Lasers in Medical Science (2025) 40:436
https://doi.org/10.1007/s10103-025-04701-7

REVIEW

Dosimetric parameters and clinical outcomes of photobiomodulation in diabetic neuropathy: a concise review

Vanessa de Souza[1] · Marlon da Palma Cruz[1] · Caroline Chaves Bittencourt[1] · Ana Paula Ligeiro de Oliveira[1] · José Antônio Silva Júnior[1] · Stella Regina Zamuner[1] · Nivaldo Antonio Parizotto[2] · Richard Eloin Liebano[3] · Rodrigo Álvaro Brandão Lopes Martins[4] · Rodrigo Labat Marcos[1]

Received: 10 July 2025 / Accepted: 6 October 2025

Abstract

Diabetes mellitus (DM) is a multifactorial metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and systemic inflammation. Diabetic neuropathy (DN) is a prevalent and debilitating complication of type 2 diabetes mellitus (T2D), associated with sensory impairment, persistent pain, and increased risk of lower limb amputations. Photobiomodulation (PBM) has been investigated as an adjunctive treatment due to its effects on cellular repair mechanisms, pain modulation, and wound healing.This review aims to synthesize evidence from clinical and preclinical studies published between 2015 and 2025, focusing on dosimetric parameters used in PBM for DN and their association with clinical outcomes.The search was conducted in the LILACS, SciELO, EMBASE, MEDLINE, PubMed e Cochrane Library, covering publications from 2015 to 2025. A total of 23 studies met the inclusion criteria. This review provides comprehensive evidence supporting PBM as a promising, safe and effective adjunctive therapy for diabetic neuropathy. The most consistent therapeutic effects were observed with wavelengths ((630–670 nm/808–904 nm), fluences of 3–10 J/cm², output power between 45 and 100 mW, and treatment protocols comprising at least 12 sessions. Despite the favorable therapeutic outcomes, the absence of standardized dosimetry among the studies remains a major challenge. Therefore, further research is needed to define optimized and reproducible therapeutic protocols.

✉ Vanessa de Souza
vanessacuidador@gmail.com

Marlon da Palma Cruz
marlonpc1302@gmail.com

Caroline Chaves Bittencourt
dracarolbittencourt@gmail.com

Ana Paula Ligeiro de Oliveira
apligeiro@gmail.com

José Antônio Silva Júnior
josejr@uni9.pro.br

Stella Regina Zamuner
stella.rz@uni9.pro.br

Nivaldo Antonio Parizotto
nivaldoaparizotto@hotmail.com

Richard Eloin Liebano
liebano@gmail.com

Rodrigo Álvaro Brandão Lopes Martins
ralopes@gmail.com

Rodrigo Labat Marcos
labatrm@gmail.com

[1] Program in Medicine – Biophotonics, Universidade Nove de Julho, São Paulo, Brazil

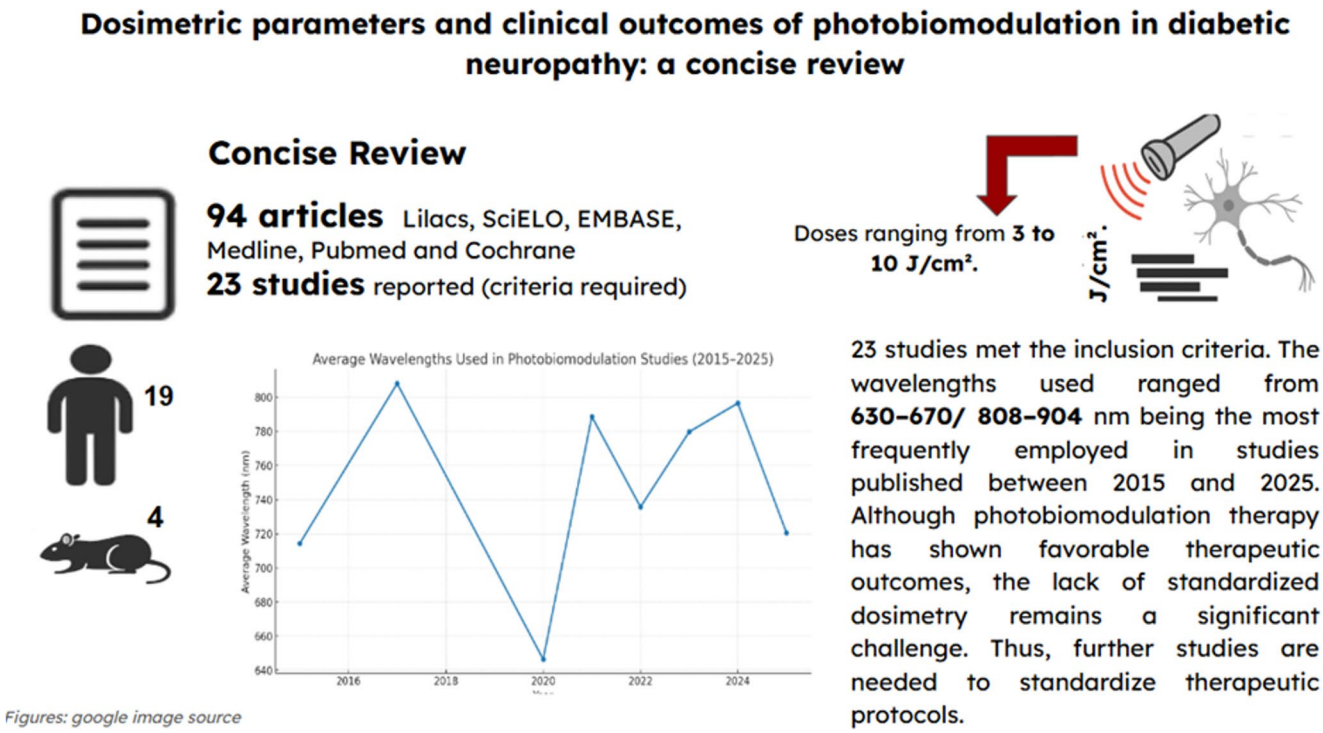
[2] 2-Programa de Engenharia Biomédica, Universidade Brasil, São Paulo, Brazil

[3] Department of Rehabilitation Sciences, University of Hartford, West Hartford, CT, USA

[4] Hospital do Câncer de Muriaé, Fundação Cristiano Varella, Minas Gerais, Brazil

Published online: 15 October 2025

Graphical abstract



Keywords Photobiomodulation · Low-level laser · Diabetic neuropathy · Allodynia · Type 2 diabetes

Introduction

Diabetes mellitus (DM) is one of the most pressing global public health challenges, with projections from the *International Diabetes Federation* (IDF) estimating that more than 700 million people will be affected by 2045. This dramatic increase highlights the urgent need for effective prevention and management strategies to reduce complications, improve patients' quality of life, and alleviate the burden on healthcare systems. Type 2 diabetes (T2D) faces significant barriers to both prevention and treatment, particularly in high-risk populations. Although lifestyle interventions such as healthy eating, regular physical activity, and weight loss can reduce the risk of progression from prediabetes by up to 70%, their practical implementation is limited by poor long-term adherence, socioeconomic inequalities, lack of structured programs, and clinical inertia [1, 2].

The main risk factors for T2D include advanced age, family history of diabetes, abdominal obesity, increased body mass index, fatty liver disease, sedentary lifestyle, smoking, diets with high insulinogenic potential or rich in processed meats, psychosocial conditions such as anxiety and depression, and comorbidities including hypertension, dyslipidemia, and impaired glucose levels [2]. Early detection is also hindered by the silent progression of the disease, the limitations of current diagnostic methods, the low coverage of population screening, insufficient risk perception among individuals, and restricted access to laboratory tests, especially in low- and middle-income countries. Together, these factors delay timely interventions and contribute to the early onset of complications [3].

DM is a heterogeneous group of metabolic disorders characterized by sustained hyperglycemia, with T2D being the most prevalent form, driven by insulin resistance, impaired insulin secretion, and frequently associated with obesity and sedentary lifestyle. Its chronic nature leads to systemic complications, both microvascular and macrovascular, and its epidemiology highlights a strong association with excess body weight and sedentary behavior, which act as triggers of a genetic predisposition that varies among individuals and ethnic groups [1, 4].The natural history of T2D typically progresses in two phases: initially, isolated insulin resistance caused by excess adiposity, in which pancreatic hypersecretion maintains normoglycemia at the expense of persistent hyperinsulinemia; followed by the onset of clinically apparent diabetes, when genetic susceptibility or β-cell exhaustion prevents adequate insulin production, resulting in chronic hyperglycemia [5]. Given this pathophysiological trajectory, insulin resistance emerges as a central target for preventive interventions, and recent

evidence demonstrates that lifestyle modifications particularly dietary adjustments and increased physical activity are highly effective in reducing adiposity, improving metabolic parameters, and delaying or even preventing the development of diabetes in high-risk individuals [6].

Among its chronic complications, diabetic neuropathy (DN) stands out due to its high prevalence, affecting up to 50% of individuals during the course of the disease and representing the leading cause of peripheral neuropathy worldwide. DN is a heterogeneous condition that may present in generalized, multifocal, or focal forms, with distal sensorimotor polyneuropathy being the most common [7]. This variant typically develops insidiously, follows a length-dependent pattern, and is often associated with other microvascular complications such as retinopathy and nephropathy. Clinical manifestations range from mild, frequently subclinical cases to severely disabling conditions, with substantial impact on functionality, quality of life, and survival [8].

T2D is characterized by persistent hyperglycemia, which, in combination with β-cell dysfunction and immune-mediated inflammation, accelerates the onset of chronic complications. In this context, DN emerges as one of the most prevalent complications, arising from the convergence of multiple pathogenic pathways [9]. Metabolic disturbances induce oxidative stress and mitochondrial dysfunction; chronic inflammation amplifies neural and vascular injury; ischemic mechanisms compromise endoneurial blood flow; and compressive processes further aggravate nerve damage. Together, these factors explain the heterogeneous clinical presentation of DN, ranging from subclinical sensory changes to severe, disabling neuropathic syndromes with significant impact on functionality [6, 9].

DN, as classified by the *Toronto Expert Panel on Diabetic Neuropathy*, encompasses distinct clinical forms that facilitate diagnostic and therapeutic standardization. The most prevalent type is distal symmetric polyneuropathy (DSPN), which manifests in a "glove and stocking" distribution with progressive sensory, motor, and autonomic fiber involvement. Patients often present with burning pain, numbness, tingling, and loss of protective sensation, significantly increasing the risk of foot ulcers and amputations. Other forms include autonomic neuropathies, which affect cardiovascular, gastrointestinal, genitourinary, and sudomotor systems; mononeuropathies, which typically involve isolated cranial or peripheral nerves with acute onset and self-limiting progression; radiculoplexopathies or diabetic amyotrophy, marked by severe proximal pain and weakness in older adults with type 2 diabetes; and thoracic and cervical polyradiculopathies, which produce band-like pain that may mimic visceral or musculoskeletal disease. Additionally, small-fiber neuropathy presents with pain and temperature disturbances, often requiring specific diagnostic tests such as skin biopsy or quantitative sensory testing [10, 11].

Clinically, DN is also characterized by chronic pain manifestations, including allodynia and hyperalgesia, which substantially impair quality of life. Allodynia, defined as pain elicited by normally non-painful stimuli (light touch or clothing contact), is particularly distressing and a frequent reason for seeking medical care [12]. Hyperalgesia, in contrast, refers to an exaggerated response to painful stimuli; the two phenomena often coexist in neuropathic pain syndromes. Both are attributed to structural and functional changes in peripheral nerves, driven largely by chronic hyperglycemia, oxidative stress, and microvascular damage affecting both myelinated and unmyelinated fibers [13]. These mechanisms contribute to progressive sensory dysfunction, chronic neuropathic pain, and autonomic disturbances, underscoring the complexity of DN and its multifactorial pathophysiology [14].

Diabetic foot evaluation is an essential component of DN assessment and risk stratification. Screening begins with a detailed clinical history and systematic foot inspection, requiring removal of shoes and socks to detect early signs of at-risk feet. A key tool is the 10 g Semmes-Weinstein monofilament test, performed on four plantar sites: the hallux (plantar surface of the distal phalanx) and the plantar surfaces of the first, third, and fifth metatarsal heads, to detect loss of protective sensation [15]. Complementary assessments include vibration perception using a 128 Hz tuning fork or biothesiometer, evaluation of ankle reflexes to assess large motor fibers, pinprick or disposable stick testing for pain perception, cotton wool for light touch, and thermal testing to examine small-fiber function. These combined approaches allow for early identification of neuropathy, prevention of ulceration, and reduction of amputation risk in individuals with diabetes [16].

Since the 1960 s, photobiomodulation (PBM), also referred to as low-level laser (LLL), has emerged as a promising non-invasive modality for the treatment of neuropathic pain [17]. PBM was officially adopted as a unifying term in 2014, replacing previous nomenclatures such as LLL. PBM refers to a non-ionizing light therapy modality that utilizes low-power lasers, light-emitting diodes (LEDs), or lamps operating in the red (RL) and near-infrared (NIR) spectrum. This therapy induces photochemical and photophysical changes within cellular structures through photon absorption, resulting in therapeutic effects such as reduced inflammation, pain relief, and accelerated wound healing [18]. PBM stimulates cellular metabolism and significantly enhances microcirculation, increasing tissue oxygenation and nutrient delivery. These improvements in blood flow directly contribute to tissue repair and have shown

promising results in conditions such as diabetic foot ulcers, where vascular impairment is a key pathological factor [18, 19].

PBM uses LEDs to stimulate cellular metabolism, enhance microcirculation, reduce inflammation, and accelerate tissue repair, with suggested benefits in diabetic foot ulcers. The primary mechanism of PBM involves photon absorption by intracellular chromophores, mainly cytochrome c oxidase within mitochondria. This interaction triggers biochemical cascades that enhance ATP synthesis, modulate oxidative stress, and regulate cell signaling pathways, thereby contributing to nerve repair and restoration of tissue function [19]. In the context of inflammation, PBM downregulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while upregulating anti-inflammatory mediators like IL-10. It also influences immune cell infiltration, promoting a controlled inflammatory response. In terms of analgesia, PBM reduces pain by inhibiting nerve conduction in unmyelinated C fibers, stimulating endorphin release, and decreasing nociceptor excitability [20]. Furthermore, it supports sensory nerve regeneration by enhancing axonal growth and remyelination. During wound healing, PBM positively influences all phases of the repair process including the inflammatory, proliferative, and remodeling stages by promoting fibroblast proliferation, collagen deposition, angiogenesis, and re-epithelialization. These cellular and molecular effects reinforce PBM as a safe, non-invasive, and effective therapeutic strategy with broad clinical applicability in regenerative medicine, neurology, and rehabilitation [20, 21].

Despite encouraging preclinical and clinical evidence suggesting that PBM can reduce pain and improve nerve function in DN patients [22, 23], there remains no consensus on the optimal dosimetric parameters. Reported treatment regimens vary widely in wavelength (630–660 nm for RL and 808–904 nm for NIR), energy density (2–15 J/cm²), and treatment duration, resulting in heterogeneous outcomes [18, 24–28]. Such variability hampers the reproducibility of results, complicates clinical translation, and raises concerns regarding treatment consistency and safety [29].

Therapeutic efficacy in PBM is strongly influenced by parameters such as total energy delivered, irradiance, exposure time, pulse configuration, and treatment area. These factors are further modulated by the biphasic dose–response described by the Arndt–Schulz law and can be affected by patient-specific factors such as Fitzpatrick skin type [30]. The lack of consistency in protocols therefore represents a major barrier to optimizing PBM for DN management [24].

This review is particularly relevant because DN is a highly prevalent and disabling complication of DM, and PBM has emerged as a promising adjunctive therapy. However, the absence of standardized dosimetric guidelines has limited its clinical adoption. By critically examining the influence of wavelength, energy dose, and treatment duration on clinical and biological outcomes, this review aims to synthesize current knowledge, identify existing gaps, and provide a foundation for protocol optimization tailored to DN management.

Here, we present a critical narrative review of the dosimetric parameters reported in preclinical and clinical studies. A systematic review following PRISMA guidelines was not feasible because of the heterogeneity of available evidence [31]. Instead, this work summarizes findings from both experimental and clinical studies, with a focus on the relationship between PBM dosimetry and clinical outcomes in DN.

Methods

This review followed the PICO framework [32] to guide evidence-based analysis.

Research question In patients with diabetic neuropathy, what dosimetric parameters have been used in clinical studies of photobiomodulation, and how are they associated with observed clinical outcomes?

Population (P) Patients with diabetic neuropathy DN (any subtype, diagnosed by clinical and/or neurophysiological criteria).

Intervention (I) PBM using LLL or LEDs with any clinical protocol. Comparator (C): Placebo, no treatment, conventional therapies (pharmacological or non-pharmacological), or experimental interventions.

Outcomes (O) Primary: Reported dosimetric parameters (wavelength, energy density, power, application time, number of sessions, treatment sites).

Secondary Clinical outcomes (pain reduction, sensory/motor improvement, quality of life, neurophysiological changes, safety, and adverse effects). In this context, the completeness of protocols plays a key role in interpreting and comparing study outcomes.

This research question was further broken down into:

1. Clinical Evidence Review: Which clinical studies have investigated PBM in DN patients, and what dosimetric parameters were reported?

2. Dosimetry–Outcome Association: How are reported dosimetric parameters associated with clinical outcomes such as pain reduction and sensory/motor function?
3. Protocol Standardization: Is there consistency in dosimetric parameters and protocols across DN studies?
4. Evidence Gaps and Recommendations: What evidence gaps remain, and what are the recommendations for future research?

We included experimental and clinical studies assessing PBM in DN with no language restrictions. *Inclusion criteria*: original articles, systematic reviews, clinical trials, clinical protocols, and randomized controlled trials. *Exclusion criteria*: case reports, book chapters, conference abstracts, or studies unrelated to DN and PBM.

Searches were conducted across LILACS, SciELO, EMBASE, MEDLINE, PubMed, and the Cochrane Library, covering the period 1990–2025. Search terms combined Medical Subject Headings (MeSH) such as *"Diabetic Neuropathy"*, *"Type 2 Diabetes"*, *"Photobiomodulation"*, *"Low-Level Laser"*, and *"Allodynia"*, using Boolean operators "AND/OR" The search, conducted from March to May 2025, initially identified 94 articles. After applying inclusion and exclusion criteria, 23 articles published between 2015 and 2025 were retained for analysis. In Fig. 1, Flow diagram Strategy used to select the studies.

Results

The variability in treatment parameters across studies has hindered consensus on standardized dosimetric guidelines. By systematically analyzing the influence of wavelength, energy dose, and treatment duration on clinical and biological outcomes, this review aims to synthesize current knowledge, identify gaps, and provide a foundation for optimizing PBM protocols tailored to DN management.

Table 1 summarizes the studies published between 2015 and 2025, including author, year, dosimetry parameters, and main results, serving as a reference for researchers and clinicians interested in PBM application in DN. In Fig. 2, dosimetry parameters on Year (2015–2025).

In Table 2, most of the studies were classified Levels of Evidence (LE) and Grades of Recommendation (GR), according to *Oxford Centre Evidence Based Medicine* [33]. In Table 3, evidence base on diabetic neuropathy is mainly composed of randomized controlled trials (RCTs), meta-analyses (MAs), and a smaller proportion of clinical trials (CTs), preclinical studies (PCs), and systematic reviews (SRs). Overall, the majority of studies were RCTs (n = 11) and meta-analyses (n = 4), both consistently rated as LE 1 and GR A [33].

Preclinical studies and clinical trials contributed fewer publications, with LE 1–2 and GR A–B, reflecting some heterogeneity in methodological rigor. Only one systematic review was identified, graded as LE 2 and GR B. Taken together, the literature indicates that most available data are derived from high-quality designs, providing robust evidence (LE 1, GR A) for therapeutic approaches in diabetic neuropathy.

Studies predominantly identified RL (600–660 nm) [18, 34–39] and NIR (800–890 nm) [22, 23, 27, 35–47] wavelengths as most effective for DN, with reported benefits in pain reduction, nerve regeneration, and wound healing. Several trials suggested synergistic effects from combined RL and NIR light. Across the sample, wavelengths clustered at 660, 808, 830, and 904 nm. However, reviews consistency highlighted the lack of standardization in wavelength selection and its impact on outcomes [48].

Energy doses varied widely, from 40 J/cm² in animal models [27] to 4–12 J/cm² in effective clinical protocols [27, 49]. Several studies reported dose-dependent effects, with moderate doses (4–8 J/cm²) being optimal for wound healing and neuropathic pain relief. Power levels ranged from 30 to 150 mW, though most recent protocols employed 45–100 mW.

Treatment duration and number of sessions varied: Short-term protocols: 10 consecutive days [34, 39]. Medium-term protocols: 12 sessions over 3–4 weeks [18, 22, 46]. Long -term protocols: ≥20 sessions up to 60 days [37, 40, 50], generally associated with more sustained benefits.

Application sites most often included the dorsal and plantar surfaces of the feet, along peripheral nerve pathways (fibular, tibial), and ulcerated regions, with some protocols irradiating proximal sites such as the popliteal fossa [39].

A critical analysis of the selected articles revealed consistent findings: PBM promotes peripheral nerve regeneration, reduction of inflammatory mediators, and pain relief, leading to faster and more effective functional recovery. However, inconsistencies in dosimetric parameters highlight the need for protocol standardization.

Discussion

The therapeutic effects of PBM are influenced by multiple variables, including skin phototype, wavelength, power mode, and dosimetry. In lighter skin types (I–III), melanin absorption is lower, enabling deeper penetration, whereas darker phototypes (IV–VI) require dose and wavelength adjustments due to higher epidermal absorption [30].

RL (600–700 nm) provides superficial penetration, making it optimal for skin and epithelial tissues, while NIR (780–1100 nm) penetrates deeper and is therefore suitable for muscle and

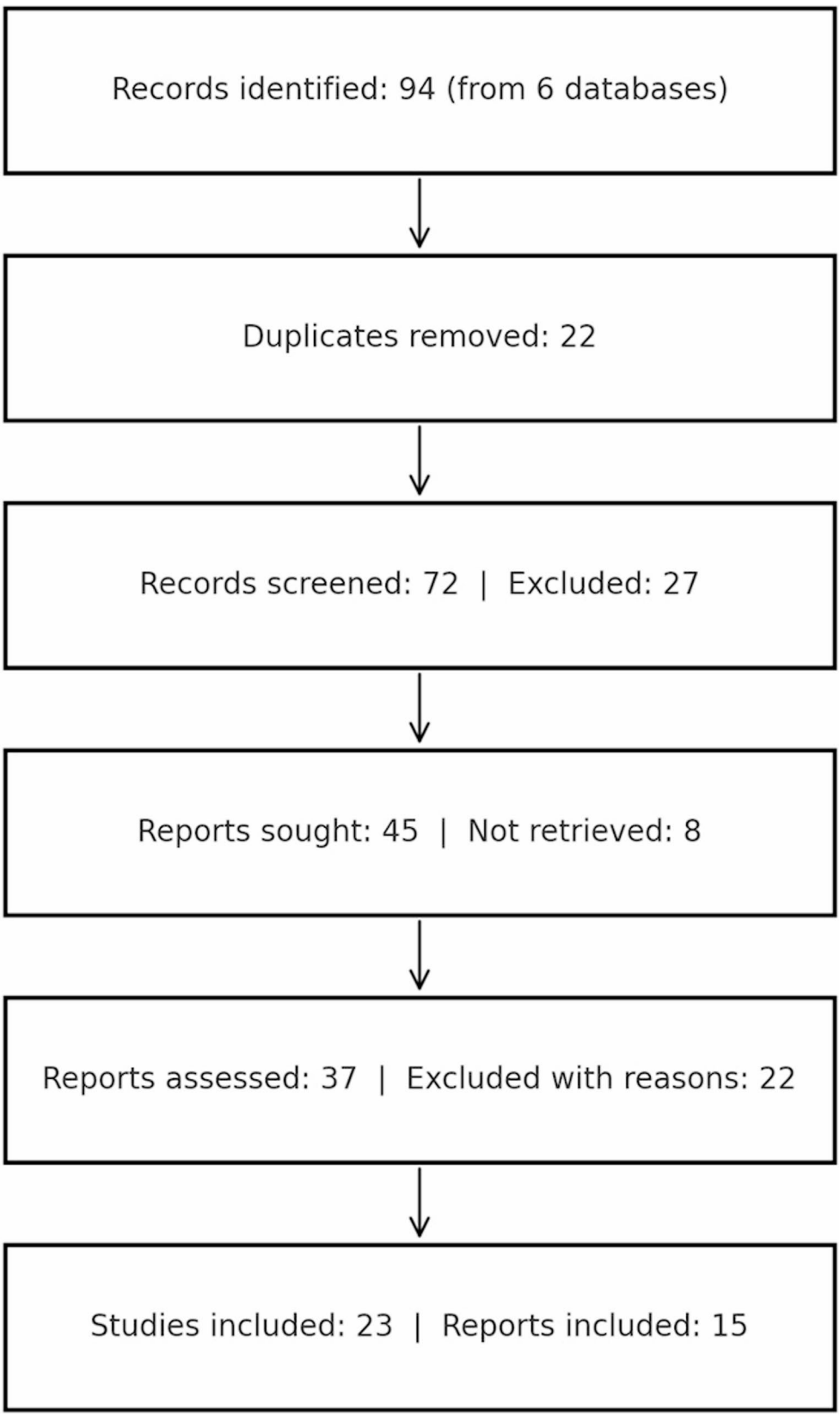


Fig. 1 Flow diagram, Strategy used to select the studies

Table 1 Articles on photobiomodulation and dosimetric parametrics in diabetic neuropathy between 2015 and 2025

Author(s) Year	Wavelength (nm)	Energy (mW)	Energy Density (J/cm2)	Radiation Amount	Summary Results
Cg SK et al. 2015 [33]	632,8 660, 850	50 150	3,1 3,4	plantar and dorsum of foot, fibula for 10 days	↓ pain ↓ nerve injury
Andrade et al. 2017 [27]	808	10,20,40	10,20,40	No related	Higher doses more effective for neuropathic pain
Santos Mendes-Costa et al. 2020 [34]	632.8 660	30 30	4 6	non-contact point; 80 s 13 s	↓pain ↓ time of tissue restoration and allowed the return of tactile sensitivity
Rastogi et al. 2021 [35]	890	No related	58,5	3 times a week, for 12 weeks Sites: 4,	↓ pain ↑ Quality of Life-Diabetic No effect on cutaneous reinnervation
Rocha et al. 2021 [23]	904	45	6,23	non-contact point;18 s	Reversing mitochondrial dynamics dysfunction in the course of peripheral nervous system damage in ND
Wadee et al. 2021 [36]	670– 950	No related	4	8 min,3 times per week for 6 weeks	↑ oxygenation, morpho-functional activity, and substantial expansion of the microcirculatory bed
Santos et al. 2021 [37]	632.8– 685	No related	3–6	30–80 s, 3 times weekly for a month	↓pain ↓ulcer area and rate of healing ↓Colony Count
Yosifova, Bokova. 2022 [38]	632,8 660, 850	50 150	3,1 3,4	plantar and dorsum of foot, fibula for 10 days	↓ pain ↓ nerve injury
Haze et al. 2022 [39]	808	80	8,8	twice daily for 1–3 weeks Site: 1, for 8 min, in contact	↑vascular cells and nitric oxide release ↑migration and collagen production, ↓apoptosis and pro-inflammatory cytokines.
Karkada et al. 2022 [40]	655– 808	No related	4, 6, 8	No related	Improved oxidative stress markers, wound healing
Leal et al. 2023 [22]	808	100	12	30 days, 3x/week, 12 sessions	↓pain improved quality of life
Nair et al. 2023 [41]	660, 800, and 970	30	No related	handpiece over a 3 min	wound area reduction and new granulomatous tissue
Ebadi et al. 2023 [18]	630, 810	35	32,08	15 min/session, 3x/week, 12 sessions	improved sensation, ↓ neuropathic symptoms
Lourenço et al. 2024 [42]	660– 850	23–28,5	8–10	Once a day for 60 days Site: 1, for 6 min, in contact with skin	↓ TNF-α and IL-1β levels, ↓ p38-MAPK mRNA expression and ↓ neuronal sensitisation through modulation of Ca^{2+} dynamics
Torkaman et al. 2024 [43]	904	90	2	3 days/week for 4 weeks (11 sessions)	↑effectively angiogenesis
Borges et al. 2024 [44]	620– 940	64–72	6	83–94 s	No effect in changes in skin temperature, sensitivity and pain
Chacur et al. 2024 [45]	850	No related	No related	2 min/session, 3x/week, 3–4 weeks	↓ allodynia
Santos et al. 2024 [46]	904	45	4,8,10	No related	↓ pain in all groups.
Tabeie et al. 2024 [47]	630– 810	35.65	64,17	Three sessions per week, for 20 sessions	↓surface and depth, improvements in the healing of their foot ulcers;13 s
Saura et al. 2024 [48]	904	30	4–8−10	13 s	10 J/cm^2: angiogenesis and hastening the inflammatory process
Miranda et al. 2025 [49]	660	No related	20	28 s per point to 5 min, with application frequencies of daily or twice daily for 6 days to 16 weeks	↓ulcer area, time and rate of healing
Chen et al. 2025 [50]	630– 890	50–180	2–10	30s–30 min	↓ pain accelerates wound healing
Anju et al. 2025 [51]	632.8 660– 850	No related No related	3.1 3.4	2,9 min, at each foot's plantar and dorsal surface contact method over popliteal fossa for 3 min daily for ten days	↓ pain and inflammation with neuroprotective effect PBM given at a dosage of 3.1 J/cm^2 at the plantar and dorsal surface of the foot improved microcirculation

*Systematic Reviews (SR); "Randomized Controlled Trial (RCT); *Meta-Analysis (MA); *Preclinical (PC), *Clinical Trial (CT)

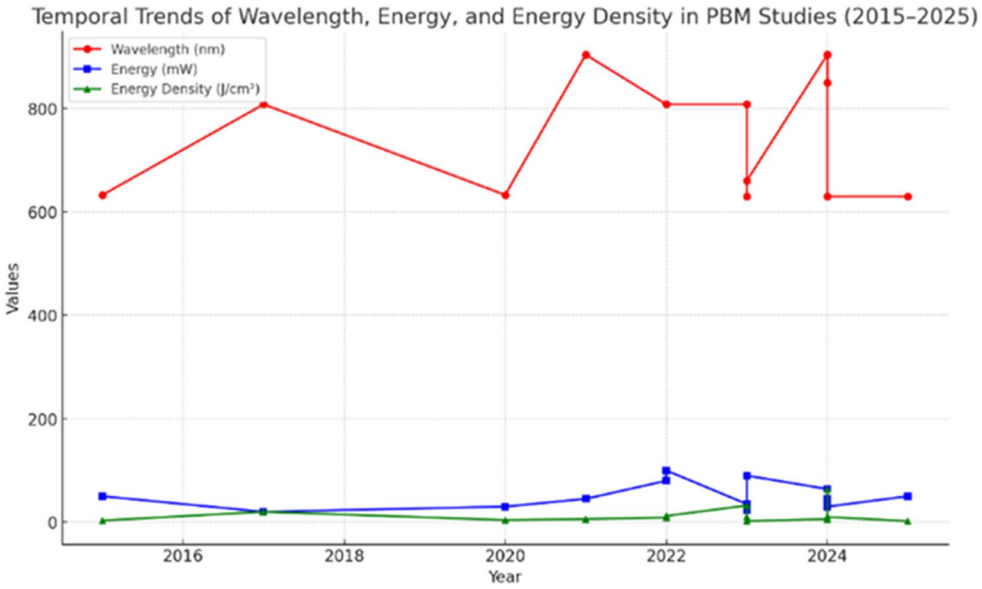


Fig. 2 Dosimetric on Year (2015–2025). n: number of studies; μ: average dose; med: median dose

Table 2 Levels of evidence (LE) and grades of recommendation (GR), according to Oxford centre evidence based medicine [33]

GR*	LE*	Type of Study
A	1	Systematic review of RCTs* (with or without meta-analysis), with homogeneity Individual RCTs with narrow confidence intervals and consistent results
B	2	Systematic review of cohort studies (with homogeneity) Individual high-quality cohort studies non-randomized controlled clinical trials
B	3	Well-conducted case-control studies
C	4	Case series and lower-quality observational studies
D	5	Expert opinion, consensus, guidelines without systematic critical appraisal

Grade of Recommendation (GR)*; Level of Evidence (LE)*; Randomized Controlled Trial (RCT)*

nerve targets. Continuous wave (CW) delivers constant stimulation with mild thermal effects, whereas superpulsed mode offers high peak power with low average energy, allowing deeper penetration without overheating [51].

PC and clinical evidence consistency supports the therapeutic potential of PBM in DN. RCTs and animal models demonstrate its role in reducing neuropathic pain, enhancing nerve conduction, and exerting neuroprotective effects. RCTs [18, 22, 52] and animal studies [23, 46] consistently support its role in reducing neuropathic pain, improving nerve conduction, and promoting tissue repair. For example, a 2024 preclinical study demonstrated decreased nociceptive thresholds in diabetic animals from the first session, suggesting PBM as a promising approach for severe peripheral pain. Clinically, PBM at a dosage of 3.1 J/cm² on the plantar and dorsal foot surfaces reduced neuropathic pain, alleviated DN symptoms, and exerted neuroprotective effects [39].

Table 3 Types of the studies, grades of Recommendation(G) and levels of evidence (LE) in the diabetic neuropathy [33]

Authors	Type of study	LE	GR
Cg SK et al. [33]	CT*	1	A
Andrade et al. [27]	PC*	1	A
Santos Mendes-Costa L et al. [34]	MA*	1	A
Rastogi A et al. [35]	RCT*	1	A
Rocha et al. [23]	PC*	1	A
Wadee AN et al. [36]	RCT*	1	A
Santos CMD et al. [37]	MA*	1	A
Yosifova, Dokova [38]	CT*	2	B
Haze A et al. [39]	RCT*	1	A
Karkada et al. [40]	PC*	1	A
Leal et al. [22]	RCT*	1	A
Ebadi et al. [18]	RCT*	1	A
Nair et al. [41]	CT*	2	B
Lourenço et al. [42]	SR*	2	B
Torkaman et al. [43]	RCT*	1	A
Borges et al. [44]	RCT*	1	A
Santos CM et al. [45]	RCT*	1	A
Tabeie et al. [46]	RCT*	1	A
Saura CV et al. [47]	RCT*	1	A
Chacur et al. [48]	PC*	1	A
Miranda et al. [49]	MA*	1	A
Chen et al. [50]	MA*	1	A
Anju et al. [51]	RCT*	1	A

*Systematic Reviews (SR); “Randomized Controlled Trial (RCT); *Meta-Analysis (MA); *Preclinical (PC), *Clinical Trial (CT)

Its efficacy is achieved in PBM through the modulation of sensory nerve fiber activity, the reduction of pro-inflammatory mediators such as prostaglandins and cytokines, and the increased production of β-endorphins, endogenous neurotransmitters with analgesic properties [23, 26, 27, 34–36, 46, 53].

Animal studies also corroborate these effects. A study 2017, investigated the effects of PBM using an 808 nm wavelength on neuropathic pain control in mice. The treatment protocol employed specific dosimetric parameters, including power output, irradiation time, and energy density tailored to modulate nociceptive pathways effectively. Results demonstrated a significant reduction in pain behaviors, indicating the analgesic potential of PBM. However, detailed reporting of key parameters such as irradiance and total energy delivered was limited, which may affect reproducibility and comparison with other studies. The findings suggest that PBM at 808 nm can effectively alleviate neuropathic pain [41].

Fan et al. 2024 and Korada et al. 2023 further highlighted improvements in safety, nerve conduction velocity, and quality of life, particularly in the plantar region [25, 29].

PBM also reduces nociceptor excitability and regulates ion channel expression, while modulating macrophages, neutrophils, and lymphocytes, thereby accelerating the resolution of inflammation [18, 37, 43, 47]. Research further indicates that PBM modulates key signaling pathways implicated in neuropathic pain, notably MAPK (p38 and ERK) signaling, intracellular calcium dynamics, and cytokine release (TNF-α, IL-1β, IL-6) [54–56].

In the context of diabetic wound healing, PBM promotes cell proliferation through ERK activation, regulates the activity of matrix metalloproteinases (MMP-1/8 and MMP-2) and their inhibitors (TIMP), and stimulates angiogenesis by modulating VEGF expression and improving tissue oxygenation. Collectively, these mechanisms contribute to enhanced microcirculation and faster ulcer healing in DN patients [57].

Clinical application of 2025 study [38] demonstrated marked variability in wavelength, dosage, power, and exposure time, complicating the establishment of optimized protocols. In several trials, methodological reporting was incomplete. The most commonly reported laser parameters were continuous mode, non-contact application, wavelengths between 632.8 and 830 nm, power of ~ 30 mW, and a dosage of 4 J/cm². For LED treatments, wavelengths ranged from 600 to 900 nm, with a power of ~ 48 mW and a dosage of 2.4 J/cm² [40].

Several clinical trials also highlight PBM potential in DN. Leal et al. 2025, investigated the effects of PBM using an 808 nm wavelength on pain relief and quality of life in patients with DN. Results demonstrated a significant reduction in neuropathic pain and a notable improvement in patients quality of life. The findings support the clinical potential of PBM at 808 nm for managing DN symptoms, highlighting the importance of detailed dosimetric reporting to optimize treatment protocols and ensure reproducibility [22].

Ebadi et al. 2023, evaluated the effects of PBM using two wavelengths, 630 nm and 810 nm, on DN. Both wavelengths significantly improved behavioral and functional outcomes related to neuropathy, with 810 nm showing slightly superior efficacy in nerve regeneration markers. However, the study lacked detailed reporting on irradiance and total energy delivered. These results highlight the therapeutic potential of dual wavelength PBM in DN and underscore the necessity of standardized dosimetric [18].

Chacur et al. 2024, investigated the effects of PBM using 850 nm near-infrared light for the prevention and reversal of neuropathic pain in rats, applying 2 min of irradiation, three times per week, for up to four weeks. Although a significant reduction in mechanical allodynia was noted, no improvement in the preservation of myelinated fibers was detected, and a reduction in C fibers was noted in treated animals. Notably, essential parameters such as irradiance, fluence, and total power were omitted, which limits reproducibility and comparison with other studies. The discrepancy between analgesic effects and the absence of structural recovery suggests that the therapeutic benefits are linked to functional neural modulation mechanisms, underscoring the necessity for future research to include the underlying molecular pathways [46].

In a 2021 RCT, the effects of LLL irradiation and hyperbaric oxygen therapy (HBOT) were investigated in patients with chronic diabetic foot ulcers. The laser treatment utilized specific dosimetric parameters, including low power output (~ 100 mW), wavelengths within the RL to NIR spectrum (630–850 nm), and irradiation times calibrated to deliver therapeutic energy doses. Both therapies significantly enhanced local oxygenation, critical for wound healing, with LLL offering the added benefit of being less invasive. The study highlighted the need for accurate dosimetric control to maximize treatment efficacy [41].

Protocols often included 12 or more sessions, though session frequency and total treatment duration varied widely. Application modes were both contact and non-contact, with inconsistent reporting of beam size, aperture diameter, or divergence. While most studies demonstrated clinical or PC benefits, these methodological inconsistencies complicate cross-study comparisons and hinder the development of standardized clinical guidelines [31, 58].

A major limitation across the literature is the incomplete reporting of essential dosimetric parameters. Many studies did not provide irradiance, fluence, treatment area, calibration procedures, or total delivered energy. Without this information, it is difficult to establish dose response relationships or compare outcomes across studies. In several cases, discrepancies were also noted between reported energy wavelength and power wavelength relationships, further complicating reproducibility. These omissions, combined

with small sample sizes and heterogeneous designs, compromise external validity and may yield inconclusive or misleading results [31, 48, 57, 58].

Future research must therefore prioritize methodological rigor and protocol standardization. Multicenter randomized controlled trials with adequate sample sizes are required to confirm PBM efficacy across diverse populations. A minimum dataset of essential parameters including wavelength, output power, irradiance, exposure time, fluence, aperture diameter, beam divergence, and calibration should be consistently reported to ensure reproducibility and enable meta-analytical synthesis. Dose-response designs will be especially important for correlating specific regimens with biological and clinical outcomes. Technological innovations, such as wearable devices and combined RL/NIRsystems, may improve coverage, adherence, and efficacy. Furthermore, long-term follow-up studies of ≥ 12 months are necessary to evaluate the durability of PBM effects [31, 57].

Current studies have primarily focused on pain relief, sensory recovery, and ulcer healing, outcomes of major importance for diabetic patients suffering from painful neuropathy. However, autonomic neuropathy, a frequent and debilitating complication manifesting as cardiovascular dysregulation, gastroparesis, urinary dysfunction, and sudomotor abnormalities remains largely unexplored. Gastroparesis, in particular, significantly worsens quality of life in diabetic patients but no PBM studies have evaluated its effects on gastric emptying, visceral innervation, or autonomic. This gap underscores the urgent need for future trials to investigate PBM not only in painful sensory neuropathy but also in autonomic dysfunction, aiming at broader and more integrated therapeutic outcomes in DN [10, 11, 59].

DN particularly painful peripheral neuropathy is a complex and challenging complication of T2D, with difficulties ranging from early diagnosis to effective treatment. Early symptoms are often subtle or nonspecific, and limited access to diagnostic tools such as nerve conduction studies contributes to under-recognition, especially of autonomic neuropathy. Pharmacological treatments, including anticonvulsants (gabapentin, pregabalin), antidepressants (tricyclics, serotonin-norepinephrine reuptake inhibitors such as duloxetine), topical agents (capsaicin, lidocaine), and antioxidant supplements (alpha-lipoic acid) offer only modest pain relief [60, 61].

Neuromodulation therapies such as transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS) show promise in refractory cases but are limited by side effects and poor adherence. While glycemic control is effective in preventing neuropathy in type 1 diabetes, its impact in T2D is less pronounced due to multifactorial contributors, including microvascular dysfunction, oxidative stress, adiposity, and dyslipidemia. Prevention remains critical, emphasizing early intervention during prediabetes and diabetes diagnosis, alongside public health efforts to improve access, education, and monitoring [62].

In this context, PBM has gained attention as a non-invasive adjunct therapy that stimulates cellular metabolism, enhances microcirculation, reduces inflammation, and promotes tissue repair by modulating mitochondrial activity through cytochrome c oxidase activation. PBM increases ATP production, mitigates oxidative stress, and influences cellular signaling pathways involved in nerve regeneration and pain modulation [63]. Clinical evidence suggests PBM can alleviate neuropathic pain and improve nerve function, providing a valuable complement or alternative to conventional treatments, particularly given its favorable safety and tolerability profile. Its ability to enhance microvascular circulation addresses a key pathological factor in diabetic neuropathy, potentially improving outcomes and quality of life. Nevertheless, further rigorous clinical trials are required to standardize protocols and validate the long-term benefits of PBM in diabetic neuropathy management [39, 49].

Conclusion

PBM emerges as a safe, effective, and non-invasive therapeutic option for DN. Clinical benefits consistently include pain reduction, sensory improvement, and accelerated ulcer healing. The most common parameters reported were RL (630–670 nm) and NIR (808–904 nm) wavelengths, energy densities of 3–10 J/cm², output powers of 45–100 mW, and treatment protocols extending to at least 12 sessions. However, considerable heterogeneity and incomplete dosimetric reporting remain significant barriers to protocol optimization. While most included studies were of high methodological quality (LE 1, GR A), future well-designed multicenter RCTs with standardized dosimetric datasets are essential for establishing optimized protocols and incorporating PBM into evidence-based clinical guidelines for DN management.

Author contributions V.S. conceived and designed the study, conducted the literature search, selected and analyzed the articles, prepared all figures and tables, and drafted the manuscript. M.P.C. and C.C.B. contributed to the literature search, screening, and data extraction. A.P.L.O. supported the literature review and data organization. J.A.S.J. and S.R.Z. critically revised the manuscript and contributed to the interpretation of the results. N.A.P. and R.E.L. assisted with methodological refinement and manuscript revision. R.A.B.L.M. and R.L.M. supervised the study, contributed to the discussion, and approved the final version of the manuscript. All authors read and approved the final manuscript.

Funding This research received no external funding.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Competing interests The authors declare no competing interests.

Clinical trial registration Not applicable.

References

1. American Diabetes Association Professional Practice Committee Standards of Care in Diabetes-2024
2. Li M (2022) Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther 7:216
3. Sun H et al (2022) IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 183:109119
4. Roikjer et al (2024) Diabetic Peripheral Neuropathy: Emerging Treatments of Neuropathic Pain and Novel Diagnostic Methods. b J Diabetes Sci Technol
5. Qu F, Shi et al (2022) Visit-to-visit glycated hemoglobin A1c variability in adults with type 2 diabetes: A systematic review and meta-analysis. Chin Med J 135:2294–2300
6. Filippatos TD et al (2022) Nonalcoholic fatty pancreas disease: role in metabolic syndrome, 'prediabetes,' diabetes and atherosclerosis. Dig Dis Sci 67:26–41
7. Lu X (2024) Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Signal Transduct Target Ther 9(1):262
8. Liu W et al (2024) Global trends in the burden of chronic kidney disease attributable to type 2 diabetes: an age-period-cohort analysis. Diabetes Obes Metab 26(2):602–610
9. Chen X et al (2025) Oxidative stress in diabetes mellitus and its complications: from pathophysiology to therapeutic strategies. Chin Med J (Engl) 5(1):15–27
10. Idiáquez Rios JF et al (2023) Spanish-speaking patients: translation and validation of the Toronto clinical neuropathy score. J Peripher Nerv Syst 28(3):471–475
11. Tesfaye S, Toronto Diabetic Neuropathy Expert Group et al (2010) Diabetic neuropathies: update on definitions, diagnostic criteria, Estimation of severity, and treatments. Diabetes Care 33(10):2285–2293
12. He Y, Peggy Y, Kim (2023) Allodynia. Stat Pearls Publishing
13. Jensen TS et al (2021) Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. Brain 144:1632–1645
14. Magliano DJ (2020) Young-onset type 2 diabetes mellitus – implications for morbidity and mortality. Nat Rev Endocrinol 16:321–331
15. Ziegler D et al (2021) Current concepts in the management of diabetic polyneuropathy. J Diabetes Investig 12:464–475
16. Galiero R et al (2023) Peripheral neuropathy in diabetes mellitus: pathogenetic mechanisms and diagnostic options. Int J Mol Sci 24(4):3554
17. Maiya GA et al (2025) Effect of novel laser shoe photobiomodulation on neuropathic pain and plantar pressure profile in type 2 diabetes mellitus with peripheral neuropathy. Curr Diabetes Rev 21(3):1–6
18. Ebadi SA et al (2023) Effects of photobiomodulation with two wavelengths of 630 and 810 Nm on diabetic neuropathy. J Lasers Med Sci 14:e22
19. Holanda VM et al (2017) The mechanistic basis for photobiomodulation therapy of neuropathic pain by near infrared laser light. Lasers Surg Med 49(5):516–524
20. Kujawa J (2014) The effect of near-infrared MLS laser radiation on cell membrane structure and radical generation. Lasers Med Sci 29(5):1663–1668
21. Glass GE, Photobiomodulation (2021) The clinical applications of Low-Level light therapy. Aesthetic Surg J 41(6):723–738
22. Leal MVS et al (2022) Evaluation of the effects of photobiomodulation (808 nm) on pain and quality of life of diabetic neuropathy patients. RSD [Internet]. Jan. 24 [cited 2025. 21] 11(2)
23. Rocha IRC et al (2021) Effect of photobiomodulation on mitochondrial dynamics in peripheral nervous system in streptozotocin-induced type 1 diabetes in rats. Photochem Photobiol Sci 20(2):293–301
24. Buzza A (2024) Photobiomodulation for pain relief: model-based estimates of effective doses of light at the neural target. J Photochem Photobiol B 256:112929
25. Korada HY et al (2023) Effectiveness of photobiomodulation therapy on neuropathic pain, nerve conduction and plantar pressure distribution in diabetic peripheral neuropathy - a systematic review. Curr Diabetes Rev 19(9). https://doi.org/10.2174/1573399818666220429085256
26. Wang JY et al (2022) Low-level light therapy/photobiomodulation for diabetic peripheral neuropathy: protocol of a systematic review and meta-analysis. BMJ Open 12(9)
27. Andrade ALM et al (2017) Effect of photobiomodulation therapy (808 nm) in the control of neuropathic pain in mice. Lasers Med Sci 32(4):865–872
28. Santos Mendes-Costa L et al (2021) Photobiomodulation: systematic review and meta-analysis of the most used parameters in the resolution diabetic foot ulcers. Lasers Med Sci 36(6):1129–1138
29. Fan X et al (2024) Effectiveness and safety of photobiomodulation therapy in diabetic peripheral neuropathy: protocol for a systematic review and meta-analysis. PLoS One 19(8)
30. Huang YY et al (2009) Biphasic dose response in low level light therapy. Dose Response 7:358–383
31. Cronshaw M et al (2020) Photobiomodulation dose parameters in dentistry: a systematic review and meta-analysis. Dentistry J Out 8(4):114
32. Schiavenato M, Chu F (2021) *PICO*: What it is and what it is not. Nurse Educ Pract 56:103194
33. Oxford Centre for Evidence-Based Medicine (2011) The Oxford 2011 levels of evidence. University of Oxford, Oxford
34. Cg SK et al (2015) Efficacy of low-level laser therapy on painful diabetic peripheral neuropathy. Laser Ther 24(3):195–200
35. Santos CM et al (2024) Adherence to self-care and quality of life of patients with diabetic foot ulcers treated with low-level laser therapy: an exploratory study. Adv Skin Wound Care 37(8):1–10
36. Santos CMD et al (2021) A systematic review and meta-analysis of the effects of low-level laser therapy in the treatment of diabetic foot ulcers. Int J Low Extrem Wounds 20(3):198–207
37. Lourenço R (2025) Effect of photobiomodulation as preventive treatment of diabetic foot ulcer: randomised, controlled, double-blind, clinical trial protocol. BMJ Open 1-8. https://doi.org/10.1136/bmjopen-2024-094594
38. Miranda MB et al (2025) Effects and parameterization of low-level laser therapy in diabetic ulcers: an umbrella review of systematic reviews and meta-umbrella. Lasers Med Sci 40(1):109
39. Anju M et al (2025) A single blinded randomized controlled trial assessing the effect of photobiomodulation therapy on neuron specific biomarkers in type II diabetes mellitus patients with peripheral neuropathy. Diabetes Res Clin Pract 222:112087
40. Rastogi A (2021) Effect of monochromatic infrared energy on quality of life and intraepidermal nerve fiber density in painful

diabetic neuropathy: a randomized, sham control study. Neurol India 69(5):1331–1337
41. Wadee AN et al (2021) The influence of low- intensity laser irradiation versus hyperbaric oxygen therapy on transcutaneous oxygen tension in chronic diabetic foot ulcers: a controlled randomized trial. J Diabetes Metab Disord 20(2):1489–1497
42. Haze A et al (2022) Treatment of diabetic foot ulcers in a frail population with severe co-morbidities using at-home photobiomodulation laser therapy: a double-blind, randomized, sham-controlled pilot clinical study. Lasers Med Sci 37(2):919–928
43. Nair HKR, Chong SSY, Selvaraj DDJ (2023) Photobiomodulation as an adjunct therapy in wound healing. Int J Low Extrem Wounds 22(2):278–282
44. Torkaman G et al (2024) Effects of photobiomodulation therapy on the expression of hypoxic inducible factor, vascular endothelial growth factor, and its specific receptor: a randomized control trial in patients with diabetic foot ulcer. Photobiomodulat Photomed Laser Surg 42(4):275–284
45. Borges NCS et al (2024) Photobiomodulation using red and infrared spectrum light emitting-diode (LED) for the healing of diabetic foot ulcers: a controlled randomized clinical trial. Lasers Med Sci 39(1):9
46. Chacur M et al (2024) Prevention and reversal of neuropathic pain by near-infrared photobiomodulation therapy in male and female rats. Physiol Behav 286:1
47. Saura CV et al (2024) Dose-response and efficacy of 904 Nm photobiomodulation on diabetic foot ulcers healing: a randomized controlled trial. Lasers Med Sci 39(1):142
48. Hadis SA, Holder MJ, Carroll JD, Cooper PR, Milward MR, Palin WM et al (2016) The dark art of light measurement: accurate radiometry for low-level light therapy. Lasers Med Sci Maio 31(4):789–809)
49. Karkada G et al (2022) Effect of photobiomodulation therapy on oxidative stress markers in healing dynamics of diabetic neuropathic wounds in Wistar rats. Cell Biochem Biophys 80(1):151–160
50. Tabeie F et al (2024) Effect of visible and infra-red photobiomodulation on diabetic foot ulcers. J Lasers Med Sci 15:e12
51. Silva TG et al (2023) Photobiomodulation at molecular, cellular, and systemic levels. Lasers Med Sci 38(1):136
52. Yosifova L, Dokova K (2022) Mls laser in diabetic sensorimotor polyneuropathy late effects. Varna Med Forum. https://doi.org/10.14748/vmf.v0i0.8517
53. Chen B et al (2025) Intervention effects of low-level laser therapy (LLLT) on grade I-II ulcers in diabetic foot patients: A meta-analysis. Wound Repair Regen 33(2):e70021
54. Ji RR, Suter MR (2007) p38 MAPK, microglial signaling, and neuropathic pain. Mol Pain. https://doi.org/10.1186/1744-8069-3-33
55. Pasternak-Mnich K (2024) Impact of photobiomodulation therapy on pro-inflammation functionality of human peripheral blood mononuclear cells - a preliminary study. Sci Rep 14(1):23111
56. Mai L et al (2020) P38 mitogen-activated protein kinase and pain. Life Sci 256:117885
57. Oliveira VR et al (2025) Photobiomodulation therapy in diabetes: benefits for pain relief, quality of life, and wound healing. Photochem Photobiol 101(4):913–924
58. Parker et al (2024) Full operating parameter recording as an essential component of the reproducibility of laser-tissue interaction and treatments. Adv Clin Exp Med 33
59. Marathe CS et al (2020) Gastrointestinal autonomic neuropathy in diabetes. Auton Neurosci 229:102718
60. Bragg S et al (2024) Diabetic peripheral neuropathy: prevention and treatment. Am Fam Physician 109(3):226–232
61. Sałat K (2013) Evaluation of analgesic, antioxidant, cytotoxic and metabolic effects of Pregabalin for the use in neuropathic pain. Neurol Res 35(9):948–958
62. Perrier Q, Moro C, Lablanche S (2024) Diabetes in spotlight: current knowledge and perspectives of photobiomodulation utilization. Front Endocrinol (Lausanne) 15. https://doi.org/10.3389/fendo.2024.1303638
63. Pandolfo IL et al (2023) Photobiomodulation in diabetic rats: effects on morphological, pancreatic parameters, and glucose homeostasis. J Biophotonics 16(11):e202300182