

# The Effects of Low-Level Laser Therapy on Wound Healing and Pain Management in Skin Wounds: A Systematic Review and Meta-Analysis

Review began 10/13/2024  
Review ended 10/19/2024  
Published 10/28/2024

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DOI: 10.7759/cureus.72542

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## Abstract

Low-level laser therapy (LLLT) is a non-invasive application of non-thermogenic light that is proven to promote tissue healing and alleviate pain. The authors aim to conduct the first meta-analysis, evaluating the effects of LLLT on wound healing and pain in skin wounds by comparing it to skin wounds not treated with LLLT. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed by searching the electronic databases. Eighteen randomised controlled trials that met the inclusion criteria were included in the study. Six hundred seventy skin wounds were analysed in the study. The primary outcome measures were the percentage reduction in wound size and the rate of complete wound healing. The secondary outcome measures included the visual analogue scale (VAS) for pain and the perineal pain score in episiotomy wounds. The percentage reduction of wound size in the LLLT group was significantly greater than that in the control group (95% confidence interval, CI, 13.93-37.70;  $p < 0.0001$ ). In addition, the rate of wound healing was significantly greater in the LLLT group (95% CI, 2.32-16.70;  $p = 0.0003$ ). LLLT has been shown to reduce pain, with the VAS scores for pain being significantly lower in the LLLT group after treatment (95% CI, -2.52 to -0.19;  $p = 0.02$ ). The authors present the first meta-analysis within the literature showing the effects of LLLT on wound healing and pain in skin wounds. Higher quality trials are recommended to enhance the current evidence base.

**Categories:** Plastic Surgery, Trauma

**Keywords:** dfu, diabetic foot ulcers, llit, low-level laser therapy, wound healing

## Introduction And Background

Low-level laser therapy (LLLT) was introduced in 1966 by Endre Mester, a professor of surgery in Budapest [1]. It is a non-invasive application of non-thermogenic light to stimulate biological activity. The light is absorbed, causing chemical changes within the body, which can result in therapeutic outcomes on the biological system to promote tissue healing and regeneration, alleviate pain, and reduce inflammation. The wavelength used is in the range of 300-10,600 nm, with the delivery of 1-4 J/cm<sup>2</sup> and an output power between 10 and 90 mW, and is therefore not comparable to other forms of laser therapy such as cutting, thermal tissue coagulation and ablation [2,3]. Absorption of the light increases adenosine triphosphate production and the induction of transcription factors through action on the mitochondria. This leads to increased cell proliferation and migration of cells, including fibroblasts, which play a crucial role in wound healing. LLLT also promotes an increase in collagen synthesis and the formation of granulation tissue, thereby encouraging tissue healing and regeneration, alleviating pain and reducing inflammation [2]. The irradiation is used in different wavelengths and energy densities to accelerate wound healing. LLLT is also used in non-skin wounds, including musculoskeletal pain and dermatological and dental conditions [4]. LLLT can be referred to as photobiomodulation therapy and includes non-ionising forms of light therapy, including lasers, light-emitting diodes (LED), and broadband light in the infrared spectrum [5].

This meta-analysis is the first in the literature to examine the effects of LLLT on wound healing and pain relief in human skin wounds. LLLT has been utilised in a variety of skin wounds, and this analysis will cover its effects on wounds from leprosy ulcers, bariatric surgery, hernia repairs, thyroidectomy scars, burns, full-thickness skin graft (FTSG) donor sites, episiotomies and diabetic foot ulcers (DFUs). Numerous studies have highlighted the therapeutic benefits of LLLT in accelerating the healing of DFUs, which are a common complication among diabetic patients. The lifetime risk of developing DFUs in diabetics can be as high as 25%, with a five-year mortality rate of up to 40% [3,6]. DFUs are often poorly managed with conventional treatments, significantly impacting patients' quality of life and posing risks of infection and amputation [7].

A secondary goal of this study is to elucidate information that may be useful to clinicians in developing treatment guidelines. There is an abundance of studies and analyses looking into LLLT on wound healing in non-human subjects. Studies have demonstrated that the effectiveness of LLLT in wound healing is

### How to cite this article

Taha N, Daoud H, Malik T, et al. (October 28, 2024) The Effects of Low-Level Laser Therapy on Wound Healing and Pain Management in Skin Wounds: A Systematic Review and Meta-Analysis. Cureus 16(10): e72542. DOI 10.7759/cureus.72542

dependent on treatment parameters such as wavelength, output power and energy density [8]. In general, output powers between 5 and 50 mW at 1–4 Jcm<sup>2</sup> have been most effective at stimulating tissue repair [1]. Conventional management of skin wounds includes debridement, antibiotics and saline irrigation. This study aims to assess if LLLT is effective as an adjunct to traditional treatment pathways for wounds. The review has not been registered. The review authors have no competing interests.

## Review

### Methods

This systematic review and meta-analysis was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards [9]. This study presents no ethical concerns, and there are no reported conflicts of interest. Furthermore, it is important to note that no external funding was received for this research.

#### *Study Types*

The eligibility criteria for this study include all randomised controlled trials (RCTs) on patients who received LLLT on skin wounds where wound healing and pain response were assessed. Male and female patients of all ages were included. There were no exclusion criteria on co-morbid status, the type of skin wound or the type of LLLT used. Case series, case reports, letters, non-randomised control studies and studies not reported in English were excluded from this review.

#### *Primary and Secondary Outcomes*

The primary outcome measures were the percentage reduction in wound size and the rate of complete wound healing. The secondary outcome measure included the visual analogue scale (VAS) for pain and the perineal pain score in episiotomy wounds.

#### *Literature Search Strategy*

Two authors, N.T. and H.D., independently searched the electronic databases Medical Literature Analysis and Retrieval System Online, PubMed, Excerpta Medica dataBASE, Google Scholar, Cumulative Index to Nursing and Allied Health Literature and the Cochrane Central Register of Controlled Trials. The World Health Organization International Clinical Trials Registry (<http://apps.who.int/trialsearch/>), ClinicalTrials.gov (<http://clinical-trials.gov/>) and the International Standard Randomised Controlled Trial Number registry (<http://www.isrctn.com/>) were also searched. The terms used in the search tool included the following: 'low level laser therapy, LLLT, photobiomodulation, laser emitting diode, LED, wound healing and randomised control trial'. These search terms were paired with the adjuncts 'or' and 'and'. The reference lists of relevant articles were screened for optimal selection.

#### *Study Selection*

Two authors, N.T. and H.D., independently reviewed the abstracts of the articles generated in the literature search. The relevant articles were extracted, and the full text was assessed. A third author, J.S., reviewed the articles for any discrepancies in the selection.

#### *Data Extraction and Management*

Relevant data from the papers were extracted by the authors from the studies and collated in a spreadsheet. Initially, this was tested with random articles and adjusted to include the relevant data. The spreadsheet comprised the first author, year of publication, total number of wounds per group, percentage change in the wound size before and after treatment, the complete healing rate of the wound, VAS score, pressure ulcer scale for healing and the wound healing index.

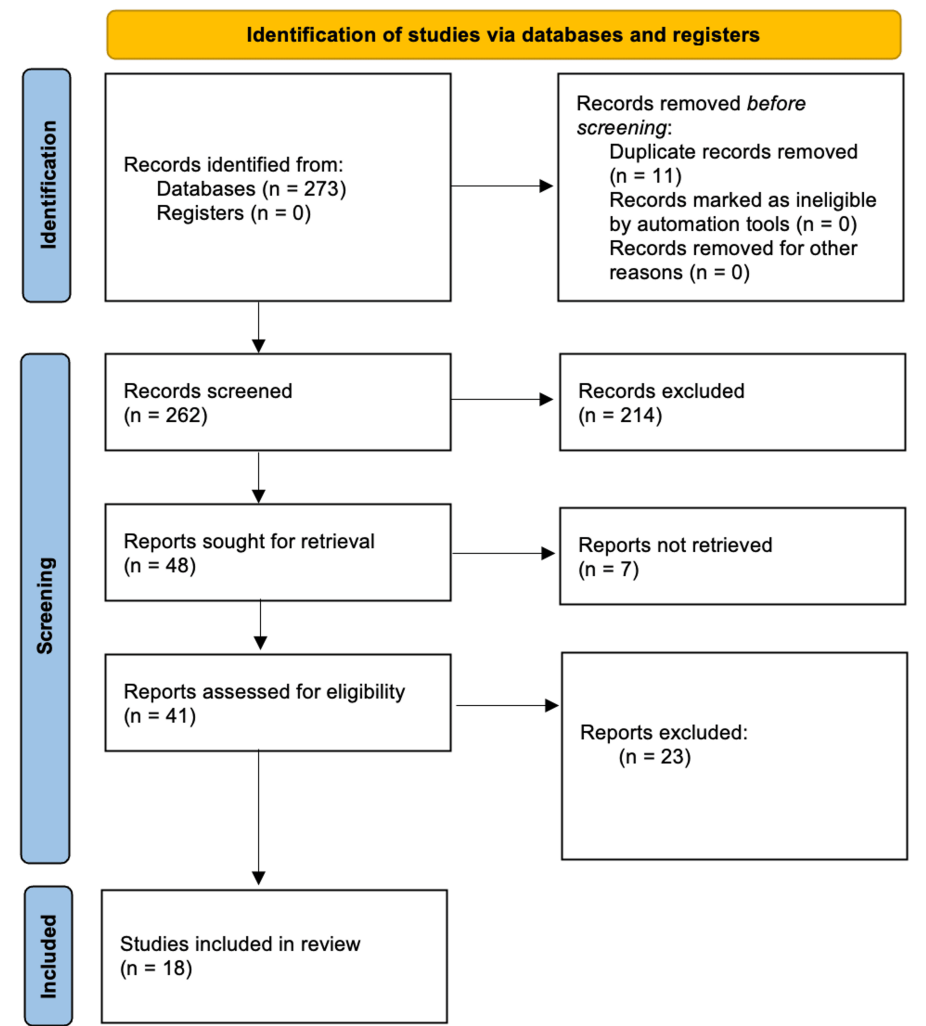
#### *Statistical Analysis*

Extracted data were entered into RevMan version 8.4.1., Cochrane Collaboration, London, UK, by the authors individually using the random effects model. The results were displayed in forest plots with 95% confidence intervals (CIs), and the mean difference was used to analyse the continuous data. The heterogeneity of the studies was assessed using Cochran's Q test ( $\chi^2$ ), and any discrepancies were quantified with the calculation of the I<sup>2</sup> assessment score. The I<sup>2</sup> score was interpreted as follows: 0%–25%, low heterogeneity; 25%–75%, moderate heterogeneity; and 75%–100%, high heterogeneity.

### Results

#### *Literature Search Results*

The two authors independently conducted a literature search, identifying 18 articles. From this selection, 18 studies were selected that met the eligibility criteria. The PRISMA flow diagram in Figure 1 demonstrates the literature search process.



**FIGURE 1: PRISMA flow diagram**

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Credit: The image has been created by the authors

Description of Studies

Table 1 amalgamates the baseline characteristics of the studies. The data analysis in this study includes 670 skin wounds, of which 216 are diabetic foot ulcers (DFUs), 50 leprosy ulcers, 18 burn wounds, 18 FTSG donor site wounds, 182 episiotomy wounds, 30 sternotomy wounds, 85 bariatric surgery wounds, 28 hernia repair skin wounds and 43 thyroidectomy scar wounds.

| Study            | Number of participants (laser/control) | Type of wound       | Type of laser (wavelength)               | Output power | Energy density        | Application site    | Frequency of application                                | Laser emitting frequency                   | Control group treatment | Laser group additional treatment |
|------------------|----------------------------------------|---------------------|------------------------------------------|--------------|-----------------------|---------------------|---------------------------------------------------------|--------------------------------------------|-------------------------|----------------------------------|
| Haze et al. [10] | 10/10                                  | Diabetic foot ulcer | Ga-Al-As laser<br>Near-infrared (808 nm) | 250 mW       | 8.8 Jcm <sup>-2</sup> | Diabetic foot ulcer | At home daily until complete ulcer closure for 12 weeks | Pulsed 8 minutes per area<br><br>10 cycles | Do                      | Do                               |

|                                      |       |                                                            |                                                             |        |                      |                                                                                                                                   |                                                                                                                                       |                                       |                                                                                                                             |                                                                                                                                                                                      |
|--------------------------------------|-------|------------------------------------------------------------|-------------------------------------------------------------|--------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim et al.<br>[11]                   | 21/22 | Thyroidectomy scar                                         | Diode laser (830 nm)                                        | -      | 4.5 Jcm <sup>2</sup> | Neck area                                                                                                                         | Daily for 30 minutes                                                                                                                  | continuous from 80 to 180 seconds     | Sham laser                                                                                                                  | -                                                                                                                                                                                    |
| Helmy et al.<br>[12]                 | 15/15 | Longitudinal median sternotomy wound                       | Probe laser device Petra, Laserklasse 2 M, Germany (660 nm) | -      | 6 Jcm <sup>2</sup>   | Five to eight points on the sternotomy scar 2 cm apart                                                                            | One session 3 times a week for 4 weeks                                                                                                | Each spot 60 seconds for 5-10 minutes | Cardiac rehabilitation programme and sternal precautions                                                                    | Cardiac rehabilitation programme and sternal precautions                                                                                                                             |
| Kazemikhoo et al. [13]               | 9/9   | Grade 3 burn ulcer covered by a split-thickness skin graft | Red diode laser (655 nm)                                    | 150 mW | 2 Jcm <sup>2</sup>   | Bed of the ulcer and the margins                                                                                                  | Once a day for 7 days                                                                                                                 | Continuous                            | Do                                                                                                                          | Do                                                                                                                                                                                   |
| De Alencar Fonseca Santos et al. [4] | 9/9   | Diabetic foot ulcer                                        | Red diode laser (660 nm)                                    | 30 mW  | 6 Jcm <sup>2</sup>   | Edge of the lesion                                                                                                                | Once every 48 hours                                                                                                                   | Continuous                            | Physiological solution 9%, hydrogel 2 mg on the wound bed with wool and gauze, every 48 hours                               | Physiological solution 9%, hydrogel 2 mg on the wound bed with wool and gauze, every 48 hours                                                                                        |
| Vaghardoost et al. [14]              | 9/9   | Split-thickness skin graft donor site                      | Red diode laser (655 nm)                                    | 150 mW | 2 Jcm <sup>2</sup>   | Donor site                                                                                                                        | Immediately after surgery, days 3, 5 and 7                                                                                            | Continuous                            | Do                                                                                                                          | Do                                                                                                                                                                                   |
| Mathur et al. [15]                   | 15/15 | Diabetic foot ulcer                                        | Diode laser (660 nm)                                        | 50 mW  | 3 Jcm <sup>2</sup>   | Five to eight spatially separated points (ulcer floor and edge)                                                                   | Daily for 15 days                                                                                                                     | Continuous for 60 seconds             | Daily wet saline or betadine dressings, antibiotic treatment, contact cast immobilisation and slough excision when required | Daily wet saline or betadine dressings, antibiotic treatment, contact cast immobilisation and slough excision when required/after laser, the wound was covered with a moist dressing |
| Alvarenga et al. [16]                | 29/25 | Episiotomy                                                 | GaAlAs laser (780 nm)                                       | 20 mW  | 5 Jcm <sup>2</sup>   | 9 points on the episiotomy equally distributed on the left and right side of the suture line 1 cm away from the edge of the wound | Three sessions of laser therapy: 6-10 hours postpartum, 20-24 hours postpartum and 40-48 hours postpartum                             | 90 seconds per session                | -                                                                                                                           | -                                                                                                                                                                                    |
| Ojea et al. [17]                     | 43/42 | Bariatric surgery wound                                    | Diode laser (808 nm)                                        | 100 mW | 10 Jcm <sup>2</sup>  | Abdominal wound 1 cm apart                                                                                                        | Immediately post-operative and on days 1 and 7                                                                                        | Continuous 20 seconds per point       | -                                                                                                                           | -                                                                                                                                                                                    |
| Sandoval Ortiz et al. [18]           | 9/9   | Diabetic foot ulcer                                        | Semiconductor laser (685 nm)                                | 30 mW  | 1.5 Jcm <sup>2</sup> | Wound edges and bed 1 cm apart                                                                                                    | Treated 3 times a week for 16 weeks or until wound closure                                                                            | Continuous                            | Daily saline wash and sharp debridement of necrotic tissue as required, maintaining a moist environment                     | -                                                                                                                                                                                    |
| Santos et al. [19]                   | 38/38 | Episiotomy wound                                           | Red diode laser (660 nm) and infrared laser (780 nm)        | 35 mW  | 8.8 Jcm <sup>2</sup> | 3 points on the wound                                                                                                             | Single session 6-56 hours post-partum                                                                                                 | -                                     | Laser procedure with the emission of irradiation                                                                            | -                                                                                                                                                                                    |
| Santos et al. [20]                   | 26/26 | Episiotomy wound                                           | Red diode laser (660 nm)                                    | 15 mW  | 3.8 Jcm <sup>2</sup> | 3 points on the wound                                                                                                             | Treated after sutures were placed, up to 2 hours post-partum, between 20 and 24 hours post-partum and between 40-48 hours post-partum | -                                     | Three treatment sessions without the emission of radiation                                                                  | -                                                                                                                                                                                    |
| Kajagar et al. [21]                  | 34/34 | Diabetic foot ulcer                                        | Multidiode cluster probe                                    | 60 mW  | 2-4 Jcm <sup>2</sup> | Ulcer floor and edge                                                                                                              | Daily for 15 days                                                                                                                     | -                                     | Daily wet saline or betadine dressings, antibiotic treatment, contact cast immobilisation and slough excision when          | Daily wet saline or betadine dressings, antibiotic treatment, contact cast immobilisation and slough excision when required                                                          |

|                          |       |                            |                                                                             |        |                           |                                         |                                                                           |                                           |                                                                                                                                                                    |                                                                                                                  |
|--------------------------|-------|----------------------------|-----------------------------------------------------------------------------|--------|---------------------------|-----------------------------------------|---------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
|                          |       |                            |                                                                             |        |                           |                                         |                                                                           |                                           | required                                                                                                                                                           |                                                                                                                  |
| Landau et al. [22]       | 10/6  | Diabetic foot ulcer        | Broadband light (400-800 nm)                                                | 180 mW | -                         | Entire wound                            | Twice a day for 4 minutes at a distance of 2 cm                           | -                                         | Non-healing light fluency 10 mW/cm <sup>2</sup> , daily cleaning and debridement as required, application of a pad of gauze soaked with saline and wound dressings | Daily cleaning and debridement as required, application of a pad of gauze soaked with saline and wound dressings |
| Kaviani et al. [23]      | 13/10 | Diabetic foot ulcer        | BTL (685 nm)                                                                | 50 mW  | 10 Jcm <sup>-2</sup>      | Ulcer surface                           | Six times a week for 2 weeks, then every other day up to complete healing | 200 seconds of illumination               | Antibiotic treatment and slough excision when required                                                                                                             | Sham irradiation, and antibiotic treatment and slough excision when required                                     |
| Barreto and Salgado [24] | 25/25 | Ulcers in leprosy patients | Indium-gallium-aluminium-phosphide semiconductor visible red light (660 nm) | 40 mW  | 2-4 Jcm <sup>-2</sup>     | Wound bed and edges                     | Three times a week for 12 weeks                                           | Continuous                                | Simple saline dressings with sterile gauze and 1% silver sulfadiazine cream                                                                                        | Simple saline dressings with sterile gauze and 1% silver sulfadiazine cream                                      |
| Carvalho et al. [25]     | 14/14 | Inguinal hernia scar       | GaAlAs diode laser (830 nm)                                                 | 40 mW  | 1.04-13 Jcm <sup>-2</sup> | 10 points across the length of the scar | Treatment on the day of surgery and then on days 3, 5 and 7               | 26 seconds per point                      | -                                                                                                                                                                  | -                                                                                                                |
| Minatel et al. [26]      | 13/10 | Diabetic foot ulcer        | Dynatron Solaris 7051 phototherapy, Salt Lake City, UT (660-890 nm)         | 100 mW | 3 Jcm <sup>-2</sup>       | Ulcer surface                           | Two times a week for 90 days or until complete healing of the ulcer       | Each spot size was treated for 30 seconds | Saline wash and ulcers cleaned with 1% sulfadiazine cream and treated with placebo phototherapy of <1.0 Jcm <sup>-2</sup> twice a week                             | Saline wash and ulcers cleaned with 1% sulfadiazine cream after laser sessions                                   |

TABLE 1: Amalgamation table

GaAlAs: gallium-aluminium-arsenate laser

Risk of Bias Assessment

The Cochrane Collaboration tool (Cochrane Collaboration, London, UK), outlined in Table 2, was used to assess the risk of bias for the RCTs by the two authors independent of each other.

| Study            | Bias                                                      | Authors judgement | Support for judgement                                                 |
|------------------|-----------------------------------------------------------|-------------------|-----------------------------------------------------------------------|
| Haze et al. [10] | Random sequence generation (selection bias)               | Low risk          | Computer-generated randomisation list                                 |
|                  | Allocation concealment (selection bias)                   | Low risk          | A researcher who was not an assessor allocated groups to participants |
|                  | Blinding of participants and personnel (performance bias) | Low risk          | Patient caregivers and personnel were blinded. A sham laser was used  |
|                  | Blinding of outcome assessment (detection bias)           | Low risk          | Evaluators were blinded                                               |
|                  | Incomplete outcome data (attrition bias)                  | Low risk          | All outcome data reported                                             |
|                  | Selective reporting (reporting bias)                      | Low risk          | Study protocol available with no missing outcomes                     |
|                  | Random sequence generation (selection bias)               | Low risk          | Participants allocated numbers with a random number generator         |
|                  | Allocation concealment                                    | Low risk          | A researcher who was not an assessor allocated groups to participants |

|                                      |                                                           |              |                                                                                         |
|--------------------------------------|-----------------------------------------------------------|--------------|-----------------------------------------------------------------------------------------|
| Kim et al. [11]                      | (selection bias)                                          |              |                                                                                         |
|                                      | Blinding of participants and personnel (performance bias) | Low risk     | Both groups received an identical laser therapy device                                  |
|                                      | Blinding of outcome assessment (detection bias)           | Low risk     | The assessors were blinded                                                              |
|                                      | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                               |
| Helmy et al. [12]                    | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                       |
|                                      | Random sequence generation (selection bias)               | Unclear risk | Randomisation method not specified                                                      |
|                                      | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                      |
|                                      | Blinding of participants and personnel (performance bias) | High risk    | Participants were not blinded to treatment, and blinding of personnel was not specified |
|                                      | Blinding of outcome assessment (detection bias)           | Unclear risk | Blinding of outcome assessment not specified                                            |
|                                      | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                               |
| Kazemikhoo et al. [13]               | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                       |
|                                      | Random sequence generation (selection bias)               | Low risk     | All patients received both the control and intervention                                 |
|                                      | Allocation concealment (selection bias)                   | Low risk     | All patients received both the control and intervention                                 |
|                                      | Blinding of participants and personnel (performance bias) | Low risk     | All patients received both the control and intervention                                 |
|                                      | Blinding of outcome assessment (detection bias)           | Low risk     | All patients received both the control and intervention                                 |
|                                      | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                               |
| De Alencar Fonseca Santos et al. [4] | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                       |
|                                      | Random sequence generation (selection bias)               | Unclear risk | Randomisation method not specified                                                      |
|                                      | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                      |
|                                      | Blinding of participants and personnel (performance bias) | High risk    | Blinding of personnel not specified. Participants were not blinded                      |
|                                      | Blinding of outcome assessment (detection bias)           | Unclear risk | Blinding of outcome assessment not specified                                            |
|                                      | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                               |
|                                      | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                       |
|                                      | Random sequence generation (selection bias)               | Unclear risk | Randomisation method not specified                                                      |
|                                      | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                      |

|                         |                                                           |              |                                                                                                                                      |
|-------------------------|-----------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Vaghardoost et al. [14] | Blinding of participants and personnel (performance bias) | Low risk     | Participants and personnel blinded                                                                                                   |
|                         | Blinding of outcome assessment (detection bias)           | Unclear risk | Blinding of outcome assessment not specified                                                                                         |
|                         | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                            |
|                         | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                                    |
| Mathur et al. [15]      | Random sequence generation (selection bias)               | Unclear risk | Randomisation technique not specified                                                                                                |
|                         | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                                                                   |
|                         | Blinding of participants and personnel (performance bias) | High risk    | Unable to blind personnel and participants                                                                                           |
|                         | Blinding of outcome assessment (detection bias)           | High risk    | Not blinded                                                                                                                          |
|                         | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                            |
|                         | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                                    |
| Alvarenga et al. [16]   | Random sequence generation (selection bias)               | Low risk     | A statistician prepared envelopes with participants' group allocation                                                                |
|                         | Allocation concealment (selection bias)                   | Low risk     | The envelopes were handed to the main researcher immediately before the laser therapy                                                |
|                         | Blinding of participants and personnel (performance bias) | Low risk     | The control group received a laser tip without the laser being emitted, and the assessor was blinded to which laser was administered |
|                         | Blinding of outcome assessment (detection bias)           | Low risk     | The assessor was blinded to the treatment given                                                                                      |
|                         | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                            |
|                         | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                                    |
| Ojea et al. [17]        | Random sequence generation (selection bias)               | Low risk     | An individual who was blinded to the patients tossed a coin to decide on group allocation                                            |
|                         | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                                                                   |
|                         | Blinding of participants and personnel (performance bias) | High risk    | Unable to blind participants                                                                                                         |
|                         | Blinding of outcome assessment (detection bias)           | Low risk     | The assessor was blinded to the treatment given                                                                                      |
|                         | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                            |
|                         | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                                    |
| Sandoval Ortiz et       | Random sequence generation (selection bias)               | Unclear risk | Randomisation technique not specified                                                                                                |
|                         | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                                                                   |
|                         | Blinding of participants and personnel (performance bias) | High risk    | Unable to blind personnel and participants                                                                                           |

|                     |                                                           |              |                                                                                                                          |
|---------------------|-----------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------|
| al. [18]            | Blinding of outcome assessment (detection bias)           | High risk    | Not blinded                                                                                                              |
|                     | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                |
|                     | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                        |
| Santos et al. [19]  | Random sequence generation (selection bias)               | Low risk     | Randomisation of the subjects was done using a randomisation table that identified each woman by a numerical code        |
|                     | Allocation concealment (selection bias)                   | Low risk     | Each number in the list was placed in an opaque sealed envelope and numbered, and the principal investigator opened them |
|                     | Blinding of participants and personnel (performance bias) | Low risk     | Participants and personnel were blinded as all received laser therapy                                                    |
|                     | Blinding of outcome assessment (detection bias)           | Unclear risk | Method not specified                                                                                                     |
|                     | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                |
|                     | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                        |
| Santos et al. [20]  | Random sequence generation (selection bias)               | Unclear risk | Randomisation method not specified                                                                                       |
|                     | Allocation concealment (selection bias)                   | Unclear risk | The allocation concealment method is not specified                                                                       |
|                     | Blinding of participants and personnel (performance bias) | Low risk     | Participants were blinded as both groups received laser therapy                                                          |
|                     | Blinding of outcome assessment (detection bias)           | High risk    | The assessor was not blinded to the study group                                                                          |
|                     | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                |
|                     | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                        |
| Landau et al. [22]  | Random sequence generation (selection bias)               | Low risk     | Randomisation performed by a person who was not involved in the evaluation of the study                                  |
|                     | Allocation concealment (selection bias)                   | Low risk     | Participants were all given identical laser devices                                                                      |
|                     | Blinding of participants and personnel (performance bias) | Low risk     | Participants received a non-treatment dose of laser. Personnel not blinded                                               |
|                     | Blinding of outcome assessment (detection bias)           | Low risk     | Surgical team blinded                                                                                                    |
|                     | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                                |
|                     | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                                        |
| Kajagar et al. [21] | Random sequence generation (selection bias)               | Low risk     | Participants were randomised with a computer-generated number                                                            |
|                     | Allocation concealment (selection bias)                   | High risk    | Participants were informed about the group allocated to                                                                  |
|                     | Blinding of participants and personnel (performance bias) | High risk    | Participants and personnel not blinded to the group allocated                                                            |
|                     | Blinding of outcome                                       | High risk    | Not blinded                                                                                                              |

|                          |                                                           |              |                                                                                                              |
|--------------------------|-----------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------|
|                          | assessment (detection bias)                               |              |                                                                                                              |
|                          | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                    |
|                          | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                            |
| Kaviani et al. [23]      | Random sequence generation (selection bias)               | Low risk     | Randomisation list prepared by an independent statistician by using a computer randomisation generator       |
|                          | Allocation concealment (selection bias)                   | Low risk     | Participants were all given identical laser devices                                                          |
|                          | Blinding of participants and personnel (performance bias) | Low risk     | Participants in the control group received a sham laser                                                      |
|                          | Blinding of outcome assessment (detection bias)           | Unclear risk | Not specified                                                                                                |
|                          | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                    |
|                          | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                            |
| Barreto and Salgado [24] | Random sequence generation (selection bias)               | Low risk     | Randomisation with computer-generated software                                                               |
|                          | Allocation concealment (selection bias)                   | Low risk     | The allocation concealment method is not specified                                                           |
|                          | Blinding of participants and personnel (performance bias) | High risk    | Unable to blind participants and personnel due to the red colour of the laser                                |
|                          | Blinding of outcome assessment (detection bias)           | High risk    | Unable to blind the assessors but used one researcher to assess all ulcers                                   |
|                          | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                    |
|                          | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                            |
| Carvalho et al. [25]     | Random sequence generation (selection bias)               | Unclear risk | Randomisation method not specified                                                                           |
|                          | Allocation concealment (selection bias)                   | Low risk     | Participants were given a stamped envelope with either number 1 or 2                                         |
|                          | Blinding of participants and personnel (performance bias) | High risk    | Unable to blind participants and personnel due to the use of a red laser or no laser                         |
|                          | Blinding of outcome assessment (detection bias)           | High risk    | Unable to blind assessors                                                                                    |
|                          | Incomplete outcome data (attrition bias)                  | Low risk     | All outcome data reported                                                                                    |
|                          | Selective reporting (reporting bias)                      | Low risk     | Study protocol available with no missing outcomes                                                            |
| Minatel et al. [26]      | Random sequence generation (selection bias)               | Low risk     | The study reports complete randomisation but does not specify the method                                     |
|                          | Allocation concealment (selection bias)                   | Low risk     | All participants received treatment from an identical laser. The control group received a non-treatment dose |
|                          | Blinding of participants and personnel (performance bias) | Low risk     | Participants and personnel were blinded until the completion of the study                                    |
|                          | Blinding of outcome assessment (detection bias)           | Low risk     | An identical light probe was used in both treatment and control groups                                       |
|                          | Incomplete outcome data                                   |              |                                                                                                              |

|  |                                      |          |                                                   |
|--|--------------------------------------|----------|---------------------------------------------------|
|  | (attrition bias)                     | Low risk | All outcome data reported                         |
|  | Selective reporting (reporting bias) | Low risk | Study protocol available with no missing outcomes |

TABLE 2: Cochrane Collaboration tool

Primary Outcome

*Percentage reduction in wound size of all wounds*: Figure 2 shows the eight studies measuring the percentage reduction in wound size from before and after treatment [4,10,13,14,21,23,24]. This included 263 of the 670 analysed wounds, with 133 receiving LLLT and 130 in the control group. The wounds analysed were ulcers, burns and skin graft donor sites. The percentage reduction in the LLLT group was significantly greater than that in the control group (95% CI, 13.93-37.70;  $p < 0.0001$ ). The results were statistically significant when using the random effects model. However, there is a high heterogeneity in the results, with the I2 score at 99%, meaning there is a lot of variation within the results.

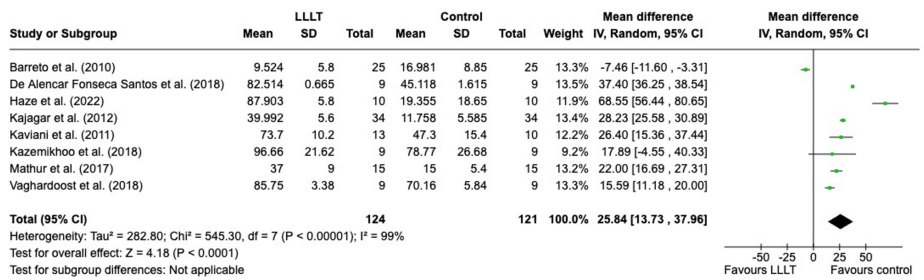


FIGURE 2: A forest plot demonstrating the percentage reduction in the wound size of all skin wounds

LLLT: low-level laser therapy; SD: standard deviation; IV: intravenous; CI: confidence interval

Credit: The forest plot has been created by the authors using RevMan version 8.4.1

*Percentage reduction in wound size of all ulcers*: Six studies looked at the percentage reduction in size of all ulcers, as shown in Figure 3 [4,10,15,21,23,24]. The ulcers were DFUs and leprosy-induced ulcers. The results for percentage reduction in the size of the ulcers are statistically significant, with a 95% CI of 14.38-42.79 and  $p < 0.0001$ . The six studies included 209 wounds, with 106 in the laser group and 103 in the control. Similar to the results of percentage reduction in all wounds in Figure 2, there is a high heterogeneity with the I2 score again at 99%.

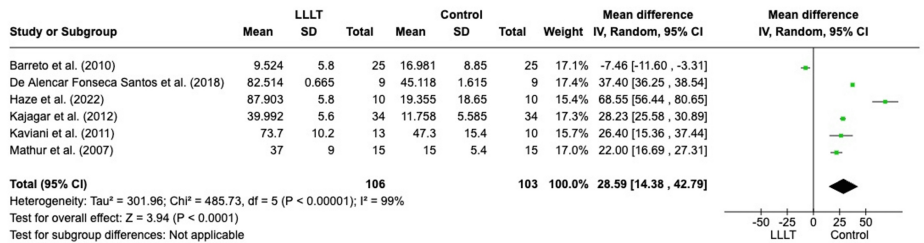


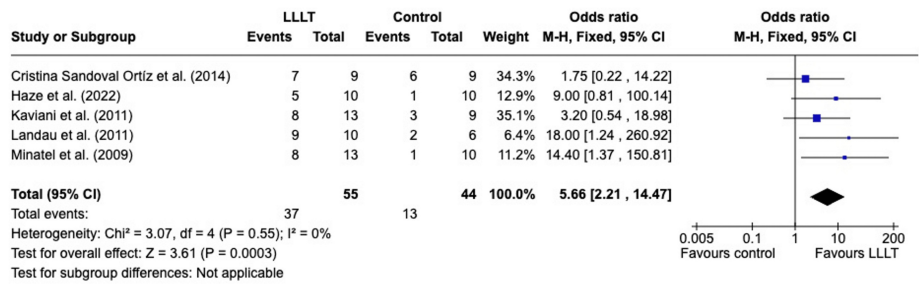
FIGURE 3: A forest plot demonstrating the percentage reduction in the wound size of all ulcers

LLLT: low-level laser therapy; SD: standard deviation; IV: intravenous; CI: confidence interval

Credit: The forest plot has been created by the authors using RevMan version 8.4.1

*Complete wound healing*: Complete wound healing rates are displayed in Figure 4 (a forest plot to show the complete wound healing rate), including five studies assessing DFUs [10,18,22,23,26]. In the work by Haze et

al., complete wound healing is defined as wound closure equal to or over 90% and, in other studies, as complete closure of the wound [10]. The rate of wound healing was greater in the treatment group than that in the control group, with statistically significant results ( $p = 0.0003$ ; 95% CI, 2.32-16.70) using the random effects model. This included 99 wounds, with 55 in the treatment and 44 in the control. There was no heterogeneity between the studies ( $I^2 = 0\%$ ).



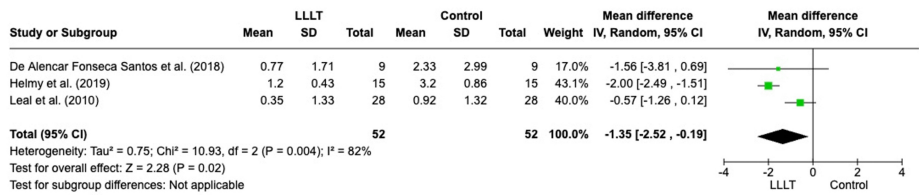
**FIGURE 4: A forest plot to show the complete wound healing rate**

LLLT: low-level laser therapy; M-H: Mantel-Haenszel; CI: confidence interval

Credit: The forest plot has been created by the authors using RevMan version 8.4.1

### Secondary Outcome

**Visual analogue scale:** The VAS scores for pain are displayed in Figure 5 (a forest plot demonstrating the VAS scores for pain), which are reported in three studies [4,12,25]. The VAS is a subjective scale from 0 to 10 on a 10-cm line, where 0 represents 'no pain' and 10 is 'worst pain' [27]. The wounds involved include DFUs, sternotomy wounds and inguinal hernia scar wounds. The results demonstrate lower VAS scores for pain in the LLLT group after treatment and a statistically significant difference (95% CI, -2.52 to -0.19;  $p = 0.02$ ).

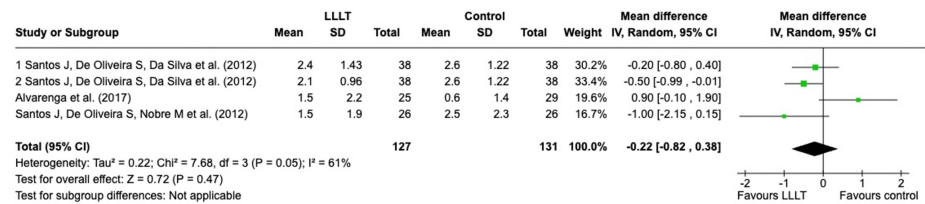


**FIGURE 5: A forest plot demonstrating the VAS scores for pain**

LLLT: low-level laser therapy; SD: standard deviation; IV: intravenous; CI: confidence interval

Credit: The forest plot has been created by the authors using RevMan version 8.4.1

**Perineal pain score:** Three studies reported the perineal pain scores, which are reported in Figure 6 (a forest plot displaying the results for the perineal pain scores in the studies with episiotomy wounds) [16,19,20]. The results suggest that LLLT is not beneficial in alleviating pain in episiotomy wounds, with statistically insignificant results ( $p = 0.47$ ).



**FIGURE 6: A forest plot displaying the results for the perineal pain scores in the studies with episiotomy wounds**

LLLT: low-level laser therapy; SD: standard deviation; IV: intravenous; CI: confidence interval

Credit: The forest plot has been created by the authors using RevMan version 8.4.1

Discussion

Unlike other forms of medical laser therapy, LLLT is non-invasive and does not have thermal or ablative mechanisms, making it a safe and low-risk treatment option [2]. This is the first meta-analysis within the literature assessing the efficacy of LLLT on wound healing and pain response in a wide variety of skin wounds. This analysis demonstrates that LLLT results in a significant reduction in wound size ( $p < 0.0001$ ), resulting in an increased rate of complete wound healing ( $p = 0.0003$ ) and pain reduction ( $p = 0.02$ ). The type of low-level laser used in the studies varied. Eight studies specified the use of a red diode laser [4,11,13-15,17,19,20]. The wavelength ranged from 400 to 890 nm, with a modal wavelength of 660 nm. In many of the control and treatment groups in the studies, additional wound treatment methods were utilised, including surgical debridement, saline irrigation and antibiotics.

Wound Size Reduction

All studies reported a reduction in the size of the wound in both the treatment and control groups. The wounds analysed were ulcers, burns and graft donor sites. Among the eight studies evaluating the percentage reduction in wound size, only Barreto and Salgado showed a greater reduction in the control group compared to the treatment group [24]. This was for ulcers in leprosy patients where both groups also received conventional treatments such as simple saline dressings with sterile gauze and 1% silver sulfadiazine cream, suggesting this may have been beneficial alone in the reduction of ulcer size. The remaining studies unanimously showed a higher rate of wound healing in the LLLT group with statistically significant results. In these studies, there was no correlation between wound size reduction and the wavelength or energy density of the laser. A previous meta-analysis by Woodruff et al. on laser therapy in wound repair on both human and non-human subjects found that energy density gave predictable dose-dependent treatment effects, and treatment effect size was greater in animals than in humans [8].

Diabetic Foot Ulcers

A third of the wounds analysed in the study were DFUs, mirroring the high prevalence within the United Kingdom patient demographic. In general, DFUs are poorly managed, and conventional treatment is often unsuccessful, highlighted by an amputation rate of around 7%-20% [3]. Standard treatment involves a multidisciplinary approach with glycaemic control, wound offloading, regular vascular assessment, infection control and wound debridement. Despite these measures, DFUs can be particularly recalcitrant and may require extended periods to heal [28]. LLLT not only enhances the healing of a wound but also promotes the healing of non-healing wounds and ulcers [8]. The meta-analysis by Huang et al. looked at LLLT on DFUs including 13 RCTs with 413 patients analysed and found that LLLT increases the rate of complete wound healing ( $p < 0.0001$ ), reduces the ulcer area ( $p = 0.0002$ ) and shortens the mean healing time ( $p < 0.0001$ ) [3]. This is consistent with the sub-analysis of the six studies looking at LLLT on DFUs and one leprosy-induced ulcer, which also demonstrated a greater reduction in the size of the ulcers in the treatment group ( $p < 0.0001$ ) [4,10,15,21,23,24]. A study by Salvi et al. investigated the vascular effects in DFUs after LLLT. They measured the total haemoglobin (Hb) concentration change before and after LLLT between a healthy control and intervention group. They found increased levels of total Hb after LLLT in DFU patients but not in the healthy controls, indicating enhanced perfusion to the wound, which promotes healing [29].

Episiotomy

The evidence suggests that LLLT is not beneficial for episiotomy wounds with limited change in the perineal pain scores. The RCT by Santos et al. [19] randomised participants into three groups, with two experimental groups and a control group. The experimental groups were split into treatments of LLLT with red and infrared lasers with wavelengths of 660 and 780 nm, respectively. The experimental group receiving the infrared laser showed a lower mean post-therapeutic pain score, suggesting that this is more effective at

reducing pain than the red diode laser variant of LLLT [19]. The study by Alvarenga et al. was the only one of the three that showed a higher mean pain score in the treatment group than in the control post-LLLT, indicating that the treatment did not show any substantial benefit with scores that were both low and under 1.5 [16]. Treatment was delivered over one or three sessions postpartum, and there was no correlation in pain scores between the number of sessions given.

#### *Limitations*

There are limitations to this analysis, including the fact that a third of the skin wounds are DFUs. However, the results do highlight the potential for LLLT use within DFUs. This has potentially significant consequences in the management of these patient cohorts and can aid in reducing the morbidity and economic impact of managing complex diabetic wounds.

## Conclusions

Unlike other forms of medical laser therapy, LLLT is non-invasive and does not have thermal or ablative mechanisms. In this analysis, LLLT was demonstrated to have therapeutic effects on the body through the promotion of wound healing and pain alleviation. It has further illustrated its efficacy in treating chronic or slow-healing wounds such as DFUs. It would be beneficial to determine the parameters for the LLLT, including the wavelength, output power and energy density, which provide optimal treatment effects. The authors recommend conducting additional high-quality trials to further broaden the existing evidence base.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Nadia Taha, Hasan Daoud, Tahira Malik, Shafiq Rahman

**Acquisition, analysis, or interpretation of data:** Nadia Taha, Hasan Daoud, Jeevith Shettysowkoor

**Drafting of the manuscript:** Nadia Taha

**Critical review of the manuscript for important intellectual content:** Nadia Taha, Hasan Daoud, Tahira Malik, Jeevith Shettysowkoor, Shafiq Rahman

**Supervision:** Shafiq Rahman

### Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

### Acknowledgements

Nadia Taha and Hasan Daoud contributed equally to the work and should be considered co-first authors.

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