.2.1 Pain investigation

Among 14 studies investigating pain, 11 reported a decrease in pain after PBM, with 4 studies conducted on preclinical models and 7 on clinical subjects. In clinical trials, pain was evaluated using a visual analogic scale (VAS), either alone or in combination with other pain assessment scores with a follow-up period ranging from 4 to 90 days. For pre-post interventional trials (n = 3), the VAS scores decreased by an average of 2.3 to 5.2 points after PBM. In RCTs (n = 4), the VAS scores decreased more in the PBM group than in the control group (0 to 3 points vs. 3 to 5 points after 10 days) (44, 54), and the VAS scores at the end of the follow-up period were lower in the PBM group than in the control group (6.9-7.9 vs. 5.9-5.3) (33, 56).

3.2.2 QoL investigation

Four studies investigated the effect of PBM on QoL. Two studies reported a positive impact of PBM on QoL associated with a decrease in pain (44, 54). Conversely, 2 studies did not report an impact of PBM on QoL but in these 2 studies PBM did not induced a decrease in pain (58, 59). The first study (58) used the highest

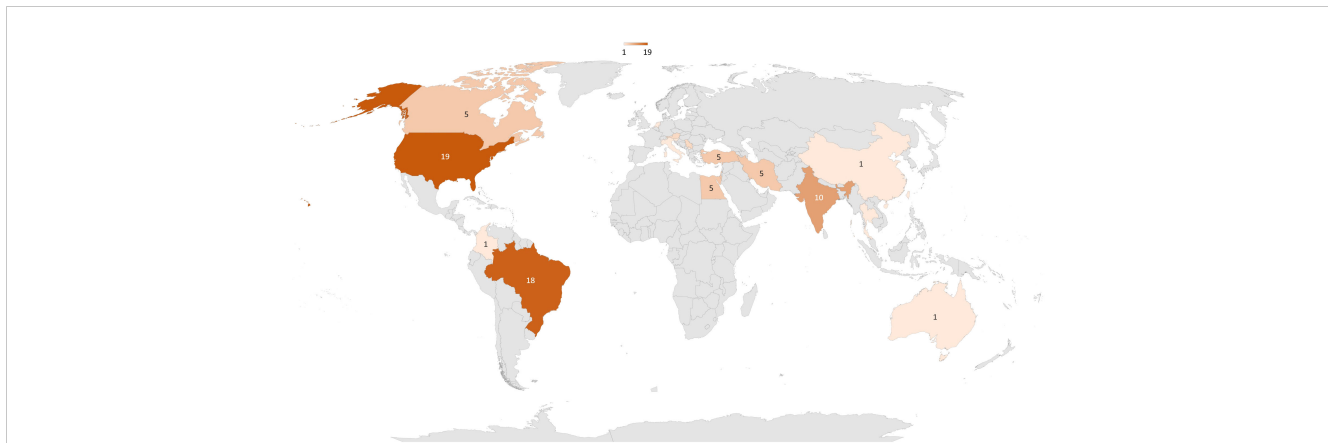


FIGURE 3
 Repartition around the world of clinical trials about PBM and diabetes. 87 trials have been conducted or are planned, 43 in America, 26 in Asia, 12 in Europe, 5 in Africa, and 1 in Oceania.

TABLE 2 Effects of PBM on diabetic neuropathy.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Vieira 2022 (49)	Lewis rat Streptozotocin induced	904	Continuous laser	7W/cm ² , 29sec, 203J/cm ² Frequency: once a day Site: 1, dorsal, direct contact	↓ pain ↓ cytokines (TNFα, IL-1β, IL-10) No effect on metabolic parameters
Rocha 2021 (50)	Wistar rat Streptozotocin induced	904	Continuous laser	340mW/cm ² , 18sec, 6,23J/cm ² Frequency: once a day, for 10 days Site: on sciatic nerve routes, direct contact	Restore fusion/fission mitochondria dynamic
Vieira 2019 (51)	Lewis rat Streptozotocin induced	904	Continuous laser	7W/cm ² , 29sec, 203J/cm ² Frequency: once a day for 8 days Sites: 4 points, direct contact	↓ pain
Abdel-Wahhab 2018 (52)	Albinos rat Streptozotocin induced	808	Continuous laser	30sec, 90J* Frequency: 3 times a week for 8 weeks Sites: 3 points	↓ pain ↓ PGE2, TNFα, IL1β, IL10
da Silva Oliveira 2018 (53)	C57BL6 mice Streptozotocin induced	660	Continuous laser	107mW/cm ² , 15sec, 1.6J/cm ² Frequency: once a day, for 21 days Site: 1, plantar hind paw, direct contact	↓ pain Prevent myelin degeneration ↓ loss of C fiber
Rastogi 2021 (54)	Human, n = 38 Diabetes RCT [†]	890	LED Unknown	30min, 58.5J/cm ² /min Frequency: 3 times a week, for 12 weeks Sites: 4, plantar foot x2, posterior & anterior distal leg	↓ pain (VAS decrease of 5.3 vs. 3 at 3 months) ↑ QoL (Norfolk-QoL DN 8 vs. 12 at 3 months) No effect on cutaneous reinnervation
Anju 2020 (31)	Human, n = 50 T2D Pre-Post ITV ^o	632.8	Continuous laser	5.7mW/cm ² , 9min, 3.1J/cm ² Frequency: once a day, for 10 days Sites: 2, plantar and dorsal foot	↓ vibration perception threshold ↓ neurone specific enolase
da Silva Leal 2020 (44)	Human, n = 30 T2D RCT [†]	660	Continuous laser	1.66mW/cm ² , 30min, 3J/cm ² Frequency: once a day, for 10 days, 20 days washout and start 2 times more Site: 1, radial artery region, direct contact	↓ pain VAS: no change vs. decrease of 3 points LANSS: no change vs. decrease of 3 points Pain detect questionnaire: no change vs. decrease of 5 points ↑ QoL (SF-36, all parameters increase)
Anju 2019 (32)	Human, n = 40 T2D Pre-Post ITV ^o	632.8	Continuous laser	5.7mW/cm ² , 9min, 3.1J/cm ² Frequency: once a day, for 10 days Sites: 2, plantar and dorsal foot	↑ Mg and Vitamin D
Kumar 2015 (55)	Human, n = 19 T2D Pre-Post ITV ^o	660 + 850	Continuous laser	5.7mW/cm ² , 9min, 3.1J/cm ² Frequency: once a day, for 10 days Sites: 2, plantar and dorsal foot, direct contact	↓ pain (VAS: decrease of 5.2 points after 10 days)

(Continued)

TABLE 2 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
					↓ vibration perception threshold ↑ microcirculation
Bashiri 2013 (56)	Human, n = 60 T1D & T2D RCT [†]	780	Continuous laser	8.3mW/cm ² , 5min, 2.5J/cm ² Frequency: 2 times a week, for 4 weeks Site: unknown	↓ pain (VAS: score of 7.9 vs. 5.9 for PBM after 4 weeks)
Yamany 2012 (33)	Human, n = 30 T2D RCT [†]	850	Continuous laser	6.3mW/cm ² , 15min, 5.7J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 2, plantar surface of foot, lombo-sacral area, 30cm above the area	↓ pain (VAS; score of 6.9 vs. 5.3 for PBM after 4 weeks) ↑ microcirculation ↑ sural nerve conduction No effect on peroneal nerve
Khamesh 2011 (57)	Human, n = 27 T2D Pre-Post ITV [†]	800	Continuous laser	1W* Frequency: 10 sessions Sites: 6 paravertebral points, 4 on sciatic nerve routes	↑ neuronal potential amplitude
		905	Pulsed laser	25W*, 10J/cm ² Frequency: 10 sessions Sites: 6 paravertebral points and 4 on sciatic nerve routes	↑ neuronal potential amplitude
Swislaki 2010 (58)	Human, n = 121 Diabetes RCT [†]	870	Continuous laser	350W*, 7min, 1800J* Frequency: Once a day, 4 days Sites: 16 on each foot	Restoration sensation No effect on pain (VAS, PQAS) No effect on quality of life (SF-36)
Lavery 2008 (59)	Human, n = 60 Diabetes RCT ^o	890	Continuous LED	40min, 1,3J/cm ² /min Frequency: once a day, for 90 days Sites: 4, plantar foot x2, medial & lateral side of the calf	No effect on pain (VAS) No effect on QoL (Neuro QoL) No effect on peripheral sensation
Arnall 2006 (60)	Human, n = 22 T1D & T2D RCT (for foot) [†]	880 + 650	Pulsed LED	30min Frequency: 3 times a week, for 8 weeks Sites: 2, volar and dorsum of foot	↑ mechanical sensation ↓ perception threshold ↑ peripheral protective sensation
Harkless 2006 (28)	Human, n = 979 Diabetes Pre-Post ITV ^o	890	Pulsed laser	Unknown	↓ pain (VAS: decrease of 4.8 points) ↑ foot sensation
Clift 2005 (61)	Human, n = 70 Diabetes RCT ^o	890	Continuous laser	30min, 58.5J/cm ² /min Frequency: 3 times a week, for 4 weeks Sites: 4, plantar foot x2, posterior & anterior distal leg	No effect on sensation
DeLellis 2005 (29)	Human, n = 790 T2D Pre-Post ITV ^o	890	Pulsed laser	No detail	↓ sensitivity impairment Restoration protective sensation
Leonard 2004 (62)	Human, n = 27 T1D & T2D Pre-Post ITV ^o	890	Continuous laser	40min, 50J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 4, inferior member	↓ pain (VAS: decrease of 2.3 points after 4 weeks) ↓ place without sensation Restoration protective sensation
Zinman 2004 (63)	Human, n = 50 Diabetes RCT [†]	905	Continuous laser	60mW*, 5min Frequency: 2 times a week, for 4 weeks Sites: 2 painful sites, direct contact	No effect on pain (p = 0.07) (VAS)
Kochman 2002 (30)	Human, n = 49 T1D & T2D Pre-Post ITV [†]	Unknown	Continuous laser	30min Sites: 4, Posterior & anterior tibia, dorsal & ventral foot	↓ sensitive impairment ↑ neural function (hot/cold discrimination)
Schindl 2002 (46)	Human, n = 30 Diabetes RCT ^o	632.8	Continuous laser	30J/cm ² Frequency: Once Site: 1	↑ microcirculation

T: no other treatment for pain, [†]:treatments for pain are permitted, but must be balanced and not change during the course of the study (i.e. amitriptylin, gabapentin, tramadol), ^o: no information provided about other treatment during the study, IL, Interleukin; LANSS, Leeds assessment of neuropathy symptoms and signs; LED, Light emitting diode; PBM, photobiomodulation; PQAS, Pain qualities assessment scale; Pre-Post ITV, Pre-post interventional trial; QoL, Quality of life; RCT, randomized controlled trial; T1D, Type 1 diabetes; T2D, Type 2 diabetes; TNF, Tumor necrosis factor; VAS, Visual analogic scale. *Surface of PBM not reported.

↑, increase; ↓, decrease.

power (350W), and the second study (59) used the longest exposure time (40 min) and application frequency (once a day for 90 days).

3.3 Impact of PBM on diabetic retinopathy

A total of 6 studies were conducted, including 4 studies on preclinical models (64–67) and 2 studies in humans (68, 69) (Table 3). Preclinical studies consistently reported a positive effect of PBM on retinal structure associated with a decrease in oxidative stress. In clinical studies focusing on macular oedema, findings were divergent regarding improvement of visual acuity between the two identified studies (68, 69). However, no side effects were reported in either study.

3.4 Impact of PBM on glucose metabolism in T2D

A total of 9 studies were conducted, with 8 studies conducted on preclinical models (70–78) and one study in humans (79) (Table 4). The preclinical studies consistently reported positive effects of PBM on metabolic parameters with an improvement in glucose tolerance [with a glucose tolerance test area under the curve (GTT AUC) decreasing by 12–28%], a decrease in insulin resistance [with a 22% decrease in homeostatic model assessment of insulin resistance (HOMA-IR (70)) and a 10% decrease in insulin tolerance test (ITT) AUC (72)] and a decrease in fasting glycemia. PBM also showed positive effects on lipid profiles with a reduction in free fatty acid,

triglycerides and cholesterol levels. In the clinical study (79), PBM applied on eight muscles in patients with T2D resulted in a decrease in glycemia (fasting and 1h post-prandial glucose) observed 30 min to 12 h after PBM treatment. This decrease was evidenced by a reduction in the GTT AUC by 37% and a reduction of 1h postprandial glucose by 16%. Importantly, no additive effect of hypoglycemic treatment was observed and no hypoglycemia were reported.

3.5 Impact of PBM on exercises and muscles in T2D

A total of 7 studies were conducted, including 3 studies on preclinical models (41, 80, 81) and 4 studies in humans (42, 43, 82, 83) (Table 5). In preclinical models, PBM has been demonstrated to have a positive impact on biochemical parameters, such as a decrease in oxidative stress and an increase in antioxidant activity. However, in clinical studies focusing on muscular performance and functionality during or after exercise, PBM has failed to show any improvement. No significant effects on the muscular performance were observed.

3.6 Impact of PBM on healing process

3.6.1 Wound healing

A total of 44 studies were conducted to evaluate impact of PBM on wound healing, including 31 studies on preclinical

TABLE 3 Effect of PBM on diabetic retinopathy.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Ahmed 2021 (64)	Wistar rat Streptozotocin induced	670	Continuous laser	5mW/cm ² , 90sec, 0.9J/cm ² Frequency: 2 times a week, for 6 weeks Sites: 2, each eye, directly in eye	Improve structure of inner nuclear layer and retinal pigmented epithelium ↓ anatomical abnormalities
Cheng 2018 (65)	C57BL/6J mice Streptozotocin induced	670	Continuous LED	25mW/cm ² , 240sec, 6J/cm ² Frequency: once a day, for 8 months Site: 1, back of the animal	↓ degeneration of retinal capillaries ↓ albumin accumulation in the inner nuclear and in the outer plexiform layers of the retina Preservation of spatial frequency threshold contrast sensitivity
Saliba 2015 (66)	C57BL/6J mice Streptozotocin induced	670	Continuous LED	20mW/cm ² , 240sec, 5J/cm ² Frequency: once a day, for 10 weeks Site: Total body	↓ superoxide in retina ↓ abnormalities induced in leukostasis No effect on contrast sensitivity
Tang 2013 (67)	Lewis rat Streptozotocin induced	670	Continuous LED	25mW/cm ² , 240sec, 6J/cm ² Frequency: once a day, for 10 weeks Site: total body	↓ diabetes induced abnormality of retinal function and abnormalities of electroretinograms ↓ retinal ganglion cell death Inhibited leukostasis
Shen 2020 (68)	Human, n = 21 Diabetes Pre-Post ITV [†]	670	Continuous LED	25-100-200mW/cm ² , 90sec, 2.25-9-18J/cm ² Frequency: 12 sessions over 5 weeks Site: fundus contact lens	↓ central macular thickness (100 and 200>25) No effect on visual acuity No adverse event
Eells 2017 (69)	Human, n = 10 Diabetes RCT [†]	670	Unknown	45mW/cm ² , 100sec, 4.5J/cm ² Frequency: 3 consecutive days per week, for 8 weeks Sites: 2, each eye, directly in eye	↓ central retinal thickness ↑ visual acuity (+ 6 letters)

[†]: PBM in addition to the best standard of care, at the investigator discretion choice, LED, Light emitting diode; Pre-post ITV, Pre-post interventional trial; RCT, Randomized controlled trial. ↑, increase; ↓, decrease.

TABLE 4 Effect of PBM on glucose metabolism in T2D.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Min 2022 (70)	Diabetic Goto Kakizaki rat	630	Continuous LED	3.7mW/cm ² , 600sec, 2.22J/cm ² Frequency: 1 session Site: intra-duodenal	No effect
		630 + 850	Continuous LED	32.72mW/cm ² , 100sec, 3.6J/cm ² Frequency: 1 session Site: intra-duodenal	↓ glucose intolerance at 4 weeks (↓GTT AUC about 14.5%) ↓ insulin resistance only at 1 week (↓HOMA-IR about 22%) ↑ expression of insulin in beta cells
Bonifacio 2021 (71)	C57BL/6 mice High fat diet	808	Continuous laser	3.57W/cm ² , 8sec, 30J/cm ² Frequency: 3 times a week, for 4 weeks Site: 1, direct contact with skin in pancreas region	No effect on glucose tolerance (GTT) No effect on insulin resistance (ITT) No effect on fasting glycemia No effect on body weight No effect on pancreas morphology No effect on adiposity tissue No effect on pancreas morphology
Gong 2021 (72)	C57BL/6 mice High fat diet and mice C57BLK5 diabetic	635	Continuous laser	72.1mW/cm ² , 10min, 43.3J/cm ² Frequency: once a day, for 10 weeks Sites: 2, direct contact with skin	↓ glucose intolerance (↓GTT AUC about 12%) ↑ insulin sensitivity (↓ITT AUC about 10%) ↓ fed glycemia (500 vs. 280mg/dL) ↓ fasted glycemia (490 vs. 200mg/dL) ↑ glycogen in muscle ↓ ectopic fat in muscle ↓ triglycerides and free fatty acid
Gong 2020 (73)	C57BL/6 mice High fat diet	635	Continuous laser	72.1mW/cm ² , 10min, 43.3J/cm ² Frequency: once a day, for 10 weeks Site: abdomen, direct contact with skin	↓ triglycerides, plasmatic FFA ↑ relative oxygen species
Guo 2020 (74)	C57BL/6 mice High fat diet	635	Continuous laser	72.1mW/cm ² , 10min, 43.3J/cm ² Frequency: once a day, for 8 weeks Site: abdomen, direct contact with skin	↓ glucose intolerance (GTT) ↑ insulin sensitivity (ITT) Protect against obesity (weight similar to control) Protect against hyperglycemia (glycemia similar to control) ↓ weight, glycemia, triglycerides, cholesterol, insulinemia ↓ hepatic steatosis
Silva 2020 (76)	Swiss albinos mice High fat diet	630	Continuous LED	779.53mW/cm ² , 40sec, 31.18J/cm ² Frequency: 5 days per week, for 4 weeks Sites: 5, direct contact with skin	↓ glucose intolerance (↓ GTT AUC about 28%) ↓ fasting hyperinsulinemia (↓insulin concentration by 3)
Silva 2018 (77)	Swiss albinos mice High fat diet	780	Continuous laser	259mW/cm ² , 40sec, 10J/cm ² Frequency: 5 days per week, for 4 weeks Sites: 5, direct contact with skin	↓ glucose intolerance (↓ GTT AUC about 16%) No effect on insulin resistance (HOMA-IR) ↓ fatty mass epididymal ↓ total cholesterol ↑ insulin signaling pathway
Yoshimura 2016 (78)	C57BL/6 mice High fat diet	843	Continuous LED	19mW/cm ² , 300sec, 5.7J/cm ² Frequency: day 1, 3, 7, 10, 14 and 21 Site: abdomen, direct contact with skin	↓ glycemia (98 vs. 118 mg/dL for non-treated group) No effect on weight ↓ abdominal fatty infiltration
Scontri 2023 (79)	Human, n = 10 T2D RCT [†]	830	Continuous LED	114.28mW/cm ² , 50 or 120sec, 5.71 or 13.71J/cm ² Frequency: One session and 7 days of washout Sites: 8, muscles, in contact with skin	Effect only with 5.71J/cm ² ↓ post prandial glycaemia (30 min to 12h after PBM) Better effect on glycaemic control than hypoglycemic treatments ↓ GTT AUG around 37% Faster glucose decay post prandial (16%, -60 vs. -70mg/dL/h) No additive effect with hypoglycemic treatments

[†]: PBM in addition to the best standard of care, at the investigator discretion choice, AUC, Area under the curve; FFA, Free fatty acid; GTT, glucose tolerance test; HOMA-IR, Homeostasis model assessment insulin resistance; ITT, insulin tolerance test; LED, Light emitting diode; PBM, photobiomodulation; RCT, randomized controlled trial; T2D, Type 2 diabetes.

↑, increase; ↓, decrease.

TABLE 5 Effect of PBM on exercise and muscle in T2D.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
da Silva Tonetto 2023 (80)	Wistar rat Streptozotocin and diet induced	660	Continuous laser	571mW/cm ² , 36.75sec, 21J/cm ² Frequency: 5 days per week, for 6 weeks Sites: 2, medial and laterally of gastrocnemius	↓ oxidative activity ↑ antioxidative activity (↑ superoxide dismutase)
de Oliveira 2019 (41)	Wistar rat Streptozotocin induced	660	Continuous laser	250mW/cm ² , 16sec, 2J/cm ² Frequency: 3 times a week, for 3 weeks Site: 1, dorsal	No effect on glucose concentration No effect on muscle parameters if PBM was not associated with exercise
Frigero 2018 (81)	Wistar rat Streptozotocin induced	808	Continuous laser	107.1mW/cm ² , 44sec, 4.71J/cm ² Frequency: 1/session of exercise Sites: 3, gastrocnemius	↓ oxidative stress (↓ lactate, ↓ catalase, ↑ superoxide dismutase) ↑ VO ₂ max and speed of run
Linares 2022 (42)	Humain, n = 13 DT2 RCT ^T	850	Continuous LED	375mW/cm ² , 140 to 1120 sec, 52.5-420J/cm ² Frequency: 1/session of exercise Sites: 7, oblique and rectus abdomen, quadriceps femoris, triceps, hamstrings bilateral	↓ glycemia and lactate 15min after PBM Improvement of cardiac parameters
Gobbi 2021 (82)	Humain, n = 17 DT2 RCT ^o	620	Continuous LED	52.86mW/cm ² , 96sec, 5.074J/cm ² Frequency: once a day, for 3 days Sites: 4, ankle flexor and extensor bilaterally	No impact on muscular performance No impact on muscular functionality
		940	Continuous LED	33.7mW/cm ² , 106sec, 3.572J/cm ² Frequency: once a day, for 3 days Sites: 4, ankle flexor and extensor bilaterally	No impact on muscular performance No impact on muscular functionality
		620 + 940	Continuous LED	Same parameters of 2 others	No impact on muscular performance No impact on muscular functionality
Milan-Mattos 2020 (43)	Humain, n = 7 T2D RCT ^T	850	Continuous LED	375mW/cm ² , 40sec, 15J/cm ² ou 80sec, 30J/cm ² Frequency: 1/session of exercise Sites: 2, quadriceps and triceps bilaterally	No impact on baroreflex during or after exercise No impact of PBM on cardiovascular autonomic control
Francisco 2019 (83)	Humain, n = 16 T2D RCT ^T	850	Continuous LED	375mW/cm ² , 40sec, 15J/cm ² Frequency: 1/session of exercise Sites: 2, quadriceps and triceps bilaterally	No impact of PBM on lactate concentration No impact on cardiopulmonary and hemodynamic adjustments

T, no other treatment for pain; o, no information provided about other treatment during the study; LED, light emitting diode; PBM, photobiomodulation; RCT, Randomized controlled trial; T2D, Type 2 diabetes.

↑, increase; ↓, decrease.

models (84–114) and 13 studies on humans (45, 47, 48, 115–124) (Table 6). In preclinical models, PBM had a predominantly positive effect on wound healing in 94% of studies. PBM improved various aspects of wound healing, including collagen density, fibroblast proliferation, angiogenesis, granulation tissue formation, and epithelialization. These effects were often accompanied by a decrease inflammatory marker. Only one study, which poorly described PBM parameters, did not report a positive effect of PBM (104). Most studies utilized wavelengths in the red to near-infrared spectrum, whereas studies investigating green wavelengths did not report positive effects of PBM (84, 94). In clinical studies, the majority (92%) reported a positive effect of PBM on chronic ulcers healing. Among the 12 RCTs, there was an increase in wound closure ranging from 15% to 47.3% in the control group compared to 37% to 90.8% in the PBM group. Consequently, the PBM groups had smaller wound areas compared to the control groups, with measurements of 2.39 cm² vs. 8.43 cm² (120), indicating a decrease in wound area of approximately 3.2 cm² vs. 10.4 cm² (122). The only study that did not report a positive effect of PBM utilized the shortest

exposure time (less than one second) (121). Two studies specified that PBM did not have any reported side effects (115, 117) while other studies did not explicitly mention it.

3.6.2 Healing of bone defect

A total of 16 studies were conducted to evaluate impact of PBM on healing of bone defect, with 15 studies conducted on preclinical models (125–139) and one study in humans (140) (Table 7). Among these studies, only one preclinical study did not report a positive impact of PBM on bone repair. This study used the highest power among all studies, with a dosage of 369.4J/cm². In addition to the effect of PBM on bone repair, several studies reported an increase in bone vascularization and a decrease in inflammation.

3.6.3 Chronic periodontitis

A total of 16 studies were conducted to evaluate the impact of PBM on chronic periodontitis in humans (34–40, 141–149) (Table 8).

■ Effect on healing process

The effects of PBM were evaluated using the following measures:

TABLE 6 Effect of PBM on wound healing and ulcer.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusion
Dungel 2023 (84)	C57BL diabetic mice	629	Pulsed LED	40mW/cm ² , 360sec, 14.4J/cm ² Frequency: day 0 and 1 Site: near to the wound	↑ wound closure ↑ angiogenesis
		540	Pulsed LED	40mW/cm ² , 360sec, 14.4J/cm ² Frequency: day 0 and 1 Site: near to the wound	↑ wound closure ↑ angiogenesis
		470	Pulsed LED	40mW/cm ² , 360sec, 14.4J/cm ² Frequency: day 0 and 1 Site: near to the wound	No effect
Ebrahimipour-Malekshah 2023 (85)	Wistar rat Streptozotocin induced	890	Pulsed laser	20mW/cm ² , 200sec, 1.08J/cm ² Frequency: once a day, for 14 days Sites: 9, direct contact	↑ granulation tissue formation ↓ neutrophils, ↑ macrophages ↑ fibroblasts ↑ vascularization (VEGF)
Mehrvar 2021 (86)	Diabetic mice	670	Continuous LED	60mW/cm ² , 90sec, 4.5J/cm ² Frequency: 5 days per week, for 2 weeks Site: 1, next to the wound	↓ wound area ↓ oxidative stress ↑ Red-Ox ratio
Ahmadi 2020 (87)	Wistar rat Streptozotocin induced	890	Pulsed laser	1mW/cm ² , 200sec, 0.2J/cm ² Frequency: once a day, for 14 sessions Sites: 9, next to the wound	↑ wound healing ↓ inflammation (neutrophils) ↑ fibroblasts ↑ vascular length
Bagheri 2020 (88)	Wistar rat Streptozotocin induced	890	Continuous laser	1mW/cm ² , 300sec, 0.324J/cm ² Frequency: once a day, for 7 days Site: 1, next to the wound	↓ inflammation (macrophages, neutrophils) ↑ fibroblast
Kouhkeil 2019 (89)	Rat Streptozotocin induced	890	Continuous laser	1.08mW/cm ² , 200sec, 0.2J/cm ² Frequency: 6 days per week, for 2 weeks Site: 1, next to the wound	↓ mast cells ↓ CFU ↑ wound strength
Fekrazad 2018 (90)	Wistar rat Streptozotocin induced	660	Continuous laser	30mW*, 33sec, 2J/cm ² Frequency: every 2 days, for 10 days Site: near to the wound	No effect
		810	Continuous laser	200mW*, 5sec, 2J/cm ² Frequency: every 2 days, for 10 days Site: near to the wound	No effect
		660 + 810	Continuous laser	Same parameters	↓ TGF-β1
Asghari 2017 (91)	Wistar rat Streptozotocin induced	890	Pulsed laser	0.324J/cm ² Frequency: 6 days per week, for 2 weeks Site: 12, next to the wound	↑ wound healing ↓ CFU
Leite 2017 (92)	Wistar rat Alloxan induced	660	Continuous laser	1W/cm ² , 9 or 130sec, 10 or 140J/cm ² Frequency: once a day, for 3 days Site: 1, next to the wound	140J/cm ² > 10J/cm ² ↑ wound healing ↑ mast cells number, VEGF, FGF, neovascularization ↓ leukocytes number
Fahimipour 2016 (93)	Albinos mice Streptozotocin induced	632.8	Continuous laser	250mW/cm ² , 16sec, 4J/cm ² Frequency: once a day, for 14	632.8 > 830 to improve healing ↑ density of collagen fibers

(Continued)

TABLE 6 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusion
				days Sites: 2, next to the wound	↑ number of fibroblasts ↑ neovascularization
		830	Continuous laser	250mW/cm ² , 16sec, 4J/cm ² Frequency: once a day, for 14 days Sites: 2, next to the wound	=
Fekrazad 2015 (94)	Wistar rat Streptozotocin induced	425	Continuous laser	55mW/cm ² , 36sec, 2J/cm ² Frequency: day 0, 1, 2, 4, 6, 8 Site: 1, next to the wound	Red > Blue & green ↑ wound healing
		532	Continuous laser	50mW/cm ² , 40sec, 2J/cm ² Frequency: day 0, 1, 2, 4, 6, 8 Site: 1, next to the wound	=
		630	Continuous laser	50mW/cm ² , 40sec, 2J/cm ² Frequency: day 0, 1, 2, 4, 6, 8 Site: 1, next to the wound	=
Dancáková 2014 (95)	SD rat Streptozotocin induced	810	Continuous laser	30mW/cm ² , 30sec, 0.9J/cm ² Frequency: once a day, for 7 days Site: 1, next to the wound	↑ wound healing ↑ wound tensile & strength ↑ granulation tissue
Aparecida da Silva 2013 (96)	Wistar rat Streptozotocin induced	660	Continuous laser	1.43W/cm ² , 80sec, 4J/cm ² Frequency: one session Site: 1, next to the wound	↑ collagen density ↓ MMP2 and MMP9
Fathabadie 2013 (97)	Wistar rat Streptozotocin induced	890	Pulsed laser	1.08mW/cm ² , 200sec, 0.2J/cm ² Frequency: once a day, for 6 days Sites: 18, next to the wound	↑ mast cells
Firat 2013 (98)	Wistar rat Streptozotocin induced	940	Continuous laser	1.1W/cm ² , 9sec, 10J/cm ² Frequency: every 2 days, for 7 days Site: 1, next to the wound	↓ inflammation ↑ collagen synthesis ↑ fibroblasts
Dadpay 2012 (99)	Wistar rat Streptozotocin induced	890	Pulsed laser	1.08mW/cm ² , 30 or 300sec, 0.03 or 0.2J/cm ² Frequency: 6 days per week, for 2 weeks Sites: 18, next to the wound	↑ Enhancing maximum stress and elastic modulus
Park 2012 (100)	SD rat Streptozotocin induced	980	Continuous laser	232.5mW/cm ² , 60sec, 13.95J/cm ² Frequency: once a day, for 14 days Site: 1, next to the wound	↓ inflammation cells infiltration ↑ number of fibroblasts ↑ wound healing
Hegde 2011 (101)	Swiss Albinos mice Streptozotocin induced	632.8	Continuous laser	4.02mW/cm ² , 255 to 1277sec, 1 to 5J/cm ² Frequency: once Site: 1, next to the wound	The best = 3J/cm ² ↑ wound healing ↑ collagen synthesis
Peplow 2011 (102)	Diabetic mice	660	Continuous laser	233-313mW/cm ² , 20sec, 2J* 116-156mW/cm ² , 40 sec, 2J* 58-78mW/cm ² , 80sec, 2J* Frequency: once a day, for 7 days Site: 1, next to the wound	Same effects between puissance ↑ wound healing ↑ epithelialization, granulation
Akyol 2010 (104)	Wistar rat Streptozotocin induced	808	Continuous laser	100mW/cm ² , 20sec, 2J/cm ² Frequency: every 2 day, for 8 days Site: 1, next to the wound	↑ wound healing No effect on inflammation No effect on epithelialization

(Continued)

TABLE 6 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusion
Carvalho 2010 (103)	Wistar rat Alloxan induced	660	Continuous laser	166mW/cm ² , 24sec, 4J/cm ² Frequency: unknown Site: 1, next to the wound	↑ fiber of collagen ↓ macrophages
Chung 2010 (105)	Diabetic mice	660	Continuous laser	10sec -> 1J*, 20sec -> 1.6J*, 40sec -> 3.2J* Frequency: once a day, for 7 days Site: 1, next to the wound	Best one = 1.6J/day ↑ wound healing
Santos 2010 (106)	Wistar rat Streptozotocin induced	660	Continuous laser	30mW* -> 2,5J/cm ² Frequency: once a day, for 8 days Sites: 16, next to the wound	790 better than 660 ↑ angiogenesis
		790	Continuous laser	40mW* -> 2,5J/cm ² Frequency: once a day, for 8 days Site: 16, next to the wound	
Al-Watban 2009 (107)	SD rat Streptozotocin induced	532	Continuous laser	20.4mW/cm ² , 290 to 1470sec, 5 to 30J/cm ² Frequency: 3 times per week	Best = Laser 633 ↑ wound healing
		633	Continuous laser	15.56mW/cm ² , 322 to 1932sec, 5 to 30J/cm ² Frequency: 3 times per week	
		810	Continuous laser	22.2mW/cm ² , 225 to 1350sec, 5 to 30J/cm ² Frequency: 3 times per week	
		980	Continuous laser	22.2mW/cm ² , 225 to 1350sec, 5 to 30J/cm ² Frequency: 3 times per week	
		1060	Continuous laser	66.37mW/cm ² , 75 to 450sec, 5 to 30J/cm ² Frequency: 3 times per week	
		510-872	Continuous LED	13.6mW/cm ² , 367 to 2206sec, 5 to 30J/cm ² Frequency: 3 times per week This was a polychromatous LED	
Güngörmüş 2009 (108)	Wistar rat Streptozotocin induced	808	Continuous laser	10J/cm ² Frequency: every 2 days for 8 days Site: unknown	↑ wound healing
Maiya 2009 (109)	Wistar rat Alloxan induced	632.8	Continuous laser	10mW/cm ² , 3 to 27min, 3 to 9J/cm ² Frequency: 5 days per week until wound healing Site: 1, next to the wound	3 to 7J/cm ² : ↑ epithelialization, tissue granulation ↑ wound healing 8-9J/cm ² : ↓ reparative process
Carvalho 2006 (110)	Wistar rat Alloxan induced	632.8	Continuous laser	200mW/cm ² , 60sec, 4J/cm ² Frequency: once a day, for 14 days Site: 1, next to the wound	↑ fiber of collagen
Rabelo 2006 (111)	Wistar rat Streptozotocin induced	632.8	Continuous laser	588mW/cm ² , 17sec, 10J/cm ² Frequency: once a day, for 15 days Site: 1, next to the wound	↓ wound area ↓ local inflammation ↓ inflammatory cells
Maiya 2005 (112)	Wistar rat Alloxan induced	632.8	Continuous laser	4.8J/cm ² Frequency: 5 days per week	↑ collagen ↑ fibroblastic and capillary proliferation ↑ granulation tissue formation, vascularization, epithelialization

(Continued)

TABLE 6 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusion
				until wound healing Site: 1, next to the wound	
Byrnes 2004 (113)	Purina sand rat chow 5L09 DT2 model	632.8	Continuous laser	16mW/cm ² , 250sec, 4J/cm ² Frequency: once a day, for 3 days Site: 1, next to the wound	↑ wound closure ↑ collagen, bFGF ↑ neovascularization
Reddy 2001 (114)	SD rat Streptozotocin induced	632.8	Continuous laser	1J/cm ² Frequency: once a day, for 5 days Site: 1, next to the wound	↑ collagen ↑ maximum strain ↑ toughness
Haze 2022 (115)	Human, n = 20 Diabetes RCT [†]	808	Continuous laser	138mW/cm ² , 8min, 1.1J/cm ² Frequency: once a day, for 12 weeks Site: next to the wounds	↓ wound area (12.5 vs. 1.5cm ²) ↑ wound closure (49.4 vs. 97.3%) No side effects link to PBM
Vitoriano 2019 (116)	Human, n = 12 Diabetes RCT [†] (for 2 sources of light)	850	Continuous LED	240mW/cm ² , 22sec, 14.64J/ cm ² Frequency: 2 times a week, for 5 weeks Sites: 6, next to the wound	Laser seems better than LED ↓ wound area (1.45 to 0.64 vs 1.76 to 0.36cm ²)
		830	Laser	250mW/cm ² , 28sec, 15.48J/ cm ² Frequency: 2 times a week, for 5 weeks Sites: 3, next to the wound	
de Alencar Fonseca Santos 2018 (45)	Human, n = 18 Diabetes RCT [†]	660	Continuous laser	490mW/cm ² , 13sec, 6J/cm ² Frequency: every 2 days, for 4 weeks Site: 1, next to the wound	↑ wound healing index ↑ pressure ulcer scale for healing No effect on pain (VAS)
Frangez 2018 (117)	Human, n = 60 Diabetes RCT [†]	625 (24%) 660 (71%) 850 (5%)	Pulsed LED	5min, 2.4J/cm ² Frequency: 3 times a week, for 8 weeks Site: 1, next to the wound	↑ Falanga score (score of healing) No effect on size
Ruh 2018 (118)	Human, n = 8 Diabetes Pre-Post ITV [†]	660	Continuous laser	167mW/cm ² , 12sec, 2J/cm ² Frequency: once a day for 12 days Site: 1, next to the wound	↓ wound size (data not shown) ↓ TNFα, ↑TGFβ, ↑VEGF No effect on IL6
Mathur 2017 (119)	Human, n = 30 T2D RCT [†]	660	Continuous laser	50mW/cm ² , 60sec, 3J/cm ² Frequency: once a day, for 15 days Sites: 5-8, above the wound	↑ wound closure (15% vs. 37%) No side effects
Carvalho 2016 (120)	Human, n = 32 DT2 RCT [†]	658	Continuous laser	50mW/cm ² , 80sec, 4J/cm ² Frequency: 3 times a week, for 4 weeks Site: 1, next to the wound	↓ wound area (8.43 vs. 2.39cm ²) ↓ pain (VAS: 4.8 vs 1.9) ↑ neovascularization
Sandoval Ortíz 2014 (121)	Human, n = 9 Diabetes RCT [†]	685	Continuous laser	-11mW/cm ² , 0.14-0.18sec, 1.5-2J/cm ² Frequency: Unknown Sites: multiple along the edges of the ulcer and in the wound bed, next to the wound	No effect on wound healing No effect on protective sensation No effect on QoL (EQ-5D)
Kajagar 2012 (122)	Human, n = 68 T2D RCT [†]	660 + 850	Pulsed LED	60mW*, 2-4J/cm ² Frequency: once a day, for 15 days Site: 1, above the wound	↓ ulcer area (decrease of 32 vs. 104cm ²)

(Continued)

TABLE 6 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusion
Kaviani 2011 (123)	Human, n = 23 T2D RCT [†]	685	Continuous laser	50mW/cm ² , 200sec, 10J/cm ² Frequency: 6 days per week, at least 2 weeks Site: 1, next to the wound	↑ wound closure (47.3% vs 73.7% after 4 weeks) ↑ wound healing (non-ischemic wound)
Minatel 2009 (124)	Human, n = 14 Diabetes RCT [†]	890 + 660	Continuous LED	100mW/cm ² , 30sec, 3J/cm ² Frequency: 2 times a week, for 3 months Site: 1, next to the wound	↑ granulation ↑ wound closure (43.3% vs. 90.8%)
Schindl 1999 (47)	Human, n = 8 Diabetes Descriptive [†]	632.8	Continuous laser	30mW*, 30J/cm ² Frequency: 3 times a week until wound healing Site: unknown	100% of closure of chronic ulcers after 32 to 130 sessions
Schindl 1998 (48)	Human, n = 30 Diabetes RCT [†]	632.8	Continuous laser	10mW/cm ² , 50min, 30J/cm ² Frequency: 1 time Site: 1, skin surface	↑ skin temperature ↑ microcirculation in patient with microangiopathy

[†]: PBM in addition to the standard wound care (rising, cleaning, drying), CFU, colony forming unit; FGF, fibroblast growth factor; LED, Light emitting diode; MMP, Matrix metalloproteinases; PBM, Photobiomodulation; Pre-Post ITV, Pre-post interventional trial; QoL, Quality of life; Rat SD, Rat Sprague Dawley; RCT, Randomized controlled trial; T2D, Type 2 diabetes; TGF, Transforming Growth factor; TNF, Tumor necrosis factor; VAS, Visual analogic scale; VEGF, Vascular endothelial growth factor. *Surface of PBM not reported.
↑, increase; ↓, decrease; =, equal/same.

TABLE 7 Effect of PBM on healing of bone defect.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Dalirsani 2021 (125)	Wistar rat Streptozotocin induced	660	Continuous laser	76.4mW/cm ² , 24sec, 7.2J/cm ² Frequency: once a day, for 14 days Site: 1, direct contact	↑ bone formation ↓ inflammation ↑ vascularization
		802	Continuous laser	127.32mW/cm ² , 14sec, 7J/cm ² Frequency: once a day, for 14 days Site: 1, direct contact	↓ inflammation ↑ vascularization
Lee 2021 (126)	Wistar rat Streptozotocin induced	660	Continuous laser	2.42mW/cm ² , 1652sec, 4J/cm ² Frequency: once a day, for 12 weeks Site: 1, near to the bone defect place	↑ bone formation ↑ bone fracture healing No effect on osteogenic factor
Diker 2019 (127)	SD rat Streptozotocin induced	808	Continuous laser	3.5W/cm ² , 22sec, 78.5J/cm ² Frequency: once a day, for 3 days Site: 1, direct contact	↑ bone formation ↑ osteoblasts
Gomes 2018 (128)	Wistar rat Streptozotocin induced	780	Continuous laser	16W/cm ² , 10, 20 or 40sec, 160, 320 or 640J/cm ² Frequency: every 2 days, for 21 days Site: 1, direct contact	Only or 640J/cm ² : Better maintenance of periodontal tissue subjected to a force
Mostafavinia 2018 (129)	Wistar rat Streptozotocin induced	890	Pulsed laser	1.5W/cm ² , 1300sec, 1.5J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 3, direct contact	↑ bone formation ↑ bone cortical volume ↑ bone trabecular volume ↑ osteoblasts and osteocytes
Mostafavinia 2017 (130)	Wistar rat Streptozotocin induced	890	Pulsed laser	8.32W/cm ² , 1300sec, 1.5J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 3, direct contact	↑ bone density
Yildirimturk 2017 (131)	SD rat Streptozotocin induced	820	Continuous laser	0.5W/cm ² , 32sec, 16J/cm ² Frequency: 3 times a week, for 4 weeks Site: 1, tibiae, direct contact	↑ bone formation ↑ vascularization No effect of osteoblast quantity

(Continued)

TABLE 7 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Patrocínio Silva 2016 (132)	Wistar rat Streptozotocin induced	808	Continuous laser	3.57W/cm ² , 33sec, 120J/cm ² Frequency: 3 times a week, for 8 weeks Site: 1, direct contact	↑ bone density ↑ bone mineral content stiffness ↑ cortical tibia area
Magri 2015 (133)	Wistar rat Streptozotocin induced	808	Continuous laser	3.57mW/cm ² , 8 or 16 or 33sec, 30, 60 or 120J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 2, direct contact	↑ bone formation No histological effect
Nascimento 2015 (134)	Wistar rat Alloxan induced	780	Continuous laser	1.75W/cm ² , 10sec, 17.5J/cm ² Frequency: every 2 days, for 7 days Site: 1, direct contact	↑ bone formation ↓ inflammation ↑ alkaline phosphatase
Patrocínio Silva 2014 (135)	Wistar rat Streptozotocin induced	808	Continuous laser	3.57W/cm ² , 33sec, 120J/cm ² Frequency: 3 times a week, for 6 weeks Sites: 4, direct contact	↑ bone density ↑ cortical area ↑ values of fracture force ↑ osteogenic potential
Akyol 2010 (136)	Wistar rat Streptozotocin induced	808	Continuous laser	100mW/cm ² , 20sec, 2J/cm ² Frequency: every 2 days, for 7 days Site: 1, right distal epiphysis	↑ bone repair ↑ substantia spongia formation No effect on union bone marrow
Abdi 2009 (137)	Wistar rat Alloxan induced	780	Continuous laser	318mW/cm ² , 1166sec, 369.4J/cm ² Frequency: 3 times a week, for 6 weeks Sites: 2, direct contact	No effect on bone repair
Bayat 2009 (138)	Wistar rat Streptozotocin induced	632.8	Continuous laser	3.17mW/cm ² , 90 or 1200sec, 88.6 or 382.2J/cm ² Frequency: once a day, for 14 days Sites: 4, direct contact	↑ bone density ↑ bone lamella meshwork ↑ maximum force and load at the break ↓ bend stiffness
Javadieh 2009 (139)	Wistar rat Streptozotocin induced	890	Pulsed laser	265 or 530sec, 5 or 10J/cm ² Frequency: 3 times a week, for 6 weeks Sites: 2, direct contact	↑ bone repair ↑ bending stiffness ↑ maximum force
Attia 2023 (140)	Human, n = 40 T2D RCT ^o	808	Continuous laser	125mW/cm ² , 1.23min, 0.15J/cm ² Frequency: 2 times, pre and post implantation Sites: 6, direct contact	↑ bone repair and density ↑ bone structure

^o: no information provided about other treatment during the study. Rat SD, Rat Sprague Dawley; RCT, Randomized controlled trial; T2D, Type 2 diabetes.
↑, increase; ↓, decrease.

- gingival index represents inflammation of the gingival tissue (150),
- the plaque index, which represents the presence of supragingival plaque on all four tooth surfaces (151).

Among the clinical studies, 11 were RCTs, 3 were RCTs specifically focused on pockets treated with PBM, and two were Pre-Post ITV. The results were heterogeneous, with a decrease in the plaque index observed in 50% of the studies, a decrease in the gingival index in 80% of the studies, a reduction in bleeding in 66% of the studies, a decrease in probing depth in 50% of the studies, and improvements in clinical attachment levels in 29% of the studies.

■ Effect on bacterial population

Two studies investigated the effect of PBM on reducing the bacterial population at periodontitis sites, but the results were contradictory.

3.7 Others utilization described in diabetes mellitus

3.7.1 Erectile function

In a preclinical study, Yang et al. (152) reported a positive impact of PBM on erectile function two weeks after PBM exposure. This suggests a potential therapeutic effect of PBM on improving erectile function (Table 9).

3.7.2 Ischemia reperfusion injury

Asghari et al. (153) conducted a preclinical study and demonstrated a protective effect of PBM against ischemia/reperfusion injury in the diabetic kidney. They observed a decrease in tubular epithelial necrosis, polymorphonuclear cells in the outer medulla, cellular oedema, tubular dilatation, hyaline casts, and medullary congestion. These findings indicate the potential of

TABLE 8 Effect of PBM on chronic diabetes periodontitis.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Kamatham 2022 (34)	Human, n = 60 T2D RCT†	650	Continuous laser	0.4W* Frequency: 1 session Site: 1/tooth, in contact with gingival tissue	↓ inflammation ↓ calprotectin No effect on probing depth, clinical attachment level
Pulivarthi 2022 (35)	Human, n = 30 T2D RCT†	650	Continuous laser	0.8W/cm ² , 15sec, 12J/cm ² Frequency: once a day, for 8 weeks Sites: 3, in contact with gingival tissue	No effect on TNFα No effect on bleeding index, probing depth, clinical attachment level
Mrasori 2021 (141)	Human, n = 80 T2D RCT†	660	Continuous laser	10mW*, 8min Frequency: 5 days per week, for 3 months Sites: 5, in contact with gingival tissue	↓ IL6
Soi 2021 (142)	Human, n = 44 T2D RCT†	940	Pulsed laser	0.8W*, 15sec, 24J* Frequency: unknown Sites: 2/tooth, into the periodontal pocket	No effect of adjunction of PBM to SRP (scaling and root planning)
Koçak 2020 (36)	Human, n = 60 T2D RCT†	940	Pulsed laser	1.061W/cm ² , 20sec Frequency: 1 session Sites: 2/tooth, intra periodontal pocket	No effect on bacteria level (<i>P.gingivalis</i> , <i>T.forsythia</i> , <i>T.denticola</i>)
Özberk 2020 (143)	Human, n = 22 T2D RCT†	980	Continuous laser	33mW/cm ² , 15sec, 0.5J/cm ² Frequency: day 0, 1, 3 and 7 Sites: 2/tooth, in contact with maxilla and mandibula	↓ probing depth (2.9 vs. 2.6 mm) ↓ clinical attachment level (3.0 vs. 2.8 mm) No effect on plaque index and gingival index
Castro dos Santos 2019 (144)	Human, n = 24 T2D RCT† (on pocket)	660	Continuous laser	1.1W/cm ² , 20sec, 22J/cm ² Frequency: 1 session Sites: 2, buccal and lingual	No effect on probing depth, clinical attachment level
Chandra 2019 (145)	Human, n = 40 T2D RCT†	808	Continuous laser	1.5-1.8W/cm ² , time in second Frequency: 1 session Site: 1, intra periodontal pocket	↓ plaque index (1.56 vs. 1.26) ↓ gingival index (1.56 vs. 1.04) ↓ probing depth (2.63 vs. 1.80) ↓ clinical attachment level (7.50 vs. 6.65) ↓ bacteria level (35% more reduction with PBM)
Dengizek Eltas 2019 (146)	Human, n = 40 T2D RCT†	810	Continuous laser	1W*, 15-20sec Frequency: once a day Sites: 3/tooth	↓ gingival index (0.91 vs. 0.58) ↓ bleeding on probing (31.7 vs. 24.7%) ↓ probing depth (2.99 vs. 2.77mm) No effect on plaque index, clinical attachment level and inflammation (CRP)
Li 2018 (147)	Human, n = 80 T2D RCT†	Unknown	Unknown	Unknown	↓level of TNF, IL-1, LPS Increase leptin
Demirturk-Gocgun 2017 (148)	Human, n = 22 T2D RCT† (on pocket)	808	Continuous laser	0.89W/cm ² , 5sec, 4.46J/cm ² Frequency: Day 1, 2 and 7 Sites: 4, in contact with gingival tissue	No effect on bleeding of probing, probing depth, clinical attachment level, plaque index
Koçak 2016 (37)	Human, n = 60 T2D RCT†	940	Pulsed laser	1.061W/cm ² , 20sec Frequency: 1 session Sites: 2/tooth, intra periodontal pocket	↓ VCAM No effect on IL1/6/8/ICAM
Javed 2015 (149)	Human, n = 22 T2D RCT† (on pocket)	1064	Pulsed laser	1430W/cm ² , 60 to 120sec (depending of the accessibility of the pocket), 240-480J* Frequency: unknown Site: 1/tooth, into the periodontal pocket	↓ plaque index (6.4 vs. 1.5) at 1 month, not 3 months ↓ bleeding probing (5.5 vs. 2.1) at 1 month, not 3 months
Obradović 2013 (38)	Human, n = 300 T1D, T2D RCT†	670	Continuous laser	2mW/cm ² , 16min, 2J/cm ² Frequency: once a day for 5 days Site: 1, in contact with gingival tissue	↓ alteration of periodontium (histologic description)
Obradović 2012 (39)	Human, n = 200 T1D, T2D	670	Continuous laser	5mW*, 14min Frequency: once a day, for 5 days Site: 1, in contact with the jaws	↓ gingival index (0.31 vs. 0.16) ↓ inflammation ↑ cytomorphometric parameters

(Continued)

TABLE 8 Continued

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
	RCT [†] (on pocket)				
Obradović 2011 (40)	Human, n = 150 T1D, T2D Pre-Post ITV [†]	Unknown	Unknown	5mW* Frequency: for 5 days Site: only right site of the jaw	↓ gingival index (data not available) ↓ nuclei areal

T: no other treatment for pain, [†]: PBM in addition to non-surgical periodontal treatment (i.e. scaling and root planning, ultrasonic periodontal debridement), CRP: C reactive protein, ICAM: Intercellular adhesion molecule, IL: Interleukin, LPS: lipopolysaccharide, PBM: photobiomodulation, Pre-post ITV: Pre-post interventional trial, RCT: Randomized controlled trial, SRP: scaling and root planning, T1D: Type 1 diabetes, T2D: Type 2 diabetes, TNF: Tumor necrosis factor, VCAM: Vascular cell adhesion molecule, *Surface of PBM not reported.
†, increase; ↓, decrease.

PBM in mitigating kidney injury associated with ischemia/reperfusion (Table 9).

3.7.3 Facial nerve palsy

Aghemohamdi et al. (154) demonstrated the positive impact of PBM in patients with T2D who experienced facial nerve palsy. After 12 sessions of PBM, 60% of the patients showed recovery on electromyogram without any reported side effects. However, the investigation of QoL outcomes were not investigated in this study (Table 9).

4 Discussion

This review shows a clear interest in the use of PBM in diabetes, both at preclinical (70 studies) and clinical level [56 studies out of 88 clinical trials identified by clinicaltrials.gov (27)]. However, the therapeutic effect of PBM is variable, with inconsistent illumination parameters that are not standardized across studies.

Regarding clinical trials, PBM has generated interest across various fields, with 2,573 clinical trials identified on clinicaltrials.gov (27). Although 42 clinical trials related to PBM in diabetes were found on clinicaltrials.gov (27), an additional 46 studies were identified through the Medline bibliographic search. Since PBM is not considered as a

drug, the reporting of trials in the global clinical trials database is not consistent. Moreover, in some cases, trials may be reported directly to national registries, as seen in many studies conducted in Brazil. Another important point to note is that among the 67 completed trials, only 56 were published, indicating a significant publication bias (16%), which is likely underestimated. Moreover, quality of clinical trials must be upgraded, as there is heterogeneity in the number of patients included, in the presence of a control group and in the parameters used. Furthermore, in terms of clinical publications, few teams have conducted more than one study, amplifying the heterogeneity of the PBM parameters used.

Currently, there is no consensus on the optimal PBM parameters to achieve biological or clinical effects. In terms of light sources, some studies have reported superior effects with coherent laser light (155, 156). However, a recent review found no difference in efficacy between LEDs and laser sources, with LEDs being more cost-effective. In the context of diabetes and wound healing, two studies compared lasers and LEDs. Al-Watban et al. (107) reported a better efficacy of a 633 nm laser compared to LEDs with polychromatic light for ulcer healing, may be due to dilution of the effect as the irradiance was comparable for both. Vitoriano et al. (116) reported a greater reduction in ulcer size with an 830 nm laser compared to 850 nm LEDs (with comparable irradiance). Despite these two studies favoring lasers, numerous studies in the field of diabetes have reported positive effects of LED-based PBM. However,

TABLE 9 Effect of PBM on other complications.

Author/Year	Model	Wave (nm)	Light	PBM parameters	Conclusions
Yang 2023 (152)	SD rat Streptozotocin induced	808	Laser	4J/cm ² Frequency: for 2 weeks Site: Unknown	↑ erectile function ↑ mitochondrial function and morphology ↓ oxidative stress
Asghari 2016 (153)	Wistar rat Streptozotocin induced	685	Continuous laser	53.6mW/cm ² , 60sec, 3.2J/cm ² Frequency: H0, H1, H2 Sites: 6, direct contact with skin	↓ ischemia-reperfusion injury ↓ plasma creatinine ↓ tubular dilatation, glomerular atrophy ↑ glutathione, superoxide dismutase and catalase
Aghemohamdi 2020 (154)	Human, n = 30 Diabetes Pre-Post ITV [†]	830	Pulsed laser	334mW*, 60sec, 16J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 9, pathway of facial nerve, direct skin contact	Recovery in electromyogram in diabetic patient with Bell's palsy
		980	Pulsed LED	9min, 5J/cm ² Frequency: 3 times a week, for 4 weeks Sites: 9, pathway of facial nerve, direct skin contact	

[†]: PBM in addition to the best standard of care, LED, Light emitting diode; Pre-Post ITV, Pre-post interventional trial. *Surface of PBM not reported.
†, increase; ↓, decrease.

the choice between laser and LED was a technologic choice and could be led by the accuracy of wavelength search, the availability of the device and energetic consumption. It is important to note that the principle of PBM is based on the Arndt-Schultz law (20), which describes a biphasic response. A dose that is too low will produce no effect while a dose that is too high can be toxic and induce mitochondrial permeabilization and apoptosis through activation of caspases (157). This biphasic response to PBM was reflected in two studies on ulcer healing in diabetes. Hedge et al. (101) tested a 632.8 nm laser with different irradiances ranging from 1 to 5 J/cm². While irradiances of 1 and 5 J/cm² resulted in poorer and slower wound healing, an irradiance of 3 J/cm² appeared to be optimal for improving and accelerating wound healing. Maiya et al. (109) tested a 632.8 nm laser with different irradiances ranging from 3 to 9 J/cm². Irradiances between 3 and 7 J/cm² had a positive effect on healing, including increased epithelialization, tissue granulation, and accelerated wound healing; whereas irradiances of 8 and 9 J/cm² hindered the healing process. To date, there is no consensus on the power or optimal irradiance to be applied, and the wavelength applied is another parameter of interest that lacks consensus and may depend on the target tissue. Red and near-infrared light correspond to the absorption wavelengths of cytochrome c oxidase in the mitochondria (23). Green light, on the other hand, is rarely used and not very effective in inducing biological changes as it was not in the specter of absorption of cytochrome c oxidase. Two studies compared blue, green, and red wavelengths in diabetes. Dungal et al. (84) reported that blue light (470 nm) had no effect on wound healing, whereas green (540 nm) and red (629 nm) light accelerated wound healing. Fekrazad et al. (94) reported no effect of blue (425 nm) and green (532 nm) light, whereas red light (630 nm) promoted wound healing. Another study (93) reported that a 632.8 nm laser is more effective than an 830 nm laser for wound healing. Given these findings, it is logical that the most commonly used wavelengths (80 studies) fall within the red and near-infrared range (600–810 nm). In any case, numerous articles have shown that the effect of PBM depends on various parameters: wavelength, fluence (J/cm²), total energy received (J), pulsed or continuous emission mode ... Moreover, the absorption characteristics of the tissue, as well as the delivery mode, and the frequency of use of the PBM (number of applications, treatment schedule etc.) add complexity. It is now necessary to standardize PBM parameters, and to precise them into papers; in order to be reproducible and identify effective application methods.

The first experiment to investigate the effect of PBM on healing showed promising results (17, 18). Extensive research has been conducted in this field, with several preclinical and clinical reviews reporting positive effects of PBM on wound healing (158), healing of bone defect (159), and periodontitis (160). In a specific population of patients with diabetes, the results regarding these healing processes were encouraging. Numerous preclinical studies have focused on ulcer and wound healing, demonstrating the beneficial effects of PBM. These effects include improved angiogenesis and associated trophic factors, increased fibroblasts, reduced inflammation, increased collagen quantity, and even a reduction in colony-forming units (CFU). Clinically, these results were supported by a significant reduction in wound area (by a factor of 3.5 to 8.2) and increased wound closure (ranging from 22% to 47.9%), which may be associated with reduced pain. Wound healing issues in patients with

diabetes significantly impact their QoL (161). However, only one study (121) has examined the impact of PBM on the QoL of patients with diabetes and ulcers and did not demonstrate any beneficial effects of PBM on QoL. Overall, the data on wound healing are encouraging. The ideal parameters may involve repeated exposure over several weeks, at multiple sites as close as possible to the lesion, with a fluence between 1 and 10 J/cm², continuous illumination using LED or laser, and a wavelength ranging from 660 to 830 nm. In wound healing, PBM appeared as a sage approach to enhance healing process in addition to wound standard of care.

Regarding healing of bone defect, 94% of preclinical studies showed positive results (improved vascularization, increased osteoblasts and osteocytes, reduced inflammation, increased bone volumes, and enhanced bone density). Clinically, only one study (140) has been conducted, demonstrating improved bone repair, density, and structure after dental implant insertion with one session of PBM before and after implantation. However, conclusions cannot be drawn from a single clinical study, but the promising results from preclinical and clinical studies should motivate further clinical trials to determine the optimal parameters for PBM.

To date, only clinical studies have investigated the effects of PBM on periodontitis, yielding heterogeneous results due to variations in the applied parameters. The exposure periods ranged from a single session to several days or even weeks. Among studies that examined the gingival index, plaque index, and clinical attachment level, 75% reported improvements in at least one of these parameters. Four studies reported negative results: one had the highest fluence (144), one had the highest exposure frequency [once a day for 8 weeks (35)], one had poorly described illumination parameters and a wavelength beyond the infrared range (142), and one had four PBM exposure sites (148), whereas most studies reported one to two exposure sites. Finally, the ideal parameters could involve a single exposure or exposure over 2 to 3 days, on one to two sites in direct contact with gingival tissue or intra-pocket, with a fluence of 1 to a few J/cm², continuous or pulsed laser illumination, and a wavelength range of 650 to 1064 nm. These data have been supported by previous results on *in vitro* model (162) reporting positive response of fibroblasts to the PBM in diabetic hypoxic wounded models. Even if three teams published several studies, the lack of rigorous methodology and the heterogeneity of PBM parameters, did not allowed to identify leader in this field. Moreover, due to the wide variability in illumination parameters and obtained results, definitive conclusions regarding the therapeutic effects of PBM on periodontitis cannot be formally drawn. Further clinical trials are required to establish clearer conclusions and defined optimal PBM parameters to use PBM as an added therapy for diabetes chronic periodontitis management.

Regarding neuropathy, five preclinical studies reported a positive effect of PBM on pain, leading to a decrease in cytokines and improvement in mitochondrial parameters. Clinically, in 77% of the studies, a 2-5 points reduction on the VAS was observed for pain. Out of the studies that considered the impact of PBM on QoL (24%), two studies reported no effect (58, 59) (similarly, no effect on pain was observed), while two studies reported a 4-point improvement in Norfolk Quality of Life-Diabetic Neuropathy (54) and SF-36 scores on all these parameters (44). No adverse effects of PBM were reported

in any of the studies. Two teams have been identified in this field. Unfortunately, studies of Burka et al. (28–30) lack methodological rigor and a description of the PBM parameters used. On the other hand, Arun G et al. (31–33), succeeded in demonstrating in their three studies (with the same PBM parameters used) an improvement of vibration perception threshold, decrease of pain, improvement of microcirculation and biological parameters. These benefits were observable as early as 10 days after daily PBM with 2 lasers (632.8 nm and 660 nm + 880 nm) over 9 min (3.1 J/cm² of fluence) on the plantar and dorsal surfaces of the feet. These parameters should therefore serve as a basis for future clinical trials aimed at defining whether MBP will be used instead of or in addition to current pharmacological treatments.

For diabetic retinopathy, only a few studies have been conducted in this field. Four preclinical studies reported promising results on the effect of PBM, showing histological improvements in the retina. However, clinically, only two studies reported a reduction in central macular thickness, with (69) or without (68) an improvement in vision. Therefore, it is not possible to conclude whether PBM must be used. Clinical trials must be conducted to demonstrate PBM safety in use and its efficacy as a complementary or alternative therapy to current therapeutic options.

PBM is also gaining popularity among its potential benefits for post-physical activity recovery, this fact was still a source of debate (163, 164). In the context of T2D, a limited number of studies (n = 7) have been conducted. The results of 3 preclinical studies reported positive effects of PBM on oxidative stress, antioxidant activity, and muscular parameters. However, clinically (n = 4), no study reported improvements in performance or muscle functionality. Only one study (42) reported a benefit in terms of lactate concentration and cardiac parameters. Based on these findings, it can be concluded that the current parameters used for PBM do not provide benefits for post-exercise muscle recovery in patients with T2D.

Lastly, since diabetes is a metabolic disease characterized by an imbalance in glycemic control, PBM has also been investigated in this field. Preclinical results have shown promising results, with 83% of the studies that examined glucose tolerance possibly due to a direct impact of PBM on islet insulin secretion capability and insulin resistance reporting an improvement in these parameters. The only negative study (71) applied the highest power (3.57 W/cm²) for the shortest period (8 seconds). Preclinical studies have also demonstrated beneficial effects of PBM on lipid profiles, including reduced ectopic fat in muscle, triglycerides, and free fatty acids. Additionally, a small-scale clinical study (79) (n = 10) reported beneficial effects of PBM, including a 37% reduction in post-meal AUC for glucose and approximately 16% faster postprandial glucose decay. No adverse effects were reported with PBM, and there was no increased risk of hypoglycemia when PBM was combined with hypoglycemic treatments. Overall, these findings support the potential of PBM in improving glycemic control in patients with type 2 diabetes. Further clinical trials with larger sample sizes are warranted to determine the optimal parameters for PBM as an additional therapy in the therapeutic arsenal, helping to improve patients' glycemic control.

Moreover, the effect of PBM on glucose intolerance could be lead to the action of PBM on beta cells and islets.

Liebman et al. (165) reported improvement of insulin secretion of beta cells and glucagon of alpha cells associated with a rise of calcium activity. Irani et al. (166) demonstrated that PBM could improve insulin secretion of rat pancreatic islets with poor insulin secretion. Huang et al. (167) investigated the effects of PBM on pig islets, which are being explored as a potential source of islets for xenotransplantation. However, they did not observe any significant positive or negative effects on glucose-stimulated insulin secretion. Further research is needed to explore the potential of PBM to enhance islet function for transplantation purposes, even if Asghari et al. (153) reported protector effect of PBM on ischemia-reperfusion injury in diabetic kidney of rats.

5 Conclusion

Overall, this review highlights the growing interest in PBM as a potential therapeutic approach for various aspects of diabetes. This study emphasizes the potential of PBM as a valuable approach for managing wound healing issues and neuropathic pain in diabetic patients in both preclinical and clinical studies. The potential benefits of PBM in healing of bone defect and glycemic control show promise. In retinopathy, the small number of studies make it impossible to draw any conclusion. In periodontitis, more extensive clinical trials are warranted to establish the optimal parameters and protocols for PBM. Likewise, the current evidence does not support the use of PBM for muscle recovery after physical exercise.

Author contributions

QP: Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. CM: Writing – review & editing, Validation, Supervision, Funding acquisition. SL: Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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