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Intravenous and Transcutaneous Laser Blood Irradiation for Diabetes Mellitus: A Systematic Review of Clinical Outcomes

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Abstract

Introduction: Diabetes mellitus (DM) is a common metabolic disorder. Intravenous laser blood irradiation (ILIB) operates on the principle of photobiomodulation and has been proposed as a complementary treatment for DM and its complications. This systematic review evaluated the effects of ILIB on glycemic control and diabetes-related complications.

Methods: We systematically searched PubMed, Scopus, Web of Science, and ProQuest from 1990 to September 2025. We included studies of adults with DM receiving ILIB or transcutaneous laser blood irradiation. Two independent reviewers screened and extracted data. Risk of bias was assessed using RoB 2 for randomized controlled trials and ROBINS-I for non-randomized studies. Given the substantial heterogeneity in study designs, laser parameters, outcome measures, and follow-up durations, we performed a narrative synthesis rather than a meta-analysis.

Results: Nine studies involving 256 participants were included: four RCTs or RCT protocols, three single-arm or repeated-measures studies, and three observational or case-series studies. Most participants had type 2 DM. Wavelengths ranged from 405 nm to 660 nm, and power output from 1.5 mW to 100 mW. Among studies reporting glycemic outcomes, one RCT found significant reductions in HbA1c (−1.18% vs −0.63%; $P=0.0001$) and fasting plasma glucose (FPG) after 12 weeks of transcutaneous laser irradiation. Two pre/post studies reported significant acute reductions in blood glucose following single and repeated sessions. In contrast, another RCT showed no significant between-group differences in HbA1c or FPG following 10 sessions of transcutaneous laser blood irradiation adjunctive to periodontal therapy. Evidence for diabetic neuropathy, wound healing, and cellular biomarkers was limited to single observational studies.

Conclusion: Evidence for ILIB in diabetes remains limited and heterogeneous. Although some studies suggest potential short-term benefits for glycemic markers, findings are inconsistent. Evidence for diabetes-related complications is insufficient. Well-designed, adequately powered RCTs with standardized protocols and clinically relevant outcomes are needed.

Keywords: Intravenous laser therapy, Photobiomodulation, Diabetes mellitus, Systematic review

Introduction

One of the most prevalent metabolic disorders is diabetes mellitus (DM), which affects more than 500 million people worldwide.[1,2] Approximately 90-95% of DM cases are classified as type 2 diabetes (T2DM), which results from impaired insulin sensitivity and an insufficient insulin supply. Chronic hyperglycemia and metabolic disturbances can cause several microvascular and macrovascular complications.[3,4] Various pharmacological interventions are used to treat T2DM. However, many patients still struggle to achieve optimal glycemic control. Furthermore, the progressive nature of the disease underscores the importance of exploring complementary therapeutic approaches.

Low-level laser therapy (LLLT), also known as photobiomodulation, is a non-invasive therapeutic

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modality that shows promising efficacy in managing T2DM.[5] The proposed mechanism involves the interaction of light with mitochondrial chromophores, with cytochrome c oxidase considered a primary target, which may initiate downstream cellular responses.[6] This pathway stimulates beneficial biochemical cascades in cells and increases adenosine triphosphate synthesis. It also modulates reactive oxygen species levels, reduces inflammation, restores metabolic homeostasis, and promotes tissue repair.[7]

Intravenous laser blood irradiation, also known as intravascular laser irradiation of blood (IVILB), applies LLLT into the bloodstream through a venous catheter. The most commonly employed wavelengths in ILIB protocols are red and near-infrared, typically ranging from 630 to 850 nm. These wavelengths show considerable tissue penetration. The laser light delivered into the blood circulation affects blood cells throughout the body. Subsequently, it exerts therapeutic effects on multiple organ systems. Studies suggest ILIB enhances erythrocyte deformability, improves microcirculatory blood flow, stimulates endogenous antioxidant systems, and modulates inflammatory mediators.[8,9] These effects suggest a therapeutic potential in DM.

Several mechanisms have been hypothesized to explain the efficacy of ILIB in glucose metabolism, including enhancing pancreatic beta-cell function, improving insulin sensitivity in peripheral tissues, and modulating the nitric oxide synthase pathway.[5,10] Thus, ILIB may modulate vascular function and glucose homeostasis. However, evidence supporting these mechanisms remains limited, and further investigation is warranted.

Moreover, some studies have suggested that this modality may reduce fasting plasma glucose (FPG) levels, lower glycated hemoglobin concentrations, and ameliorate diabetes-related complications, such as neuropathy, nephropathy, and retinopathy.[11]

Optimizing laser parameters, such as wavelength, power density, total energy dose, treatment duration, and session frequency, is critical for therapeutic outcomes, yet optimal protocols remain unestablished. In addition, reported treatment regimens show considerable variability, with some studies using daily sessions and others using weekly sessions.

Although growing evidence suggests potential benefits of ILIB in managing diabetes, the efficacy of different laser parameters, the optimal duration of treatment courses, the long-term efficacy of this treatment, and the underlying molecular mechanisms remain to be investigated. Due to the rising incidence of T2DM and the limitations of current therapeutic approaches, the effects of complementary modalities warrant further study. The main objective of this systematic review is to determine the efficacy of ILIB in FPG, glycated hemoglobin (HbA1c), and serum insulin levels in T2DM patients. We will also explore optimal ILIB parameters and the effects of ILIB on diabetic complications.

Materials and Methods

Registration and Protocol

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[12] The Research Ethics Board of Shahid Beheshti University of Medical Sciences approved the protocol (IR.SBMU.LASER.REC.1401.008). We prospectively registered this systematic review with the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number [CRD420261412594].[13]

Eligibility Criteria

The study-selection criteria were determined according to the review question structured with the PICO framework, encompassing the population, intervention, comparator, and outcomes of interest. We investigated the efficacy of intravenous laser blood irradiation (ILIB) versus placebo, sham treatment, or standard care in adult patients (aged ≥ 18 years) with diabetes mellitus. Primary outcomes of interest included improvements in glycemic control (FPG, HbA1c, and insulin levels) and the mitigation of diabetes-related complications. Comparators included control conditions and analyses of varying ILIB dosimetry parameters.

Definitions

Diabetes Mellitus: Defined per the diagnostic criteria of the American Diabetes Association (ADA) (FPG ≥ 126 mg/dL, HbA1c ≥ 6.5%, or 2-hour plasma glucose ≥ 200 mg/dL during a 75 g oral glucose tolerance test, or a random plasma glucose ≥ 200 mg/dL in a patient with classic hyperglycemic symptoms). Studies were included if they clearly identified participants as having T2DM, which was confirmed by a physician-reported diagnosis.

Intravenous Laser Therapy (ILIB): Defined as therapeutic low-level laser application to the bloodstream via a peripheral vein catheter (invasive ILIB) or transcutaneously over superficial vessels. Both modalities were eligible for inclusion.

Inclusion and/or Exclusion Criteria

Studies meeting the following criteria were included: (1) The study design was one of the following: randomized controlled trials (RCTs), quasi-experimental studies, cohort studies, case-control studies, and pre–post observational studies published between 1990 and September 2025; (2) The study population comprised adult patients (aged ≥ 18 years) with a confirmed clinical diagnosis of T2DM; (3) The intervention involved any form of intravenous or transcutaneous laser blood irradiation, regardless of wavelength, dose, or session protocol; (4) The study reported at least one quantitative measure of glycemic regulation or insulin sensitivity (FPG, HbA1c, HOMA-IR, insulin levels) or a diabetes-related complication (neuropathy, nephropathy, retinopathy, wound healing); (5) The full-text article was available in English.

Reports were excluded when quantitative outcome data could not be extracted. We also excluded case reports, editorial letters, narrative reviews, conference abstracts without adequate extractable information, or animal and in vitro experiments. Furthermore, studies that did not involve ILIB or transcutaneous laser blood irradiation as the primary intervention, such as topical LLLT alone, were also excluded. Finally, studies without a confirmed diabetes diagnosis in participants, or a pediatric population (age < 18 years), were not considered for inclusion.

Sources and Search Strategy

Relevant studies published between 1990 and September 2025 were systematically retrieved from major electronic databases, including Web of Science, PubMed, and Scopus. The ProQuest database was also manually reviewed for relevant dissertations. To ensure comprehensive coverage, gray literature, such as conference abstracts and meeting proceedings from organizations like the ADA and the European Association for the Study of Diabetes (EASD), was examined. Expert opinions were also solicited via email to identify any unpublished or ongoing research. To supplement the database searches, we screened the reference lists of relevant systematic reviews and eligible primary studies for additional records. Study selection was not restricted by geographic settings; however, only reports available in full text were considered for inclusion.

For database searching, we used the Medical Subject Headings (MeSH) database to identify relevant terms related to diabetes, intravenous laser therapy, and glycemic markers. The primary search keywords included 'Diabetes Mellitus', 'intravenous laser therapy', and 'fasting blood glucose'. We developed a structured search strategy combining free-text terms, MeSH terms, and Boolean operators (AND/OR/NOT) to improve search accuracy. Search performance was evaluated using the number needed to read (NNR), a metric reflecting the number of records that must be screened to identify one relevant study. The complete search strategies for each database are reported in Supplementary Material 1.

Records retrieved from all sources were imported into an EndNote reference library (Version X7; Thomson Reuters Corporation, Toronto, ON, Canada) to identify and eliminate duplicate records. The initial screening phase involved reviewing titles and abstracts to determine potential relevance. Two independent reviewers (P.RF. and R.D.) conducted a full-text evaluation of the selected studies and classified them into three categories: relevant, irrelevant, or uncertain, based on predefined eligibility criteria. Disagreements among reviewers were referred to a third evaluator (Z.R.) for resolution through discussion. If uncertainties persisted, the entire research team participated in the final decision-making process to ensure consistency and accuracy in study selection.

Quality and Risk of Bias Assessment

Two reviewers (P.RF. and R.D.) independently appraised the risk of bias in each included study using assessment tools selected according to study design. Disagreements between the two assessors were addressed through discussion to reach consensus. Unsolved issues were resolved by a third reviewer (A.F.). For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was used.[14] Using RoB 2, we evaluated risk of bias for each relevant result across five domains: bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and the selection of the reported results. Domain-level judgments were categorized as "low risk of bias", "some concerns", or "high risk of bias". These judgments informed the overall risk-of-bias assessment. For non-randomized studies, including pre/post single-arm studies, before/after repeated measures studies, and case series, the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool was applied.[15] We used the ROBINS-I to evaluate bias attributable to confounding, participant selection, intervention classification, missing data, departures from intended interventions, outcome measurements, and selective reporting. The overall risk-of-bias judgement was classified as low, moderate, serious, or critical.

Data Extraction

Two researchers (P.RF. and A.F.) independently extracted data from each study according to a pre-defined protocol. The extracted data were grouped into three categories: (1) General Information, first author's name, publication year, journal, and country; (2) Risk of bias assessment; and (3) study characteristics, study design, duration, sample size, inclusion/exclusion criteria, age distribution, sex distribution, diabetes definition, diagnostic methods, laser parameters (wavelength, dose, session duration, total number of sessions), comparator, and quantitative outcome data (pre-treatment and post-treatment means ± SD or medians [IQR], change from baseline, and *P* values). For missing or additional required information, corresponding authors of the respective studies were contacted via email.

Certainty of Evidence Assessment

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach[16] to assess outcome certainty. As meta-analysis was precluded by substantial clinical and methodological heterogeneity, GRADE was applied to the narrative synthesis. Two reviewers (P.RF. and R.D.) independently rated certainty for four pre-specified outcomes: HbA1c change, FPG change, neuropathic pain reduction, and diabetic foot ulcer healing. Ratings (high, moderate, low, or very low) were based on five domains: risk of bias (RoB 2 or ROBINS-I), inconsistency of results, indirectness of evidence, imprecision of effect estimates, and suspicion of publication bias. Downgrades were explicitly justified, and disagreements were resolved by consensus or arbitration by a third reviewer (A.F.).

Data Synthesis and Analysis

Due to substantial methodological and clinical heterogeneity across the included studies, encompassing differences in study design, laser wavelength and power, route of administration, session number, and outcome measures, quantitative meta-analysis was not feasible and was not performed. Accordingly, findings are presented as a narrative synthesis, organized by outcome domain (glycemic control, neuropathy/pain, wound healing, and cellular/metabolomic biomarkers). Within each domain, studies are described with respect to direction of effect, magnitude of reported changes, and statistical significance. We also discussed laser parameter variability and its potential relationship to outcomes narratively.

Results

Search Results

The systematic database search yielded 1,921 records from PubMed, Scopus, Web of Science, and ProQuest. After removing duplicates, we screened 1,025 unique records at title and abstract levels. Following full-text review, nine studies met the predefined eligibility criteria and were included in the final synthesis.

Figure 1 presents a PRISMA flowchart depicting the literature search, screening process, and study selection.

Characteristics of Included Studies

This systematic review included nine studies published between 2010 and 2025, originating from Iran (n = 5), Brazil (n = 3), and Egypt (n = 1).[17-25] Across all included studies, the total number of participants was approximately 256. Only a small subset had diabetes, all enrolled in one mechanistic study (Martins Benevento 2024: 2 of 28 participants), which was retained for its metabolomic findings but excluded from all glycemic-outcome pooling, vote-counting, and GRADE assessments.[18] Among the included studies, three were RCTs or had an RCT design (da Silva Júnior 2022; Leal 2020; Serry 2021),[20,23,25] two were pre/post single-arm studies examining acute metabolic responses (Kazemikhoo 2016; KazemiKhoo 2013),[17,21] one was a before/after repeated measures study comparing two wavelengths within subjects (KazemiKhoo 2015),[22] one was a prospective observational pre/post study (Martins Benevento 2024),[18] and two were uncontrolled case series or observational studies (Dahmardehei 2016; Mokmeli 2010).[19,24] All included studies involved patients with type 2 diabetes mellitus, except Martins Benevento (2024),[18] in which only 2 of 28 participants had diabetes. The key characteristics of the included studies are summarized in Table 1.

Laser Parameters and Intervention Protocols

Laser parameters varied considerably across studies. Wavelengths used included 405 nm (blue; KazemiKhoo 2013; KazemiKhoo 2015),[21,22] 630 nm (red; Kazemikhoo 2016; KazemiKhoo 2015),[17,22] 650 nm (Mokmeli 2010;

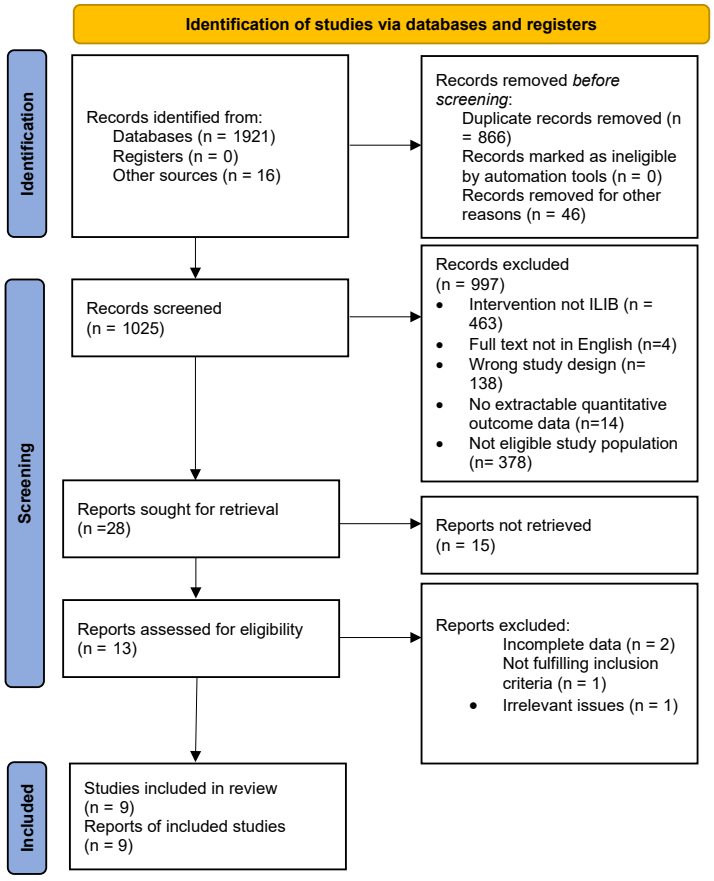


Figure 1. Flowchart depicting the literature search, screening process, and selection of studies for this systematic review

Table 1. Summary of Key Study Characteristics

First Author	Year	Country	Study Design	Study Duration	Definition of DM	N (Total)	Sex (F, n%)	Outcomes of Interest
Kazem khoo et al.[17]	2016	Iran	Pre/post single-arm	Single session (30 min)	T2DM	13	Missing data	Change in arginase and EGFR expression in blood cells after treatment
Martins Benevento et al.[18]	2024	Brazil	Observational pre/post (single-arm)	Single session	2 participants with DM (community women)	28	28 (100%)	Change in plasma metabolome and specific plasma metabolites after ILIB
Dahmardehei et al.[19]	2016	Iran	Case series (non-comparative)	Not reported (sessions in days)	T2DM with grade 3 burn ulcers	6 patients / 13 ulcers	2 (33.3%)	Complete healing of diabetic grade 3 burn ulcers and wound healing outcome
da Silva Júnior et al.[20]	2022	Brazil	RCT, parallel-group, blinded	4 months	T2DM, HbA1c ≥ 6.5%, on therapy + periodontitis	21 (10 laser, 11 control)	16 (76.1%)	Periodontal clinical parameters and glycemic control
Kazemi Khoo et al.[21]	2013	Iran	Pre/post single-arm (metabolomics)	Single session (30 min)	T2DM (criteria NR)	9	4 (44.4%)	Blood metabolite changes, especially glucose and L-arginine
KazemiKhoo et al.[22]	2015	Iran	Before–after, repeated measures (within-subject)	14 sessions (alternating days)	T2DM (criteria NR)	24	15 (62.5%)	Serum blood sugar (comparison of blue vs red ILIB light)
Leal et al.[23]	2020	Brazil	RCT, 3-arm (Control/ILIB/Sham)	30 sessions (3 cycles)	T2DM with diabetic neuropathy; glycemia 150–350 mg/dL	30	Missing data	Pain reduction and quality of life in diabetic neuropathy
Mokmeli et al.[24]	2010	Iran	Uncontrolled case series	2 months of laser treatment	T2DM with diabetic foot ulcers (treatment-resistant)	65 patients / 74 ulcers	22 (29.7%)	Diabetic foot ulcer healing and wound healing response
Serry et al.[25]	2021	Egypt	RCT, 2-arm parallel	12 weeks (3 sessions/week)	T2DM > 1 year; HbA1c ~7%; BMI 25–34.9; on metformin + sulphonylurea	60 (30/group)	Laser: 22 (73.3%); Control: 24 (80%)	Glycemic control measures: HbA1c, fasting plasma glucose, oral glucose tolerance, fasting c-peptide, and acute blood glucose change after laser sessions

Abbreviations: DM = diabetes mellitus; T2DM = type 2 diabetes mellitus; NR = not reported; DPN = diabetic peripheral neuropathy; NCS = nerve conduction studies; BMI = body mass index; RCT = randomized controlled trial.

Serry 2021),[24,25] and 660 nm (Dahmardehei 2016; da Silva Júnior 2022; Leal 2020; Martins Benevento 2024).[18-20,23] Power output ranged from 1.5 mW (Kazemikhoo 2016; KazemiKhoo 2013; KazemiKhoo 2015)[17,21,22] to 100 mW (da Silva Júnior 2022; Leal 2020; Martins Benevento 2024).[18,20,23] Session durations were uniformly 30 minutes across most studies, with one exception (Dahmardehei 2016: 16 minutes for local LLLT).[19] The route of administration varied between invasive ILIB via an intravenous catheter (Kazemikhoo 2016; KazemiKhoo 2013; KazemiKhoo 2015; Mokmeli 2010)[17,21,22,24] and non-invasive transcutaneous application over the radial artery or wrist vessels (da Silva Júnior 2022; Leal 2020; Martins Benevento 2024; Serry 2021).[18,20,23,25] The number of sessions ranged from a single session to 36 sessions (Serry 2021).[25] Detailed laser parameters are presented in Table 2.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers (P.RF. and R.D.) using design-appropriate tools. Disagreements were resolved by consensus or by a third reviewer (A.F.).

For RCTs, the RoB 2 tool was used, which evaluates bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[14] Each domain was judged as "low risk", "some concerns", or "high risk", leading to an overall risk-of-bias judgment.

For non-randomized studies, including pre/post single-arm studies, before/after repeated measures studies, and case series, the ROBINS-I tool was applied.[15] This tool assesses seven domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Overall risk of bias was categorized as "low", "moderate", "serious", or "critical". For pre/post designs lacking a control group, we typically assign a "moderate" or "serious" rating because of inherent confounding and the inability to account for temporal trends or regression to the mean.

Among the included studies, all three RCTs (da Silva Júnior 2022; Serry 2021; Leal 2020)[20,23,25] were evaluated using RoB 2 and were judged to have "some concerns". (Leal 2020)[23] received this rating because it did not report per-group sample sizes, the number of dropouts, or a participant flow diagram, making it impossible to verify whether outcome data were complete. In the da Silva Júnior study, the allocation-concealment procedure was not described, and no trial registration was provided, leading to some concerns.[20] (Serry 2021)[25] was also rated as having some concerns, as the methods for random-sequence generation and allocation concealment were not reported; the trial was open-label with no blinding of participants or personnel.

Among the six non-randomized studies assessed with ROBINS-I, all were rated as having "moderate" or "serious" risk of bias. The pre/post single-arm

Table 2. Laser Parameters and Intervention Protocols Across Included Studies

First Author	Laser Type	Wavelength (nm)	Dose (mW)	Session Duration	Sessions (total)	Comparator
Kazemikhoo 2016 [17]	ILBI (IV catheter)	630 (red)	1.5 mW	30 min	1	None (pre/post)
Martins Benevento 2024 [18]	Transcutaneous ILIB (non-invasive)	660 (red)	100 mW	30 min	1	None (pre/post)
Dahmardehei 2016 [19]	Local LLLT + ILBI + STSG	660 (red)	10 mW	16 min	10–15	None (all treated)
da Silva Júnior 2022 [20]	Modified ILIB (transcutaneous, radial artery)	660	100 mW	30 min (15 min for dark-skinned)	10	Conventional periodontal therapy only
KazemiKhoo 2013 [21]	ILBI (IV catheter)	405 (blue)	1.5 mW	30 min	1	None (pre/post)
KazemiKhoo 2015 [22]	ILIB (IV catheter, forearm vein)	630 (red) / 405 (blue)	1.5 mW	30 min	14 (7 blue + 7 red)	Within-subject wavelength comparison
Leal 2020 [23]	Transcutaneous ILIB (bracelet, radial artery)	660 ± 10	100 mW	30 min	30 (3 cycles × 10 days)	Control (no laser) + Sham ILIB
Mokmeli 2010 [24]	ILBI (IV catheter, large veins upper limb)	650	2.5 mW	30 min	NR	None (case series)
Serry 2021 [25]	Transcutaneous (laser watch, radial/ulnar)	650	5 mW	30 min	36 (3 × / week × 12 weeks)	Medications only (metformin + sulphonylurea)

Abbreviations: ILBI = intravenous laser blood irradiation; ILIB = intravenous laser irradiation of blood; LLLT = low-level laser therapy; STSG = split-thickness skin graft; NR = not reported.

studies (Kazemikhoo 2016; Martins Benevento 2024; KazemiKhoo 2013; KazemiKhoo 2015)[17,18,21,22] were rated as "moderate" risk of bias, as they provided objective outcome measurements but lacked control groups, making the causal attribution of observed changes to the intervention uncertain. The two case series (Dahmardehei 2016; Mokmeli 2010)[19,24] were rated as "serious" risk of bias due to the absence of comparator groups, selected populations, and uncontrolled confounding. A summary of the risk-of-bias assessments is presented in Table 3.

Outcomes

Glycemic Outcomes

Four studies reported quantitative glycemic outcomes. Serry et al.[25] conducted the most methodologically robust glycemic study: a 12-week RCT using a transcutaneous laser watch (650 nm, 5 mW) over radial and ulnar vessels for 30 minutes per session, three sessions per week (36 total sessions), in 60 T2DM patients on stable medication. Compared to controls, the laser group showed a greater reduction in HbA1c (−1.18% vs −0.63%; between-group $P = 0.0001$) and FPG (−22.43 mg/dL vs −13.46 mg/dL; between-group $P = 0.01$), with significant within-group improvements in both arms.

In contrast, da Silva Júnior et al.[20] found no statistically significant between-group differences in HbA1c (laser: 8.15 to 8.15%; control: 6.90 to 7.30%) or FPG (laser: 133.50 to 154.00 mg/dL; control: 124.00 to 153.00 mg/dL) after 10 sessions of transcutaneous laser irradiation (660 nm, 100 mW) adjunctive to periodontal therapy over four months (all between-group $P > 0.39$). The small sample (10 vs 11) and concurrent periodontal treatment limit interpretation.

KazemiKhoo et al.[21] reported an acute reduction in glucose from 190 ± 17 to 165 ± 20 mg/dL (change: −25 mg/dL) 30 minutes after a single 405-nm ILIB session in nine T2DM patients ($P < 0.0018$). Similarly, in another study, KazemiKhoo et al.[22] observed a reduction from 228 ± 46 to 188 ± 36 mg/dL ($P < 0.0001$) across 14 sessions of alternating red (630 nm) and blue (405 nm) ILIB in 24 T2DM patients; no difference was observed between the two wavelengths ($P = 0.417$). Both studies lacked control groups.

Glycemic outcomes across the included studies reporting quantitative data are summarized in Table 4.

Diabetic Neuropathy and Pain Outcomes

Leal et al.[23] conducted a three-arm RCT in 30 T2DM patients with diabetic peripheral neuropathy, comparing ILIB (660 nm, 100 mW, 30 sessions), sham ILIB, and control. Pain was assessed using the Visual Analogue Scale (VAS), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and Pain DETECT. ILIB significantly reduced pain compared with both the sham and control groups. Detailed numerical outcome data were not fully available.

Wound Healing in Diabetic Foot Ulcers

Two studies examined LLLT for wound healing in diabetic patients. Dahmardehei et al.[19] described six T2DM patients with 13 Wagner grade 3 burn ulcers treated with local LLLT (660 nm, 10 J/cm², 16 min, 10–15 sessions), ILIB, and split-thickness skin graft (STSG). All grafts healed completely, and the authors reported no graft failures. Baseline HbA1c was 8.1 ± 1.93 (reported as mg/dL in the paper, likely %). The descriptive design and lack of a comparator group limit conclusions about the specific contribution of LLLT to healing outcomes. Mokmeli et al.[24] reported an uncontrolled case series of 65 T2DM patients and 74 treatment-resistant diabetic foot ulcers treated with ILIB (650 nm, 2.5 mW, 30 min sessions) combined with local LLLT and conventional wound care over an average of two months. Complete healing occurred in 62.2% of ulcers (46/74), with an additional 12.2% (9/74) healing more than 50%, 8.1% (6/74) healing less than 50%, and 5.4% (4/74) not healing; 12.2% (9/74) discontinued treatment before completing five sessions. Healing rates varied by wound stage, ranging from 86.8%

Table 3. Risk of Bias Assessment Using Design-Appropriate Tools

Study	Study Design	Assessment Tool	Overall Risk of Bias	Key Justification
Kazemikhoo 2016 [17]	Pre/post single-arm	ROBINS-I	Moderate	No control group; objective outcome
Martins Benevento 2024 [18]	Pre/post single-arm	ROBINS-I	Moderate	No control group; only 2/28 had diabetes
Dahmardehei 2016 [19]	Case series	ROBINS-I	Serious	No comparator; selected population; concomitant interventions
da Silva Júnior 2022 [20]	RCT	RoB 2	Some concerns	Baseline HbA1c imbalance, one intervention-related loss, unclear concealment and adjustment
KazemiKhoo 2013 [21]	Pre/post single-arm	ROBINS-I	Moderate	No control group; small sample (n = 9)
KazemiKhoo 2015 [22]	Before/after repeated measures	ROBINS-I	Moderate	Within-subject design; no external control
Leal 2020 [23]	RCT (3-arm)	RoB 2	Some concerns	Incomplete outcome data reporting
Mokmeli 2010 [24]	Case series	ROBINS-I	Serious	No comparator; retrospective
Serry 2021 [25]	RCT	RoB 2	Some concerns	Randomization and allocation details insufficient; retrospective registration; blinding unclear

Table 4. Glycemic Outcomes across Included Studies Reporting Quantitative Data

First Author	Outcome	Laser Pre	Laser Post	Control Pre	Control Post	Between-group *P*	Effect
KazemiKhoo 2013 [21]	Blood glucose (mg/dL)	190 ± 17	165 ± 20 (−25)	—	—	< 0.0018 (within-subject)	Favours laser
KazemiKhoo 2015 [22]	Blood sugar (mg/dL)	228 ± 46	188 ± 36	—	—	< 0.0001 (both wavelengths)	Favours laser; No significant difference between blue and red lasers ($P = 0.417$)
da Silva Júnior 2022 [20]	HbA1c (%)	8.15 (6.20–9.77)	8.15 (6.22–12.20)	6.90 (6.10–10.30)	7.30 (6.50–10.40)	0.647	No clear effect*
da Silva Júnior 2022 [20]	FBG (mg/dL)	133.50 (104.75–272.00)	154.00 (97.00–263.25)	124.00 (107.00–272.00)	153.00 (93.00–174.00)	0.398	No clear effect*
Serry 2021 [25]	HbA1c (%)	7.65 ± 0.60	6.47 ± 0.52 (−1.18)	7.60 ± 0.47	6.97 ± 0.41 (−0.63)	0.0001	Favours laser
Serry 2021 [25]	FPG (mg/dL)	150.06 ± 23.18	127.63 ± 19.91 (−22.43)	153.46 ± 20.30	140.00 ± 19.17	0.01	Favours laser

Abbreviations: FBG = fasting blood glucose; FPG = fasting plasma glucose.
*Substantial baseline imbalance in HbA1c between groups (laser: 8.15% vs control: 6.90%) limits the interpretation of between-group differences; the study was not powered or designed to adjust for this imbalance.

complete healing in stage 2 ulcers to 33.3% in stage 5 ulcers. No glycemic outcomes were reported in this study.

Cellular and Metabolomic Biomarkers

Kazemikhoo et al.[17] examined the acute effects of a single ILIB session (630 nm, 1.5 mW, 30 min) on circulating cellular markers in 13 T2DM patients. Repeated-measures ANOVA showed significant reductions in EGFR-positive cells (4.013 ± 0.69 to 2.50 ± 0.43; $P = 0.009$) and arginase-positive cells (4.96 ± 0.70 to 2.53 ± 0.45; $P = 0.001$) at 30 minutes. The clinical significance of these acute changes in DM management is unclear.

Martins Benevento et al.[18] conducted untargeted liquid chromatography high-resolution mass spectrometry (LC-HRMS) metabolomics in 28 women, including two with diabetes, after a single session of transcutaneous ILIB (660 nm, 100 mW, 30 min). Using partial least squares discriminant analysis (PLS-DA) with variable importance in projection (VIP ≥ 1) and paired t-tests with false discovery rate (FDR) correction, the study identified both increases and decreases in specific plasma metabolites. No traditional glycemic outcomes were reported; with only two diabetic participants, clinical relevance to DM is limited.

Certainty of Evidence (GRADE Assessment)

The GRADE assessment for the four key outcomes is summarized in Table 5. Glycemic outcomes (HbA1c and FPG) were rated very low and were downgraded for bias (small sample sizes, baseline imbalance in one RCT), inconsistency (conflicting results across two RCTs), indirectness (varied pain tools/ protocols), and imprecision (wide confidence intervals not reported, small total participant numbers). Neuropathic pain was very low and was downgraded for bias (incomplete reporting in one RCT), indirectness (variation in pain assessment tools and laser protocols), and serious imprecision (single small trial, n = 30). Wound healing was very low, based solely on uncontrolled case series with serious bias, high indirectness (adjunctive interventions such as skin grafting outcomes), and extreme imprecision. No outcomes were upgraded for effect size or dose-response, given the exploratory data and lack of controlled comparisons.

Narrative Subgroup Analysis

To explore sources of heterogeneity, the studies were stratified by route of administration, treatment dose, and study design. Four studies used invasive ILIB via an intravenous catheter, all of which were uncontrolled pre/post or case series reporting acute glucose reductions or wound healing. Five studies used transcutaneous ILIB, including the two RCTs that reported glycemic outcomes; one of these showed benefits,[25] while the other found no difference,[20] and no superiority of either route could be

established due to confounding. Regarding treatment dose, studies with ≤ 10 sessions (including single-session studies and the 10-session RCT by da Silva Júnior 2022 [20]) showed either acute effects only or no between-group benefit. In contrast, studies with ≥ 30 sessions (Serry 2021 with 36 sessions[25]; Leal 2020 with 30 sessions[23]) demonstrated significant glycemic improvement[25] or pain reduction,[23] suggesting that longer treatment courses may be associated with more consistent benefits. When considering study design, the three RCTs showed mixed results (one positive, one null, one with some concerns); in contrast, the six non-randomized studies (pre/post, case series) uniformly reported positive findings but lacked control groups, raising the possibility of overestimating effects in uncontrolled designs. Overall, higher session numbers (≥ 30) and RCT designs provide more reliable but still limited evidence, while uncontrolled studies consistently report positive findings, underscoring the need for rigorous controlled trials.

Semi-Quantitative Synthesis (Vote Counting)

Because meta-analysis was not feasible, a vote-counting approach based on effect direction was used for the primary outcome of glycemic control. Each study was classified as positive (statistically significant improvement in at least one glycemic measure), neutral (no statistically significant change or between-group difference), or negative (statistically significant worsening). Only studies reporting quantitative glycemic data were included (n = 4). (Leal 2020)[23] was excluded from this analysis because it assessed neuropathic pain and quality of life rather than glycemic outcomes. The results are summarized in Table 6.

Feasibility of Meta-Analysis

Quantitative meta-analysis was precluded by substantial clinical and methodological heterogeneity and the unreliability of pooling small, high-risk-of-bias studies. Sources of heterogeneity included study design (RCTs to uncontrolled case series), laser parameters (405-660 nm, 1.5-100 mW, 1-36 sessions), non-overlapping outcomes, follow-up (30 minutes – 4 months), missing numerical data, and mostly uncontrolled groups. Only two RCTs reported comparable glycemic outcomes (da Silva Júnior 2022; Serry 2021)[20,25]; too few for stable pooling. Hence, we present only a narrative synthesis.

Discussion

This systematic review synthesized nine heterogeneous studies on ILIB in diabetes, spanning diverse designs, laser parameters, and outcomes. Overall, small sample sizes, uncontrolled or single-arm designs, and wide variability limited the strength of the conclusions. Among glycemic outcomes, Serry et al.[25] reported the most favorable findings. However, this single positive RCT should not be interpreted as establishing efficacy, particularly as it was rated as having "some concerns" on RoB 2 assessment (Table 3). It reported statistically significant and clinically meaningful reductions in both HbA1c and FPG after 12 weeks of transcutaneous laser therapy. The HbA1c reduction (−1.18% in the laser group versus −0.63% in controls) is clinically relevant and associated with a decreased risk of microvascular complications. However, the relatively small sample size (n = 30 per group) warrants cautious interpretation. In contrast, da Silva Júnior et al.[20] found no significant between-group differences in glycemic markers despite using a similar transcutaneous device and wavelength. This trial was also judged to have "some concerns" on the RoB 2 tool because the allocation concealment procedure was not described, and no trial registration was reported in the manuscript. In addition, one participant was excluded after randomization because of an intervention-related adverse event (a skin burn). Potential contributors include differences in treatment sessions (10 vs 36), concurrent periodontal therapy in both

Table 5. GRADE Summary of Findings: Certainty of Evidence for Key Outcomes

Outcome	No. of Studies (Design)	Participants (Laser/ Control)	Effect Estimate (Narrative Summary)	Certainty Assessment	Final Certainty
HbA1c change	2 RCTs [20, 25]	81 total (40 laser / 41 control)	One RCT showed significant reduction favoring laser (−1.18% vs −0.63%; $P = 0.0001$); one RCT showed no between-group difference.	⊕⊖⊖⊖ Very Low	Very Low
Fasting glucose change	2 RCTs [20, 25] + 2 pre/post[21,22]	~104 total (laser arms)	Mixed results: one RCT favored laser (−22.43 mg/dL; $P = 0.01$); one RCT showed no difference; pre/post studies showed acute reductions but lacked controls.	⊕⊖⊖⊖ Very Low	Very Low
Neuropathic pain reduction	1 RCT [23]	30 total (10 per arm)	Significant reduction in VAS, LANSS, PainDETECT favoring ILIB vs sham/control; numerical data not fully reported.	⊕⊖⊖⊖ Very Low	Very Low
Complete wound healing	2 case series[19,24]	71 patients / 87 ulcers (all laser)	Descriptive reports of healing; no comparator group; adjunctive interventions present.	⊕⊖⊖⊖ Very Low	Very Low

Table 6. Vote Counting Based on Effect Direction for Glycemic Outcomes

Study	Effect direction	Key glycemic measure	Statistical significance
Serry 2021 [25]	Positive	HbA1c, FPG	$P = 0.0001$, $P = 0.01$
KazemiKhoo 2013 [21]	Positive	Blood glucose (acute)	$P < 0.0018$
KazemiKhoo 2015 [22]	Positive	Blood sugar (acute)	$P < 0.0001$
da Silva Júnior 2022 [20]	Neutral	HbA1c, FBG	$P = 0.647$, $P = 0.398$

*Numerical data not fully available.

groups (potentially confounding glycemic outcomes), and small sample sizes (10 vs 30 patients per arm). However, evidence remains insufficient to determine whether dose or protocol characteristics modify glycemic outcomes. This inconsistency aligns with previous photobiomodulation (PBM) literature describing systemic glycemic effects as preliminary and variable.[27,28]

Acute blood glucose reductions reported by KazemiKhoo (2013, 2015) after single or repeated ILIB sessions are noteworthy but require cautious interpretation.[21,22] The 30-minute follow-up captures only acute physiological responses and does not provide insight into sustained glycemic improvements. Lack of control groups makes it difficult to rule out spontaneous fluctuations. Nevertheless, consistent effect direction provides preliminary support for short-term photobiomodulatory effects on glucose metabolism.

KazemiKhoo et al.[22] found no significant difference between red (630 nm) and blue (405 nm) wavelengths ($P = 0.417$). This suggests that wavelength alone may not be the primary determinant of glycemic effect. This highlights the complexity of dose-response relationships and the importance of total energy delivered rather than wavelength alone.[29,30]

Evidence for ILIB in diabetic peripheral neuropathy is limited but potentially promising. Leal et al.[23] reported pain reduction in the transcutaneous ILIB group across multiple pain scales compared to the sham and control groups. This represents a clinically important finding, considering the high burden of neuropathic pain in T2DM. However, the full numerical outcome data were unavailable, limiting effect magnitude assessment.

A registered RCT protocol by Meyer-Hamme et al.,[26] aiming to enroll 180 neuropathy patients with neurophysiological endpoints, has been published, but outcomes are pending. Completion of this trial would significantly advance the evidence base. This aligns with a recent RCT by Anju et al,[31] reporting significant neuropathic pain and quality-of-life improvements with PBM. An earlier systematic review concluded LLLT consistently demonstrates positive effects on diabetic neuropathy despite limited evidence.[32]

Evidence for ILIB wound-healing applications (Dahmardehei 2016; Mokmeli 2010) is descriptive, deriving from uncontrolled case series.[19,24] Although outcomes appear promising, interpretation requires caution due to absent controls, heterogeneous adjunctive interventions (such as skin grafting in Dahmardehei 2016), and selection bias. These studies primarily inform future trial design. Despite these methodological limitations, the observations are consistent with a body of evidence supporting the use of PBM in diabetic wound healing. A recent systematic review reported a significant reduction in diabetic foot ulcer size following PBM, likely mediated by reductions in inflammation and oxidative stress.[33]

The metabolomic and cellular biomarker studies (Martins Benevento 2024; Kazemikhoo 2016) offer mechanistic insights but are not designed to assess clinical efficacy and should be interpreted as exploratory.[17,18] The acute reduction in arginase-positive and EGFR-positive cells observed by Kazemikhoo et al.[17] could reflect the modulation of inflammation and cellular signaling pathways. Still, the clinical relevance of these findings requires further investigation.

Notably, all RCTs included in this review achieved an overall "some concerns" rating under the RoB 2 tool. Serry et al.[25] findings demonstrated significant between-group improvements in HbA1c and FPG following 36 sessions of transcutaneous ILIB, though the open-label design and retrospective registration of this trial limit confidence in this result. In contrast, the other RCT by da Silva Júnior et al.[20] found no significant glycemic benefit after 10 sessions. This discrepancy in findings highlights the sensitivity of outcomes to treatment dose and protocol design.

Several methodological limitations were identified across the included studies. Most studies lacked control groups, had small sample sizes, used heterogeneous and inconsistently reported laser parameters, and did not report long-term follow-up beyond the immediate post-treatment period. Even among the RCTs, methodological reporting was incomplete: none of the three RCTs described allocation concealment, two were open-label with no blinding of participants or personnel, and only one reported trial registration, which was retrospective. Transcutaneous ILIB, while non-invasive, introduces additional uncertainty regarding the actual dose of laser energy reaching the bloodstream, which is influenced by skin pigmentation, subcutaneous tissue thickness, and device contact pressure.

In addition, in the study by da Silva Júnior et al.,[20] the control group had better glycemic control at baseline than the laser group (lower HbA1c), creating a baseline imbalance that limits the interpretation of between-group glycemic differences.

Most studies did not report adverse events or safety monitoring procedures, except for da Silva Júnior et al..[20] The adverse event reported in da Silva Júnior et al.[20] (a skin burn in a dark-skinned participant after 30 minutes of transcutaneous application) underscores the importance of dose adjustment by skin phototype. This aspect of safety reporting and dose individualization by skin phenotype is inconsistently addressed in the current literature and should be considered a key limitation of the evidence base.

Thus, standardized, adequately powered RCTs with rigorous methodology, consistent reporting of parameters, systematic adverse-event monitoring, validated outcomes, and extended follow-up are essential. Future research should investigate molecular mechanisms, optimize protocols for diabetes phenotypes, and assess safety across diverse populations.

Conclusion

In this systematic review, nine studies were identified, encompassing diverse designs, laser parameters, and endpoints. The current evidence is insufficient and

inconsistent to determine whether ILIB improves glycemic control. One small RCT reported favorable HbA1c and FPG outcomes, whereas another RCT found no significant between-group effect on glycemic markers. All three RCTs included in this review were assessed as having "some concerns" on the RoB 2 risk of bias assessment tool. Furthermore, none of the nine included studies achieved an overall "low risk of bias" rating, further limiting confidence in the existing evidence. Uncontrolled studies reporting short-term changes in blood glucose cannot determine whether ILIB produces sustained improvements in glycemic control. The evidence base remains limited by high heterogeneity, small sample sizes, and the predominance of uncontrolled study designs. In addition, a meta-analysis was not feasible due to these limitations. Larger RCTs with standardized parameters, validated outcomes, and long-term follow-up are required to establish ILIB's role as a complementary therapy.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

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Supplementary Files

Supplementary Material 1. Search Strategies

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