Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

# Efficacy of low-level light therapy for treatment of diabetic foot ulcer: A systematic review and meta-analysis of randomized controlled trials

*Shengbing Li, Cong Wang, Bo Wang, Li Liu, Liang Tang, Dongfang Liu, Gangyi Yang, Lili Zhang* *

*Department of Endocrinology, The Second Affiliated Hospital, Chongqing Medical University, 400010 Chongqing, China*

ARTICLE INFO

*Article history:*
Received 8 April 2018
Received in revised form
17 May 2018
Accepted 5 July 2018

*Keywords:*
Diabetic foot ulcer
Low-level light therapy
Randomized control trials
Systemic review
Meta-analysis

ABSTRACT

*Aims:* The goal of this systematic review and meta-analysis based on seven Randomized control trials (RCTs) is to examine whether Low-level light therapy (LLLT) is effective at healing diabetic foot ulcer (DFU) and to provide evidence-based recommendations and clinical guidelines for the future clinical treatment of DFUs.

*Methods:* Medline, Embase, Scopus, Cochrane Library, and Web of Science databases were searched for studies published up to June 30, 2017, without language or data restrictions. RCTs that investigated the use of LLLT for DFU treatment were included. Standard methods of meta-analysis were performed to evaluate outcomes of LLLT on the healing of DFU.

*Results:* Seven RCTs involving 194 participants were eligible for this systematic review and meta-analysis. The results of meta-analysis showed that LLLT has emerged as a potential noninvasive treatment for DFUs, as LLLT was found to effectively reduce the ulcer area [weighted mean difference (WMD) 34.18, 95% confidence intervals (CI) 19.38–48.99, $P < 0.00001$], improve the complete healing rate [odds ratio (OR) 6.72, 95% CI 1.99–22.64, $P = 0.002$]. Qualitative analysis of the included RCTs found that LLLT also played a role in the treatment of DFUs through promoting rapid granulation formation and shortening ulcer closure time, as well as alleviating foot ulcer pain. None of the treatment-related adverse event was reported.

*Conclusions:* LLLT was recognized as a potential method in the comprehensive treatment of DFUs. Further well designed and high-quality studies are required to confirm the role of LLLT in the management of DFUs.



## 1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM), which results in many micro- and macrovascular complications with major morbidity, mortality, reduced quality of life and increased society costs, is rapidly increasing worldwide and is becoming a major global health issue [1–3]. Diabetic foot ulcer (DFU), which is often associated with infection, peripheral neuropathy and peripheral arterial disease, is one of the most serious and problematic complications of diabetes and has been considered the most important predictor for lower-extremity amputations [4].

* Corresponding author.
E-mail address: zhanglili.jl@foxmail.com (L. Zhang).
https://doi.org/10.1016/j.diabres.2018.07.014
0168-8227/

The global prevalence of DFU disease is approximately 6%, and the 5-year mortality rate of this disease is up to 77% [5,6]. However, management of DFU remains a major therapeutic challenge throughout the world, and it is imperative to investigate strategies and treatments to reduce the burden of this disease in an efficient and cost-effective way.

Wound repair in diabetic patients is relatively slower than that in healthy individuals due to impaired leukocyte chemotaxis and phagocytosis, decreased function of macrophages in the wound matrix, reduced collagen synthesis and deposition, and decreased release of growth factors [7,8]. The poor wound healing ability of diabetic patients increases the difficulty of disease management. Therefore, a multidisciplinary approach including glycemic control, daily local care, antimicrobials, antiseptics, surgical revascularization and engineered biological tissues should be considered in the development of a cure for DFUs [8,9]. Furthermore, several previous studies reported that nonpharmacological therapies such as foot off-loading, electrical stimulation [10], hyperbaric oxygen therapy [11], and low-level laser therapy (LLLT) may also play effective roles in DFU healing.

LLLT, also called low-intensity laser therapy (LILT) or low-energy photon therapy (LEPT), includes wavelengths from 500 to 1100 nm and delivers 1–4 J/cm$^2$ to treatment sites with lasers possessing output powers between 10 and 90 mW/cm$^2$[12]. LLLT is conducted at low irradiation intensities, and its biological effects are secondary to direct effects of photonic radiation without thermal reactions. LLLT was first introduced by the work of Mester and colleagues [13,14] and has been known to supply direct biostimulative light energy to body cells, thereby enhancing normal cell function and tissue repair [15]. Low-intensity laser irradiations have been reported to positively influence the processes of impaired microcirculation and delayed wound healing. Both in vitro and in vivo studies suggest that LLLT stimulates specific metabolic processes in wound healing [16,17]. Cellular studies reported an increase in the proliferation of human endothelial cells and fibroblasts, together with fibroblast-mediated procollagen production induced by LLLT [18]. Animal studies also showed the positive effect of LLLT on cellular function and molecular pathways and showed the ability of LLLT to promote wound healing in different animal models, suggesting that it may also be effective in humans [19,20]. Therefore, the human studies conducted by Mester and colleagues pioneered LLLT as an alternative noninvasive procedure to promote chronic wound healing [13,14]. Subsequently, several follow-up studies in humans presented LLLT as a promising treatment for wound healing, particularly as a therapeutic for DFU. Therefore, increasingly more investigators consider LLLT an effective treatment for DFU. However, this nonpharmacological treatment requires careful investigation to ascertain its effectiveness because of the limited sample size and insufficient statistical power of the previous independent studies. In the present study, to examine whether LLLT is effective in DFU healing, we aimed to systematically review the available literature and summarize the findings by performing meta-analysis of randomized controlled trials (RCTs); moreover, we also aim to provide evidence-based recommendations and clinical guidelines for the future clinical practice of DFU therapy.

## 2. Methods

The present study was conducted in accordance with the Preferred Reporting Items for Meta-Analyses (PRISMA) guidelines [21].

### 2.1. Search strategy

The databases searched in this study are as following: Medline, Embase, Scopus, Cochrane Library, and Web of Science databases. The last search update was conducted on June 30, 2017. There were no language restrictions. The search terms were as follows: diabetic ulcer/diabetic foot/diabetic foot ulcer/diabetic foot disease and low-level light therapy/LLLT/low-intensity laser therapy/LILT/low-energy photon therapy/LEPT/phototherapy/laser. The bibliographies of all relevant articles and review articles were examined to obtain additional articles that were not identified in our search.

### 2.2. Study selection criteria

Of the collected studies, those that investigated the effect of LLLT on treatment of DFU were considered for our analysis. Title and abstracts were separately screened for inclusion in the full-text assessment. Afterwards, the filtered abstracts were further searched for the corresponding full-text documents, the inclusion criteria was applied, and the eligible results were included in this systematic review and meta-analysis. Articles were eligible for inclusion if they fulfilled all the following criteria: (i) the studies were RCTs; (ii) the participants were patients with DFU; (iii) the treatment of DFU involved LLLT and an appropriate control; and (iv) the study provided specific results about DFU healing, i.e., healing rate, reduction of ulcer area, etc. We excluded the following types of studies: non-RCT (i.e., review articles, editorials, case reports or case series), in vitro (i.e., cell culture), animal-based, and non-LLLT. Three authors (Bo Wang, Shengbing Li and Lili Zhang) independently identified and reviewed each relevant paper. Disagreement about eligibility was resolved by consensus between all authors.

### 2.3. Data extraction

Three investigators (Bo Wang, Shengbing Li and Lili Zhang) independently extracted data after assessing and reaching consensus for eligible studies by using a standardized data extraction form. The reviewers extracted the following information from each included RCT: the first author's name, year of publication, study design, demographic information, sample size, number of ulcers, DFU duration, Wagner grades of DFU, outcomes of treatment, parameters of LLLT and treatment-related adverse events.

### 2.4. Quality assessment

Assessment of risk of bias in the included RCTs was performed according to the Cochrane Collaboration's Tool for Systematic Reviews of Intervention [22] which included the follow domains: random sequence generation, allocation concealment, participant blinding, outcome assessment