A systematic review of low-level light therapy for treatment of diabetic foot ulcer

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Abstract

Diabetes mellitus (DM) is a significant international health concern affecting more than 387 million individuals. A diabetic person has a 25% lifetime risk of developing a diabetic foot ulcer (DFU), leading to limb amputation in up to one in six DFU patients. Low-level light therapy (LLLT) uses low-power lasers or light-emitting diodes to alter cellular function and molecular pathways, and may be a promising treatment for DFU. The goal of this systematic review is to examine whether the clinical use of LLLT is effective in the healing of DFU at 12 and 20 weeks in comparison with the standard of care, and to provide evidence-based recommendation and future clinical guidelines for the treatment of DFU using LLLT. On September 30, 2015, we searched PubMed, EMBASE, CINAHL, and Web of Science databases using the following terms: "diabetic foot" AND "low level light therapy," OR "light emitting diode," OR "phototherapy," OR "laser." The relevant articles that met the following criteria were selected for inclusion: randomized control trials (RCTs) that investigated the use of LLLT for treatment of DFU. Four RCTs involving 131 participants were suitable for inclusion based upon our criteria. The clinical trials used sham irriadiation, low dose, or nontherapeutic LLLT as placebo or control in comparison to LLLT. The endpoints included ulcer size and time to complete healing with follow-up ranging from 2 to 16 weeks. Each article was assigned a level of evidence (LOE) and graded according to the Oxford Center for Evidence-based Medicine Levels of Evidence Grades of Recommendation criteria. Limitations of reviewed RCTs include a small sample size ($N < 100$), unclear allocation concealment, lack of screening phase to exclude rapid healers, unclear inclusion/exclusion criteria, short (<30 days) follow-up period, and unclear treatment settings (wavelength and treatment time). However, all reviewed RCTs demonstrated therapeutic outcomes with no adverse events using LLLT for treatment of DFU. This systematic review reports that LLLT has significant potential to become a portable, minimally invasive, easy-to-use, and cost effective modality for treatment of DFU. To enthusiastically recommend LLLT for treatment of DFU, additional studies with comparable laser parameters, screening period to exclude rapid healers, larger sample sizes and longer follow-up periods are required. We envision future stringent RCTs may validate LLLT for treatment of DFU. Systematic review registration number: PROSPERO CRD42015029825.

Diabetes mellitus (DM) is a significant international health concern affecting more than 387 million individuals.[1] In the United States, the diabetic population exceeds 29.1 million people (about 1 in every 11 people) and 25% of those individuals are currently undiagnosed.[2] Diabetic sequelae contribute to multiorgan dysfunction including cardiovascular disease, chronic kidney disease, blindness, sensory loss, and lower limb amputation.[3,4] The long-term consequences of diabetes complications and comorbidities

cm	Centimeter
DFU	Diabetic foot ulcer
J	Joules
LED	Light-emitting diode
LLLT	Low-level light therapy
mW	Milliwatt
nm	Nanometer
RCT	Randomized controlled trial
sec	Seconds

have a profound and negative impact on patient quality-of-life (QOL) and productivity.[5] It is estimated that $245 billion dollars are spent in total medical costs and lost work and wages related to the disease.[6]

A diabetic person has a 25% lifetime risk of developing a diabetic foot ulcer (DFU).[7] DFU is a chronic wound that has impaired wound healing, and is often difficult to manage and increases the risk for acquiring future infections.[3,8] One in six DFU patients will require a limb amputation, resulting in a 5-year mortality rate of up to 77%.[9] Perhaps it is not widely recognized that this mortality rate is higher than that for breast cancer, colon cancer, and prostate cancer.[10] Despite the proposed advances in the areas of antiseptics, antimicrobial applications, wound dressing agents, bioengineered skin matrices,[11–14] negative pressure devices,[15] hyperbaric oxygen,[15] and electrical stimulation devices,[16] the treatment of DFU remains a challenge, and continues to pose a substantial concern and financial strain to the healthcare system.[6]

Low-level light therapy (LLLT) uses either low-level, low-power lasers, or light-emitting diodes (LED) to alter cellular function and molecular pathways, and may be a promising treatment for DFU. Several pieces of evidence contribute to LLLT's proposed therapeutic use for treatment of DFU. In 1967, Endre Mester investigated the tumorigenic potential of low-level ruby laser radiation (694 nm, 1 J/cm^2) on the shaved dorsum of mice.[17] Serendipitously, he discovered that the irradiated mice did not develop cancer, but rather grew hair on their backs more quickly than the nonirradiated mice.[18,19] Mester continued to pursue his clinical investigations of LLLT on patients with skin ulcers and found that treatment with LLLT achieved more rapid wound epithelialization and wound closure.[20–22] Mester's pioneering work helped develop the field of "low-level intensity" or "low-level light therapy."

Since then, there have been significant advancements of LLLT in the medical field and data suggesting LLLT improves therapeutic outcomes in nerve damage,[23] pain,[24] muscle repair,[24] and wound healing.[20] It may seem counterintuitive that laser, a device that inherently provides thermal energy, may provide a positive healing effect at the cellular level.[25] However, minimal change in temperature is associated with the application of LLLT over brief therapeutic durations.[26] The currently proposed theory regarding the biologic mechanism of LLLT resides in the absorption of light by photoacceptors or chromophores at the molecular, cellular, and tissue levels, that results in cellular changes including synthesis of collagen and extracellular matrix, recruitment of cytokines and growth factors, migration, proliferation, and differentiation of cells. LLLT is dependent on the optical absorption properties of the skin, frequency of treatment, and treatment intervention time,[27] and is also a function of the device characteristics such as wavelength (nm), power density (mW/cm^2), fluence (J/cm^2), irradiation time (seconds), and treatment protocol (duration and interval).

The goal of this systematic review is to examine whether the clinical use of LLLT is effective in the healing of DFU at 12 and 20 weeks in comparison with the standard of care, and to provide evidence-based recommendation and future clinical guidelines for the treatment of DFU using LLLT.

MATERIALS AND METHODS

Search strategy

A systematic review of the published literature was performed on LLLT for treatment of DFU. We employed the following search strategy: on September 30, 2015, we searched PubMed, EMBASE, CINAHL, and Web of Science databases using the following terms: "diabetic foot" AND "low-level light therapy," OR "light-emitting diode," OR "phototherapy," OR "laser." The bibliographies of all relevant articles were checked for additional articles that were not identified in our search. Systematic review registration number: PROSPERO CRD42015029825.

Inclusion and exclusion criteria

The relevant articles that met the following criteria were selected for inclusion: randomized control trials (RCTs) that investigated the use of LLLT for treatment of DFU (Figure 1).[28] Exclusion criteria included: LLLT not involved with DFU, photodynamic or anodyne therapy for DFU, in vitro or animal studies, case reports, case series, and non-English articles.

Study selection and data extraction

CTF, DH, and SD independently screened the titles and abstracts from the electronic search results based on our inclusion and exclusion criteria. Clinical outcome measures of wound healing were not limited to complete wound healing but also included surrogate outcomes provided by the clinical studies such as reduction in ulcer surface area or wound closure rate.

The three independent reviewers extracted and synthesized the information on study design, sample size, treatment regimen, follow-up periods, study outcomes, and adverse events.

Risk of bias assessment

Based on the Cochrane Handbook for Systematic Reviews of Intervention,[29] CTF, DH, and SD independently assessed the risk of bias in each clinical trial. Such risk included the following domains: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other source of bias. The limited number of studies and data provided did not allow performing a meta-analysis.

RESULTS

Study selection of low-level light therapy for treatment of diabetic foot ulcer

A total of 1,051 articles were generated from the initial search. Additional suitable articles identified from the bibliography screening are also included.[2] Duplicate records were removed and resulted in 511 unique articles. After screening of titles, abstracts and full-text, four original articles were suitable for inclusion based upon our criteria. Our systematic review contains four RCTs, which were assigned a level of evidence (LOE) and graded according to the Oxford Center for Evidence-based Medicine Levels of Evidence Grades of Recommendation (GOR) criteria

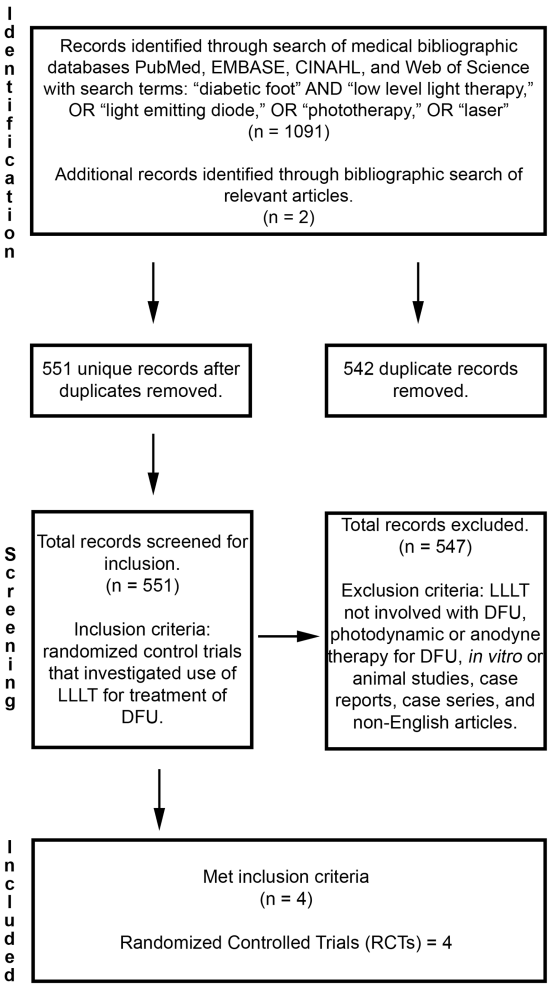

Figure 1. Schematic of the search strategy listing the number of articles matching inclusion or exclusion criteria.[28]

(Table 1).[30] Table 2 contains detailed information of RCTs using LLLT for treatment of DFU.

Clinical studies of low-level light therapy for treatment of diabetic foot ulcer

Four RCTs included in our review evaluated the efficacy and safety of LLLT for treatment of DFU. All studies demonstrated positive healing outcomes with LLLT compared with placebo or control groups, and there were no adverse events associated with study treatment.

A RCT demonstrated significant reduction in ulcer area after 15 days of LLLT for treatment of DFU (LOE 1b).[31] Treatment arm patients ($N = 32$) received LLLT (wavelengths 660 and 850 nm; power density 60 mW/cm^2; fluence 2 to 4 J/cm^2; irradiation time varied to achieve relevant fluence) once daily for 15 days, while control arm patients ($N = 32$) received conventional treatment including saline dressings, antibiotic treatment, cast immobilization, and excisions as needed. The study primary outcome was the ulcer surface area that was obtained after transferring the imprint of the ulcer floor from a cellophane paper to a graph paper. At 15 days posttreatment, there was significant reduction in ulcer area for the treatment arm (1,043.20 mm^2) compared with the control arm (322.44 mm^2, $p < 0.01$). This study was limited in many aspects, including a small sample size ($N < 100$), with unclear allocation concealment, no screening phase to exclude rapid healers, unclear inclusion/exclusion criteria, short (<30 days) follow-up period, and unclear treatment settings (wavelength and treatment time).

Table 1. Level of evidence (LOE) and grades of recommendation (GOR)[30]

Level of evidence
1a. Systematic review of RCTs
1b. Individual RCT
2a. Systematic review of cohort studies
2b. Individual cohort study (including low-quality RCT)
3a. Systematic review of case-control studies
3b. Individual case-control study
4b. Case series
5. Case reports, expert opinion, bench research
Grades of recommendation
A. Studies with consistent LOE 1a and/or 1b
B. Studies with consistent LOE 2a, 2b, 3a, or 3b; or extrapolations from studies with LOE 1a or 1b
C. Studies with LOE 4 or extrapolations from studies with LOE 2a, 2b, 3a, or 3b
D. Studies with LOE 5 or troubling inconsistent or inconclusive studies of any level

Data from Oxford Center for Evidence-based Medicine Levels of Evidence. RCT, randomized controlled trial.

Another double-blind, placebo-controlled RCT investigated the efficacy and safety of LLLT for treatment of DFU in 23 patients (LOE 1b).[32] Treatment arm patients ($N = 13$) received LLLT (wavelength 685 nm; power density 50 mW/cm^2; fluence 10 J/cm^2; irradiation time 200 seconds) and placebo arm patients ($N = 10$) received sham irradiation. The intervention occurred six times per week for at least two consecutive weeks, then every other day up to complete healing. At 2 weeks post–initial treatment, treatment arm patients achieved significantly greater reduction in ulcer size compared with placebo arm patients ($58 \pm 10.4\%$ vs. $23.5 \pm 14.1\%$, respectively; $p = 0.046$). The number of completely healed ulcers did not achieve statistical significance between the two arms (66.6 vs. 38.4%, respectively; $p = 0.470$) although the mean time to complete healing showed a trend toward faster healing in the treatment arm (11 weeks; 95% CI: 7.3–14.7) compared with the placebo arm (14 weeks; 95% CI: 8.76–19.2). This study was limited in its small sample size ($N < 100$), and the lack of screening phase to exclude rapid healers.

A third study, a double-blind, placebo-controlled RCT demonstrated that LLLT-treated patients achieved significantly higher rate of DFU closure compared with placebo-treated patients (LOE 1b).[33] Fourteen patients with DFU were randomized to the treatment arm ($N = 10$) and

Table 2. Randomized controlled trials of low-level light therapy for treatment of diabetic foot ulcers

Authors	Study type (T), study limitations (L), and level of risk bias (R)*	LOE	Sample size	Intervention methods/ parameters	Follow-up period	Findings/conclusion	Adverse events
Kajagar et al.,[31] 2012	T: RCT L: a,b,c,d,e R: moderate	1b	64	Treatment arm (32)—received LLLT (wavelength unspecified, 60 mW/cm^2, 2–4 J/cm^2, duration unspecified) once daily for 15 days Control arm (32)—received conventional treatment (saline dressings, antibiotic treatment, cast immobilization and excision as needed)	15 days	At 15 days post–initial treatment, there was a significant reduction in ulcer area between treatment arm (1,043.20 mm^2) and control arm (322.44 mm^2).	None
Kaviani et al.,[32] 2011	T: Double-blind, placebo-controlled RCT L: a,c R: low	1b	23	Intervention occurred six times per week for at least two successive weeks, and then every other day up to complete healing: Treatment arm (13)—received LLLT (685 nm, 50 mW/cm^2, 10 J/cm^2, 200 seconds) Placebo arm (10)—sham irradiation	20 weeks	Median number of intervention sessions was 27. After 2 weeks, the reduction in ulcer size from the treatment arm was significantly greater than placebo group. No significant difference in: • complete healing of ulcers between treatment arm (8 of 13) and placebo arm (3 of 9) • mean time of complete healing between treatment arm (11 weeks) and placebo arm (14 weeks)	None related to study treatment

Table 2. Continued.

Authors	Study type (T), study limitations (L), and level of risk bias (R)*	LOE	Sample size	Intervention methods/ parameters	Follow-up period	Findings/conclusion	Adverse events
Landau et al.,[33] 2011	T: Double-blind, placebo-controlled RCT L: a,c R: low	1b	16 (14 diabetic patients)	Intervention for 12 weeks: Treatment arm (10)—received LLLT (400–800 nm, 180 mW/cm^2, [43.2 J/cm^2], 4 minutes) twice daily Placebo arm (6)—received very low dose (400–800 nm, 10 mW/cm^2, [2.4 J/cm^2], 4 minutes) twice daily	16.6 weeks	At end of follow-up, there was significantly higher rate of wound closure in treatment arm (9 of 10) compared with placebo arm (2 of 6). Wound size reduction achieved significant results between treatment arm (89%) compared with placebo arm (54%). Mean time to wound closure for treatment and placebo arm was 7.14 weeks and 11.16 weeks, respectively.	None
Minatel et al.,[34] 2009	T: Double-blind, placebo-controlled RCT L: a,b,c R: low	1b	28	Intervention occurred until ulcer is fully healed or for maximum of 90 days (twice weekly): Treatment arm (14)—received LLLT (thirty-two 890 nm and four 660 nm diodes, 100 mW/cm^2, 3 J/cm^2, 30 seconds) Placebo arm (14)—received lower powered LLLT (one 660 nm diode, <1 mW/cm^2, <1 J/cm^2, 30 seconds)	90 days	At each of 15, 30, 45, 60, 75, and 90 days of healing, treatment arm achieved significantly higher rate of mean ulcer healing and granulation. At 90 days, 58.3% of treatment arm ulcers were fully healed with 75% of ulcers achieved 90–100% healing, compared with placebo arm which had one fully healed ulcer and none achieved >90%	None

Table 2. Continued.

Authors	Study type (T), study limitations (L), and level of risk bias (R)*	LOE	Sample size	Intervention methods/ parameters	Follow-up period	Findings/conclusion	Adverse events
						healing. Treatment arm subjects reported feeling less pain and achieved better sleep 1 week post-initial treatment.	

Grade of recommendation for all studies is B. CR, case report; CS, case series; CVI, chronic venous insufficiency; LOE, level of evidence; mW, milliwatt; nm, nanometer; ns, nanoseconds; RCT, randomized controlled trials; sec, seconds.

*Study Limitations Key: a, small sample size ($n < 100$); b, unclear or inadequate allocation concealment; c, no screening phase to exclude rapid healers; d, unclear inclusion/exclusion criteria; e, short follow-up period (<30 days).

received LLLT (wavelength broadband visible light at 400–800 nm; power density 180 mW/cm^2; fluence not specified; irradiation time 24 seconds) twice daily, or to placebo arm ($N = 6$) and received a very low dose, deemed nontherapeutic by study researchers (wavelength broadband visible light at 400–800 nm; power density 10 mW/cm^2; fluence not specified; irradiation time 1,440 seconds) twice daily. At sixteen weeks, treatment arm patients achieved a significantly higher rate, compared with placebo arm patients, of wound closure (9/10 vs. 2/6, respectively; $p = 0.0357$) and of wound size reduction (89 vs. 54%, respectively; statistically significant according to Mann–Whitney U test). This study was also limited in its small sample size ($N < 100$) and the lack of screening phase to exclude rapid healers.

A fourth double-blind, placebo-controlled RCT performed with LLLT for treatment of DFU demonstrated improvement at 90 days follow-up (LOE 1b).[34] Fourteen patients in the treatment arm received LLLT (unit 1: cluster of 32 diodes with wavelength 890 nm and four diodes with wavelength 660 nm; power density 100 mW/cm^2; fluence 3 J/cm^2; irradiation time 30 seconds), while fourteen placebo patients received lower powered LLLT (unit 2: one diode with wavelength 660 nm; power density <1 mW/cm^2; fluence <1 J/cm^2; irradiation time 30 seconds). Treatment was performed twice weekly until the DFU was fully healed or for a maximum of ninety days. After the 90-day follow-up, 58.3% of treated ulcers were fully healed with 75% of ulcers achieving 90–100% healing ($p < 0.02$). On the other end, in the placebo group, there was one fully healed ulcer and no ulcer achieved greater than 90% healing. The limitations include a small sample size ($N < 100$), unclear allocation concealment, no screening phase to exclude rapid healers, and unclear inclusion/exclusion criteria.

Grade of recommendation

The limited number of published reports prompted the use of the Oxford GOR instead of a more stringent (for example, Cochrane Review) grading system. Based strictly on Oxford GOR criteria, LLLT treatment for DFU would receive a B based on: four RCTs (LOE 1b) that demonstrated positive results with no adverse effects. Nevertheless, Oxford GOR criteria do not take into account the study design and study quality, and many of the studies included in this systematic review have significant design flaws. To enthusiastically recommend LLLT for treatment of DFU, additional studies with comparable laser parameters, screening period to exclude rapid healers, larger sample sizes, and longer follow-up periods are required.

DISCUSSION

DFU has a heavy economic burden on society, negatively impacts patient QOL, and increases the risk of limb amputation and mortality. LLLT has emerged as a potential treatment option for DFU, supported by a large body of evidence of LLLT for wound healing in various cell systems and animal models. Based upon a small number of published clinical studies that demonstrated therapeutic outcomes with no adverse events using LLLT for treatment of DFU, this systematic review reports that LLLT

has significant potential to become a portable, minimally invasive, easy-to-use, and cost effective modality for treatment of DFU. However, future researchers may consider performing high-quality studies with stringent study criteria to validate the efficacy and safety data demonstrated in this review.

We, and others, hypothesize that LLLT for treatment of DFU may be beneficial due to its effects on various cellular functions and molecular pathways. LLLT for treatment of DFU may alter synthesis of collagen and extracellular matrix, recruitment of cytokines and growth factors, migration, proliferation, and differentiation of different cell types.

In diabetic patients, the chronic state of hyperglycemia leads to an unbalanced level of metalloproteases that excessively degrades the extracellular matrix, reduces the tensile strength of the skin, and delays wound healing.[35] LLLT has been shown to stimulate collagen synthesis in various study models,[36–38] including murine diabetic wounded fibroblasts,[39] and murine surgical wounds.[40] It is possible that LLLT may promote treatment of DFU by stabilizing the extracellular structural support required to facilitate the wound healing process in diabetic patients.

LLLT may recruit important cytokines and growth factors to stimulate wound healing. Studies have demonstrated that LLLT stimulates expression of regulators for cell proliferation, migration, survival and wound healing,[41] such as basic fibroblast growth factor,[42,43] interleukin-1 and interleukin-8,[37] platelet derived growth factor, transforming growth factor-beta,[44] and the phagocytic activity of macrophages.[20,45–48] The recruitment of these key cytokines and growth factors may be an important contributor to healing of DFU.

In vitro studies have shown that LLLT can induce proliferation of murine diabetic fibroblasts,[49] human fibroblasts,[50–55] human keratinocytes, lymphocytes, and endothelial cells.[56] One study also observed that LLLT promoted differentiation of fibroblasts into myofibroblasts.[57] The proliferation and differentiation of different cell lines may have an important role for improving treatment of DFU.

In spite of the large number of articles generated in our search, there were only four RCTs that met our criteria. The first study endpoint was described as the healing or percent reduction in the size of the ulcer after a 15-day treatment interval with LLLT. The authors observed significant reduction in size in the treated group but did not report on complete wound closure beyond the 15 days post-treatment. Similarly, the second RCT showed reduction in ulcer size in the LLLT-treated group compared with the control group at 15 days; however, this difference was not demonstrated at the 20-week endpoint. In addition, based on the confidence interval reported, the standard deviation for the time to complete healing were quite wide with 6.8 weeks for the LLLT-treated group compared with 8.4 weeks in the control group. Although the third RCT had a more restrictive study design, it included two venous ulcers to the treatment group. The trial outcomes were wound closure and mean of wound size reduction, which were achieved in the treatment group compared with the control group. The authors used the Mann–Whitney *U* test for statistical analysis but the standard deviation was not reported. The fourth RCT reported a longer follow-up period of up to 90 days with outcome measures including healing rate and ulcer granulation. The study also reported encouraging results, however, similar to the other trials, their sample size was very small ($N < 100$).

There are numerous case reports and case series[34,58–61] that have also demonstrated positive healing outcomes with LLLT for treatment of DFU with no adverse events, including the anecdotal report of a toe ulcer with osteomyelitis that healed completely after 4 weeks of antibiotics along with 16 sessions of LLLT.

Overall, in vitro, in vivo, and human clinical studies have supported the role of LLLT for improving diabetic wound healing. To our knowledge, all published clinical studies have reported positive healing outcomes using LLLT for treatment of DFU. With a lack of effective treatment options for DFU in the published medical literature, we envision that future clinical trials on phototherapy, especially LLLT, could provide a needed alternative therapeutic option for treatment of DFU.

LIMITATIONS

All clinical studies included in our systematic review performed LLLT for treatment of DFU were conducted with different parameters (wavelength, power density, fluence, treatment duration, and frequency). While some studies had specific LLLT parameters, other reported parameters based on the wound size. The studies also differ in terms of methods and design, as well as having small sample sizes, limited or no details of wound description (size, location, age), vascular status (important to rule out the presence of peripheral vascular disease, ischemia, and mixed ulcer), glucose control and offloading measures used. More importantly, all the RCTs lacked a screening period to exclude rapid healers. This screening phase prior to randomization allows for a consistent baseline and standard of care. When subjects experience a reduction in size greater than 35% during this run-in period, they should be exited from the study as their wounds would be deemed not chronic. In addition, patients with osteomyelitis were not determined. None of these studies used standard outcome end points (healing at 12 or 20 weeks) to compare healing rates.[62] The reviewed RCTs have a low to moderate level of risk of bias and failed to adequately report the random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other source of bias (Table 1). All the aforementioned limitations make direct head-to-head comparisons regarding efficacy and safety particularly challenging. Furthermore, we were unable to perform a meta-analysis of the clinical studies due to limited published outcome data (such as reduction in ulcer area, number of completely healed ulcers, time to complete healing, and wound closure).

As LLLT is very dependent on specific and precise parameters, we hope future researchers will use comparable parameters (to reduce the risk of bias) or provide a rationale for experimenting with new settings. Based on published in vitro and in vivo experiments and the technical advances in semiconductor-based laser diodes, we recommend the use of multiprobes units with cluster diodes, with wavelength of 660 and 890 nm, power density of 50 mW/cm^2, fluence of 2 J/cm^2, irradiation time of 30 seconds, and a distance of 1 cm away from the wound. Larger sample size and longer follow-up period are required to demonstrate long-term efficacy and safety data of LLLT

for treatment of DFU. As diabetes and DFU are often chronic conditions, it is important to monitor for any recurrences of DFU and long-term adverse effects from treatment with LLLT.

In conclusion, all clinical studies included in our systematic review (4) demonstrated improved healing outcomes of DFU with no adverse events using LLLT. Although the evidence is limited, LLLT may be an effective and safe treatment to heal wounds in the setting of diabetes. There are no studies on the cost effectiveness of LLLT for DFU; however, the literature suggests that LLLT may significantly reduce the enormous cost associated with the medical management of DFU and decrease the risk of limb amputation and mortality. We hope future researchers will continue to investigate the potential of LLLT for treatment of DFU with comparable parameters for head-to-head comparisons, larger sample sizes, and longer follow-up periods. We envision future stringent RCTs may validate LLLT for treatment of DFU.

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APPENDIX

Sample Search Strategy: (diabetic foot) AND (low level light therapy OR light emitting diode OR phototherapy OR laser).

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