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Laser Therapy for Diabetic Peripheral Neuropathy: Protocol of a Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, and strongly impact the quality of life and working ability of patients. Evidence indicated that laser therapy might be effective for neuropathy, however, the effect of laser therapy for DPN is not clear. The objective of this systematic review and meta-analysis is to determine the effectiveness and safety of laser therapy for DPN, in comparison with sham laser therapy, no treatment, or other active treatment, or as an additional treatment compared with another treatment alone.

Methods and analysis: We will search PubMed (MEDLINE), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science, as well as four Chinese language databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database and SinoMed. Randomized controlled trials will be included. Two reviewers will independently extract data using a structured data extraction method and assess the risk of bias in the included studies. We will conduct meta-analysis with RevMan 5.3 and evaluate quality of the evidence with GRADE approach.

Ethics and dissemination: This study doesn't require ethics approval. Our findings will

be disseminated in the peer-reviewed publications.

Systematic review registration: submitted in PROSPERO ID: CRD42021276056

Strengths and limitations of this study

- We will update the search to date to include more recent studies and will expand our search scope to Chinese language databases.
- We will evaluate more outcomes including global symptom improvement and other patient-reported outcomes including pain, function impairment and quality of life, as well as adverse events~~,~~.
- We only search English and Chinese databases, but not other language databases, which may increase reporting bias.

INTRODUCTION

Diabetic peripheral neuropathy (DPN), one of the most common complications of diabetes, strongly impact the quality of patients' life and capacity for work. It leads to foot ulcer in 50% diabetes, and even cause lower limb amputation. People with type 2 diabetes suffered more risks of DPN than type 1.[1] DPN is recognized by the damage of peripheral nerve, which commonly occur in lower limbs, and hands were occasionally affected. However, up to 50% of patients never experience symptoms, thus the diagnosis only can be made in accidental examination or until the foot ulcer appear. For patients who have already experienced symptoms, numbness, dryness, burning pain, needle-like pain and some other abnormal sensations are most frequently mentioned. [2]

The biggest risk factors of DPN are chronic hyperglycemia exposure and diabetes duration. Whereas some other factors, including hypertension, hyperlipidaemia, smoking, age at onset of diabetes, type of diabetes and genetic factors, may also play a role at varying degrees. [3,4]

Enhanced glucose control is the only way that has been proved to be effective for preventing the development of diabetic neuropathy. It could reduce nerve conduction and vibration threshold abnormalities in type 1 diabetes, while in type 2 diabetes, the effectiveness was not statistically significant. In addition, enhanced glucose control can increase the risk of severe hypoglycemic episodes.[5] Some symptomatic therapies, such as the tricyclic antidepressants; selective serotonin-reuptake inhibitors; antiepileptics; zonisamide and non-steroidal anti-inflammatory drugs (NSADs), has been proved to be effective for painful symptom. Nevertheless, these drugs are accompanied with varies of adverse events, including dry mouth, sedation, dizziness, confusion, orthostatic hypotension, headache, nausea, constipation, diarrhea, etc.[6]

Non-pharmacological therapy, such as laser therapy, especially low level laser, has also been used to treat DPN due to its function in alleviating pain[7] and improving lower limbs

sensation[8,9]. The mechanism of laser action is not completely clearly. It may inhibit apoptosis and increasing neurogenesis so that the damage of nervous system can be recovered. The effect of laser therapy is closely related to the type of laser, irradiation mode, power density and the properties of irradiated tissue.[10]

While two systematic reviews have evaluated the effects of laser therapy for DPN, [11, 12] they both included only a small number of studies, and one of them only provided qualitative description of the included studies. With some new and larger-sample size RCTs [13-16] published, it is important to conduct an update of the systematic review and meta-analysis of laser therapy for DPN.

OBJECTIVE

The objective of this review is to determine the benefit and potential harm of laser therapy, in comparison to sham laser therapy, no treatment, or other active treatment, or as an additional treatment compared with another treatment alone in patients with DPN.

METHOD AND ANALYSIS

● Eligibility criteria for included studies

Types of studies

We will include randomized controlled trials assessing the benefits and harms of laser therapy for DPN. Trials with randomization of interventions taking place within individuals to different body parts (e.g., to the two legs) will also be included.

Types of population

We will include participants of any age and sex, with either form of diabetes, that were diagnosed to be DPN.

Types of intervention

Laser therapies for DPN mainly refers to using non-invasively low-level laser or photobiomodulation in the treatment of DPN. The types of laser may include ultraviolet light such as nitrogen molecular laser (337.1nm); violet laser such as helium-cadmium laser (441.6nm); red laser such as argon ion laser (514.5nm) and He-Ne laser (632.8), as well as infrared laser such as semiconductor laser (805nm) and CO_2 laser (10.6μm).[17]

Types of outcome measures

Main outcome

The main outcome will be global symptom improvement measured by a validated instrument such as Michigan neuropathy screening instrument (MNSI), Michigan diabetic neuropathy score (MDNS), Toronto clinical scoring system (TCSS) or visual analogue scale (VAS).

Additional outcomes

1. Change in or absolute values of pain evaluated by the visual analogue scale (VAS), numeric rating scale (NRS) or verbal description scale (VDS), etc;

2. Change in or absolute values of functional impairment and disability by NIS (Neuropathy Impairment Score) or NDS (Neuropathy defects Score);

2. Change in or absolute values of impairment of sensation in quantitative sensory testing (e.g., vibration perception threshold and thermal threshold);

3. Change in or absolute values of quality of life by SF-36 or NeurQol, etc;

4. Change in or absolute values of nerve conduction function measured by motor or sensory nerve conduction velocity (NCV), sensory nerve action potential (SNAP) or compound muscle action potential (CMAP);

5. Number of participants experiencing adverse events;

6. Serious adverse events.

The time point of follow-up will be at equal or less than 3 months (closest to 2 months) after randomization for short term and at more than 3 months (closest to 6 months) after randomization for long term.

● Search methods for identification of studies

We will search, with no time and language restrictions, the following databases for relevant literature: PubMed (MEDLINE), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science, as well as Chinese language databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database (VIP) and SinoMed. Two trial registries including Clinical Trials. gov and the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) will be also searched. The electronic database search will be supplemented by a manual search of the reference lists of included articles. The search strategy is shown in Table. 1.

● Data collection and analysis

Study selection

At least one author will screen the title and abstract of all records identified by searching. We will obtain the full text of potentially relevant reports and two authors will independently review the full text to assess its eligibility. We will resolve disagreements by discussion.

Data extraction and management

Two review authors (JYW and ZQH) independently will extract data concerning details of study population, intervention, and outcomes using a structured data extraction form following the section 7.7 of Cochrane Handbook.[18] We will consult the other review author (KC) if there is any conflict.

If the publication did not report outcome data or the data was reported ambiguously, we will request the corresponding authors of the study to provide additional information or clarification by email.

Assessment of treatment adequacy

Two experts, who have a clinical or research experience of more than 5 years in laser therapy or in DPN treatment, and who have previously worked on RCTs or systematic reviews, will independently assess the adequacy of the laser therapy and the control therapy in the trials. Five aspects of the laser treatment will be assessed for adequacy: 1) selection of laser (including wavelength, power density and energy density) 2) choice of irradiation location; 3) total number of sessions; 4) treatment duration; 5) treatment frequency. The validity of the sham intervention will also be assessed to using an open-ended question. The experts will be provided with only the part of each publication that describes the laser and control procedures, so that their assessments cannot be influenced by the results of the trials. Discrepancies between the two experts will achieve consensus by discussion.

Assessment of risk of bias

Two review authors (JYW and ZQH) independently will assess the risk of bias in the studies that were included in this review according to the criteria described in the section 8.2.3 of Cochrane Handbook for Systematic Reviews of Interventions. [19] We will resolve conflicts by consulting the other review author (KC).

The items involve the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

Mean difference or standards mean difference with 95% CI will be used for continues outcome and odds ratios (OR) or relative ratios (RR) with 95% CI will be used for dichotomous data.

Unit of analysis issues

We will also include data from trials with different interventions being applied to different body parts, if the information is available. The analysis will be account for the pairing of parts within individuals in the same way that pairing of intervention periods in the crossover trial.[20] Continuous data from this kind of trial will be analyzed using one of the two approaches: use the results from paired analyses if reported in the original article; treat the study as a parallel trial and pool the interventional parts and compare these to the pooled control parts. Dichotomous outcomes for this kind of trial require more complicated analysis methods and we will consult with a statistician. [21]

Dealing with missing data

For the missing data, we will contact the original author. If it's failed to gather the missing data, we will discuss the potential impact of the dropout for the conclusion of the review.

Assessment of heterogeneity

We will use I^2 statistic to assess Statistical heterogeneity. If the I^2 value greater than 50%, we will conduct subgroups to explore the sources of heterogeneity.

Reporting bias

We will make a funnel plot to assess publication bias if the number of studies is more than 10.

Data synthesis and sensitivity analysis

Data of studies that are sufficiently similar in terms of their comparisons and outcome measurements will be pooled. The data will be pooled by using random-effects model when studies are heterogeneous, and on the contrary, by using fixed-effect model when they are homogeneous. We will report the data separately if the study can't be combined. We will use mean difference (MD) for single trial comparisons and for RCTs that used same instrument to measure the same outcome. For the RCTs that assessed same outcome by various instruments, we will use standard mean difference (SMD). Analyses will be performed by intention to treat, where possible.

We will perform sensitivity analysis excluding the trials with high risk of bias when data are adequate.

Subgroup analysis

If we find sufficient number of RCTs, we will perform subgroup analyses according to:

1. type of diabetes (type 1 or type 2 diabetes mellitus)

2. type of laser (red, infrared, or other)

3. dosage of laser treatment: including power density, energy density, as well as duration and frequency of the treatment according to the assessment results of treatment adequacy by the experts.

Confidence in cumulative evidence

We will use GRADE system to assess the confidence of our evidence considering five criteria: study limitations, consistency of effect, imprecision, indirectness, and publication bias. We will conduct the assessment in terms of section 14.2 of Cochrane Handbook [22] by GRADEpro software.

Patient and Public Involvement

This is a study for systematic review which will not involve patients and public.

DISCUSSION

Up to now, evidences for laser therapy treating diabetic peripheral neuropathy are deficient. A 2017 systematic review researched the efficacy of infrared laser for DPN.[12] The other systematic review published more recently in 2019 studied low-level laser therapy (LLLT) for painful diabetic neuropathy.[11] The two reviews included only six studies, respectively. Three studies in the 2019 review [11] were non-RCTs, thus the 2019 review only narratively described the results of the individual study without conducting any meta-analysis or assessing risk of bias of the included studies. In addition, the conclusions of the two reviews were inconsistent.

Compared to the two previous reviews, we will update the search to date to include more recent studies and will expand our search scope to Chinese language databases to collect more evidences. Additionally, we will include more types of lasers, not focusing only on infrared laser as in the 2017 review, since lasers other than infrared laser are also commonly used in clinic for DPN. In terms of the outcomes, the 2017 review [12] investigated plantar tactile sensitivity and pain; the 2019 review [12] focused on pain and nerve conduction velocity. While we are more concerned about global symptom, because global symptom outcome is more patient-centered and more comprehensive, including various forms of pain and various abnormal sensations in DPN patients. Besides global symptom, we will also consider additional outcomes such as sensation impairment, nerve conduction function, quality of life and adverse events. Compared with the 2017 review [12] which performed subgroup analysis according to the

type of comparison and length of follow-up, we will carry out subgroup analysis considering more on the differences in the populations and intervention characteristics (e.g., type of diabetes, type of laser and dosage of therapy) according to the suggestion in Cochrane Handbook.[23]

The limitation of our review may be that we only search English and Chinese databases, but not other language databases, which may increase reporting bias.

In conclusion, our review will integrate more and newer clinical trials and will provide more recent and rigorous evidence for the effectiveness and safety of laser therapy in treating DPN.

List of abbreviations

DPN; diabetic peripheral neuropathy; VAS: visual analogue scale; MNSI: Michigan neuropathy screening instrument; MDNS: Michigan diabetic neuropathy score; TCSS: Toronto clinical scoring system; NIS: Neuropathy Impairment Score; NDS; Neuropathy defects Score; NCV: never conduction velocity; CMAP: compound muscle action potential. SNAP: sensory nerve action potential.

DECLARE

Ethics and dissemination

This study doesn't require ethics approval. Our findings will be disseminated in the peer-reviewed publications.

Contributors

KC and XS conceived and designed the topic; KC, JYW, and ZQH contributed to writing the protocol; all of the authors commented on the drafts of the protocol.

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Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author according to the institution guideline on materials and data transfer agreements.

Competing interests

The authors declare that they have no competing interests

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Interventions version 6.2 (updated February 2021). Cochrane, 2021. Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Table 1 Search strategy for the MEDLINE (PubMed) database

disease terms
1. "Diabetic Neuropathies"[Mesh]
2. 2. (Diabetic Neuropathy[Title/Abstract] OR Neuropathies, Diabetic[Title/Abstract] OR Neuropathy, Diabetic[Title/Abstract] OR Diabetic Autonomic Neuropathy[Title/Abstract] OR Autonomic Neuropathies, Diabetic[Title/Abstract] OR Autonomic Neuropathy, Diabetic[Title/Abstract] OR Diabetic Autonomic Neuropathies[Title/Abstract] OR Neuropathies, Diabetic Autonomic[Title/Abstract] OR Neuropathy, Diabetic Autonomic[Title/Abstract] OR Diabetic Neuralgia[Title/Abstract] OR Diabetic Neuralgias[Title/Abstract] OR Neuralgias, Diabetic[Title/Abstract] OR Diabetic Neuropathy, Painful[Title/Abstract] OR Diabetic Neuropathies, Painful[Title/Abstract] OR Neuropathies, Painful Diabetic[Title/Abstract] OR Neuropathy, Painful Diabetic[Title/Abstract] OR Painful Diabetic Neuropathies[Title/Abstract] OR Painful Diabetic Neuropathy[Title/Abstract] OR Neuralgia, Diabetic[Title/Abstract] OR Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract] OR Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract] OR Diabetic Asymmetric Polyneuropathy[Title/Abstract] OR Asymmetric Polyneuropathies, Diabetic[Title/Abstract] OR Asymmetric Polyneuropathy, Diabetic[Title/Abstract] OR Diabetic Asymmetric Polyneuropathies[Title/Abstract] OR Polyneuropathies, Diabetic Asymmetric[Title/Abstract] OR Polyneuropathy, Diabetic Asymmetric[Title/Abstract] OR Diabetic Mononeuropathy[Title/Abstract] OR Diabetic Mononeuropathies[Title/Abstract] OR Mononeuropathies, Diabetic[Title/Abstract] OR Mononeuropathy, Diabetic[Title/Abstract] OR Diabetic Mononeuropathy Simplex[Title/Abstract] OR Diabetic Mononeuropathy Simplices[Title/Abstract] OR Mononeuropathy Simplex, Diabetic[Title/Abstract] OR Mononeuropathy Simplices, Diabetic[Title/Abstract] OR Simplex, Diabetic Mononeuropathy[Title/Abstract] OR Simplices, Diabetic Mononeuropathy[Title/Abstract] OR Diabetic Amyotrophy[Title/Abstract] OR

Amyotrophies, Diabetic[Title/Abstract] OR Amyotrophy, Diabetic[Title/Abstract] OR Diabetic Amyotrophies[Title/Abstract] OR Diabetic Polyneuropathy[Title/Abstract] OR Diabetic Polyneuropathies[Title/Abstract] OR Polyneuropathies, Diabetic[Title/Abstract] OR Polyneuropathy, Diabetic[Title/Abstract])

3. 1 OR 2

intervention terms

4. "laser therapy"[MeSH Terms]
5. (Infrared Ray[Title/Abstract] OR Ray, Infrared[Title/Abstract] OR Rays, Infrared[Title/Abstract] OR Heat Waves[Title/Abstract] OR Therapy, Near Infrared[Title/Abstract] OR Phototherapies[Title/Abstract] OR Therapy, Photoradiation[Title/Abstract] OR Photoradiation Therapies[Title/Abstract] OR Therapies, Photoradiation[Title/Abstract] OR Light Therapy[Title/Abstract] OR Light Therapies[Title/Abstract] OR Therapies, Light[Title/Abstract] OR Therapy, Light[Title/Abstract] OR Photoradiation Therapy[Title/Abstract] OR Light Therapies[Title/Abstract] OR Therapies, Light[Title/Abstract] OR Light Irradiation[Title/Abstract] OR Irradiation, Light[Title/Abstract] OR Light Phototherapy[Title/Abstract] OR Phototherapy, Ligth[Title/Abstract] OR Light Biostimulation[Title/Abstract] OR Monochromatic Near Infrared Therapy[Title/Abstract] OR Therapy, Monochromatic Near Infrared[Title/Abstract] OR MIRE[Title/Abstract] OR Anodyne Theraphy[Title/Abstract] OR Therapy, Anodyne[Title/Abstract] OR PILT[Title/Abstract] OR Pulsed Infrared Light Therapy[Title/Abstract] OR Light Emitting[Title/Abstract] OR Photo Energy[Title/Abstract] OR Light Emitting Diodes[Title/Abstract] OR Laser Therapies[Title/Abstract] OR Therapies, Laser[Title/Abstract] OR Therapy, Laser[Title/Abstract]) OR Laser[Title/Abstract]
6. 4 OR 5
7. 3 AND 6

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not amendments
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Low Level Laser Therapy/Photobiomodulation for Diabetic Peripheral Neuropathy: Protocol of a Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, and strongly impact the quality of life and working ability of patients. Evidence indicated that Low level laser therapy (LLLT)/photobiomodulation might be effective for neuropathy, however, the effect of LLLT for DPN is not clear. The objective of this systematic review and meta-analysis is to determine the effectiveness and safety of LLLT/photobiomodulation for DPN, in comparison with sham light, no treatment, or other active treatment, or as an additional treatment compared with another treatment alone.

Methods and analysis: We will search eight databases from their inception to July 2022. Randomized controlled trials (RCTs) will be included. Two reviewers will independently extract data using a structured data extraction method and assess the risk of bias in the included studies. Data will be synthesized using standardized mean difference (SMD) or risk ratio (RR) with 95% confidence intervals (CI) for continuous and dichotomous data, respectively. The primary outcome will be change in pain and secondary outcomes will include global symptom improvement, functional impairment and disability, impairment of sensation, quality of life, nerve conduction, as well as adverse events. Sensitivity and subgroup analysis will be employed to explore the influence of possible clinical and methodological characteristics. Publication bias will be assessed using funnel plot. We will conduct meta-analysis with RevMan 5.4 and evaluate quality of the evidence with GRADE approach.

Ethics and dissemination: This study doesn't require ethics approval. Our findings will be disseminated in the peer-reviewed publications.

Systematic review registration: submitted in PROSPERO ID: CRD42021276056

Keywords: low level laser therapy, photobiomodulation, diabetic peripheral neuropathy, pain, systematic review

Strengths and limitations of this study

- We will update the search to date to include more recent studies and will expand our search scope to Chinese language databases.
- We will evaluate more outcomes including pain, global symptom improvement, functional impairment and disability, impairment of sensation, quality of life, nerve conduction, as well as adverse events.
- We only search English and Chinese databases, but not other language databases, which may increase reporting bias.

INTRODUCTION

Diabetic peripheral neuropathy (DPN), one of the most common complications of

diabetes, strongly impact the quality of patients' life and capacity for work. It leads to foot ulcer in 50% diabetes, and even cause lower limb amputation. People with type 2 diabetes suffered more risks of DPN than type 1.[1] DPN is recognized by the damage of peripheral nerve, which commonly occur in lower limbs, and hands were occasionally affected. However, up to 50% of patients never experience symptoms, thus the diagnosis only can be made in accidental examination or until the foot ulcer appear. For patients who have already experienced symptoms, numbness, dryness, burning pain, needle-like pain and some other abnormal sensations are most frequently mentioned. [2]

Significant risk factors for DPN include diabetes duration, age and glycosylated hemoglobin.[3,4] Some other factors, including hypertension, hyperlipidaemia and obesity may also play a role at varying degrees. [5]

Other than improving glycemic control, there is no specific treatment for the underlying nerve damage. Enhanced glucose control can effectively prevent diabetic peripheral neuropathy in type 1 diabetes, whereas the evidence for the effect of glycemic control is not strong in type 2 diabetes.[6] What's more, enhanced glucose control can increase the risk of severe hypoglycemic episodes.[6] Some symptomatic therapies, such as pregabalin, duloxetine or gabapentin are recommended as first-line pharmacological treatment for relieving painful symptoms. Tricyclic antidepressants, venlafaxine, carbamazepine, opioids and topical capsaicin are also probably effective in relieving pain.[7,8] However, these drugs are accompanied with varies of adverse events, including dry mouth, sedation, dizziness, confusion, orthostatic hypotension, headache, nausea, constipation, diarrhea, etc.[9]

Non-pharmacological therapy, such as Low level laser therapy (LLLT), has also been used to treat DPN due to its function in alleviating pain[10] and improving lower limbs sensation[11,12]. LLLT, also known as photobiomodulation, has been in use from its invention in 1960s. The light used in LLLT is mainly in the red (wavelength of 600-700 nm) and near-infrared (NIR, wavelength of 780-1100 nm) region.[13,14] The red and NIR light is mostly absorbed by the mitochondrial enzyme (i.e., cytochrome-c-oxidase), the key chromophore in the cellular response to LLLT, to increase adenosine triphosphate (ATP) production, modulation of reactive oxygen species (ROS), and the induction of transcription factors. [13,14,15] The mid-IR (infrared) including carbon dioxide laser at wavelength of 10.6 μm and broad band IR source in the 10-50 μm are also reported as effective LLLT light, and they are considered to be absorbed by water in some nanostructured form possibly present in biological membranes.[13] On the tissue level, LLLT has been used to inhibit pain and pathological conditions associated with the nervous system. It exerts potent anti-inflammatory effects in the peripheral nervous system and promotes functional recovery and regeneration of peripheral nerves after injury, also in DPN.[14,16] The effect of LLLT is also closely related to the type of light, irradiation mode, power density and the properties of irradiated tissue.[13]

Although two systematic reviews have evaluated the effects of LLLT/photobiomudulation for DPN, [17, 18] they both included only a small number of

studies in English language, and one of them only provided qualitative description of the included studies. With some new and larger-sample size RCTs [19-22] published, it is important to conduct an update of the systematic review and meta-analysis of LLLT for DPN.

OBJECTIVE

The objective of this review is to determine the benefit of LLLT/photobiomodulation in relieving pain and global symptoms, improving nerve function as well as quality of life and its potential harm, in comparison to sham light, no treatment, or other active treatment, or as an additional treatment compared with another treatment alone in patients with DPN.

METHOD AND ANALYSIS

We will use standard methodological procedures following Cochrane Handbook.

- **Eligibility criteria for included studies**

Types of studies

We will include randomized controlled trials assessing the benefits and harms of LLLT/photobiomodulation for DPN. Trials with randomization of interventions taking place within individuals to different body parts (e.g., to the two legs) will also be included.

Types of population

We will include participants of any age and sex, with either form of diabetes, that were diagnosed to be DPN.

Types of intervention

LLLT/photobiomodulation utilizes non-ionizing forms of light sources, including lasers, LEDs, and broadband light, in the visible and infrared spectrum.[23] The commonly used lights in DPN may include red (wavelength of 780-1100 nm), NIR (wavelength of 780-1100 nm), mid-IR (e.g., 10.6μm) and broad band IR light in the 10-50 μm.[13] We will compare true LLLT versus sham LLLT, LLLT versus no specific treatment, LLLT versus other specific treatment, or LLLT plus another treatment (usually conventional treatment) versus another same treatment alone. In order to eliminate confounding effects, we will only include RCTs that used the same co-intervention in each group.

Types of outcome measures

Main outcome

The main outcome will be change in pain measured using a validated scale including visual analogue scale (VAS), numeric rating scale (NRS), Likert scale, or verbal description scale (VDS), etc.

Additional outcomes

1. Global symptom improvement measured by a validated instrument such as neuropathy symptom score (NSS), Michigan diabetic neuropathy score (MDNS) [24] or Toronto clinical scoring system (TCSS).[25] Where this continuous outcome was not available, the primary outcome will be an improvement of 30% or more in a validated clinical global symptom score.[26]

2. Change in functional impairment and disability by neuropathy impairment score (NIS) or neuropathy defects score (NDS) in the lower limbs.

3. Change in impairment of sensation in quantitative sensory testing (e.g., vibration perception threshold, thermal threshold and Semmes-Weinstein Monofilaments (SWM)).

4. Change in quality of life by SF-36 or NeurQol, etc.

5. Change in nerve conduction function measured by motor or sensory nerve conduction velocity (NCV), sensory nerve action potential (SNAP) or compound muscle action potential (CMAP).

6. Number of participants experiencing adverse events.

7. Serious adverse events.

The time point of follow-up will be at equal or less than 3 months (closest to 2 months) after randomization for short term and at more than 3 months (closest to 6 months) after randomization for long term.

- **Search methods for identification of studies**

We will search, with no time and language restrictions, the following databases for relevant literature: PubMed (MEDLINE), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science, as well as Chinese language databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database (VIP) and SinoMed. Two trial registries including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) will be also searched. The electronic database search will be supplemented by a manual search of the reference lists of included articles. The search strategy is shown in Appendix 1. The last search

date will be the date before the submission of the full review. The studies in Chinese language will be translated by JYW and checked by KC.

- **Data collection and analysis**

Study selection

At least one author (JYW or ZQH) will screen the title and abstract of all records identified by searching. We will obtain the full text of potentially relevant reports and two authors (JYW and ZQH) will independently review the full text to assess its eligibility. We will resolve disagreements by discussion. In case of disagreement, a third author (KC) will make the final decision on the study selection.

Data extraction and management

Two review authors (JYW and ZQH) independently will extract data concerning details of study population, intervention, and outcomes using a structured data extraction form and enter into Microsoft excel spreadsheet following the section 7.7 of Cochrane Handbook.[27] We will consult the other review author (KC) if there is any conflict.

If the publication did not report outcome data or the data was reported ambiguously, we will request the corresponding authors of the study to provide additional information or clarification by email.

Assessment of treatment adequacy

Two experts, who have a clinical or research experience of more than 5 years in LLLT/photobiomodulation therapy or in DPN treatment, and who have previously worked on RCTs or systematic reviews, will independently assess the adequacy of the light therapy and the control therapy in the trials. Five aspects of the light treatment will be assessed for adequacy: 1) selection of light (including wavelength, power density and energy density) 2) choice of irradiation location; 3) total number of sessions; 4) treatment duration; 5) treatment frequency. The validity of the sham intervention will also be assessed to using an open-ended question. The experts will be provided with only the part of each publication that describes the light and control procedures, so that their assessments cannot be influenced by the results of the trials. Discrepancies between the two experts will achieve consensus by discussion.

Assessment of risk of bias

Two review authors (JYW and ZQH) independently will assess the risk of bias in the studies that were included in this review according to the criteria described in the section 8.2.3 of Cochrane Handbook for Systematic Reviews of Interventions. [28] We will resolve conflicts by consulting the other review author (KC).

The items involve the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

Mean difference or standards mean difference with 95% CI will be used for continuous outcome and relative ratios (RR) with 95% CI will be used for dichotomous data. Data of studies that are sufficiently similar in terms of their comparisons and outcome measurements will be pooled. The data will be pooled by using random-effects model when studies are heterogeneous on clinical and methodological characteristics, and on the contrary, by using fixed-effect model when they are homogeneous. We will report the data separately if the study can't be combined. We will use mean difference (MD) for single trial comparisons and for RCTs that used same instrument to measure the same outcome. For the RCTs that assessed same outcome by various instruments, we will use standard mean difference (SMD). Analyses will be performed by intention to treat, where possible.

Unit of analysis issues

We will also include data from trials with different interventions being applied to different body parts, if the information is available. The analysis will be account for the pairing of parts within individuals in the same way that pairing of intervention periods in the crossover trial.[29] Continuous data from this kind of trial will be analyzed using one of the two approaches: use the results from paired analyses if reported in the original article; treat the study as a parallel trial and pool the interventional parts and compare these to the pooled control parts. Dichotomous outcomes for this kind of trial require more complicated analysis methods and we will consult with a statistician. [30]

Dealing with missing data

For the missing data, we will contact the original author. If it's failed to gather the missing data, we will discuss the potential impact of the dropout for the conclusion of the review.

Assessment of heterogeneity

We will use I^2 statistic to assess Statistical heterogeneity. If the I^2 value greater than 50%, we will conduct subgroups to explore the sources of heterogeneity.

Reporting bias

We will make a funnel plot to assess publication bias if the number of studies is more than 10.

Sensitivity analysis

We will perform sensitivity analysis excluding the trials with high risk of bias when data are adequate. For pooled analyses with continuous data, we will consider analyses based on change scores to be primary analysis, and analyses based on post-treatment scores to be sensitivity analysis.

Subgroup analysis

If we find sufficient number of RCTs, we will perform subgroup analyses according to:

1. type of diabetes (type 1 or type 2 diabetes mellitus)

2. type of light (red, infrared, or other)

3. dosage of light treatment: including power density, energy density, as well as duration and frequency of the treatment according to the assessment results of treatment adequacy by the experts.

Confidence in cumulative evidence

We will use GRADE system to assess the confidence of our evidence considering five criteria: study limitations, consistency of effect, imprecision, indirectness, and publication bias. We will conduct the assessment in terms of section 14.2 of Cochrane Handbook [31] by GRADEpro software.

DISCUSSION

Up to now, evidences for LLLT/photobiomudulation treating diabetic peripheral neuropathy are deficient. A 2017 systematic review focused on the infrared light for DPN.[18] The other more recent systematic review in 2019 studied LLLT for painful diabetic neuropathy.[17] Each of the two reviews included only six studies. Among the six studies included the 2019 review, three were non-RCTs, thus the 2019 review only narratively described the results of the individual study without conducting any meta-analysis or assessing risk of bias of the included studies. In addition, the conclusions of the two reviews were inconsistent with each other. That is, the 2017 review showed limited evidence of infrared phototherapy resulting in short-term improvement of tactile sensitivity, but not in neuropathic pain relief, whereas the 2019 review concluded LLLT is associated with a positive effect in relieving neuropathic pain.

Compared to the two previous reviews, we will update the search to date to include more recent studies and will expand our search scope to Chinese language databases to collect more evidences. Additionally, we will include more types of lights, not focusing only on infrared lights as in the 2017 review, since other than infrared light, visible lights are also used in clinic for DPN. In terms of the outcomes, the 2017 review [18] investigated plantar tactile sensitivity and pain; the 2019 review [17] focused on pain

and nerve conduction velocity. In additional to the aforementioned outcomes, we will also be concerned about global symptom improvement, functional impairment and disability, quality of life, as well as adverse events due to the therapy. Compared with the 2017 review [18] which performed subgroup analysis according to the type of comparison and length of follow-up, we will carry out subgroup analysis considering more on the differences in the populations and intervention characteristics (e.g., type of diabetes, type of light and dosage of therapy) according to the suggestion in Cochrane Handbook.[32]

The limitation of our review may be that we only search English and Chinese databases, but not other language databases, which may increase reporting bias.

In conclusion, our review will be an update of the topic by updating with new trials and sound methodology and thus will provide more rigorous and generalized evidence for the effectiveness and safety of LLLT/photobiomodulation in treating DPN.

List of abbreviations

CMAP: compound muscle action potential; DPN; diabetic peripheral neuropathy; LLLT: low level laser therapy; GRADE: grading of recommendations, assessment, development and evaluations; MDNS: Michigan diabetic neuropathy score; MNSI: Michigan neuropathy screening instrument; NCV: nerve conduction velocity; NDS: neuropathy defects score; NeuQoL: quality of life in neurological disorders; NIR: near- infrared; NIS: neuropathy impairment score; NRS: numeric rating scale; RCT: randomized controlled trial; SF-36: 36-item short-form health survey ; SNAP: sensory nerve action potential; TCSS: Toronto clinical scoring system; VAS: visual analogue scale; VDS: Likert scale, or verbal description scale.

DECLARE

Ethics and dissemination

This study doesn't require ethics approval. Our findings will be disseminated in the peer-reviewed publications.

Contributors

JYW: data acquisition and original draft writing; ZQH: clinical guidance, data acquisition and original draft writing; HPD: clinical guidance and draft revision; LZ: clinical guidance and draft revision; HYD: methodology support and draft revision; JPL: methodology support and revision of protocol and manuscript; XYS: topic conception, clinical guidance and revision of manuscript; KC: topic conception, protocol design, original draft writing and revision of manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author according to the institution guideline on materials and data transfer agreements.

Competing interests

Xueyong Shen and Ke Cheng have had a patent issued for a type of laser therapy apparatus simulating the infrared radiation spectrum of traditional Chinese moxibustion (China Invention Patent ZL 200910056991.4; issued December 1, 2010).

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Appendix 1. PubMed Search strategy

No	Item
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials as topic [mesh: noexp]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [mh] NOT humans [mh]
#10	#8 NOT #9
#11	diabetes mellitus [mh]
#12	diabet [tiab]
#13	#11 OR #12
#14	peripheral nervous system diseases[mh]
#15	#14 OR (neuropath OR polyneuropath)[tiab]
#16	#13 AND #15
#17	Diabetic Neuropathies[mh]
#18	#16 OR #17
#19	Low-Level Light Therapy [mh] OR photobiomodulation [mh]
#20	(Light Therapies, Low-Level OR Light Therapy, Low-Level OR Low Level Light Therapy OR Low-Level Light Therapies OR Therapies, Low-Level Light OR Therapy, Low-Level Light OR Photobiomodulation Therapy OR Photobiomodulation Therapies OR Therapies, Photobiomodulation OR Therapy, Photobiomodulation OR LLLT OR Laser Therapy, Low-Level OR Laser Therapies, Low-Level OR Laser Therapy, Low Level OR Low-Level Laser Therapies OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Laser Irradiation, Low Power OR Low-Power Laser Therapy OR Low Power Laser Therapy OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low Power OR Low-Power Laser Therapies OR Low-Level Laser Therapy OR Low Level Laser Therapy OR Low-Power Laser Irradiation OR Low Power Laser Irradiation OR Laser Biostimulation OR Biostimulation, Laser OR Laser Phototherapy OR Phototherapy, Laser) [tiab]
#21	#19 OR #20
#22	#10 AND #18 AND #21

[pt] denotes a publication type term;
[ti] denotes a word in the title;
[mh] denotes a Medical Subject Heading (MeSH) term (‘exploded’);
[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (‘exploded’)
[tiab] denotes a word in the title or abstract.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not amendments
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Low Level Light Therapy/Photobiomodulation for Diabetic Peripheral Neuropathy: Protocol of a Systematic Review and Meta-analysis

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Low Level Light Therapy/Photobiomodulation for Diabetic Peripheral Neuropathy: Protocol of a Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes that strongly impact the patients' quality of life and working ability. Evidence indicated that low level light therapy (LLLT)/photobiomodulation might be effective for neuropathy. However, the effect of LLLT for DPN is not clear. The objective of this systematic review and meta-analysis is to determine the effects and safety of LLLT/photobiomodulation for DPN, in comparison with other methods such as sham light, no treatment, other active treatment, and LLLT as an additional treatment compared with another treatment alone.

Methods and analysis: We will search eight databases from their inception to the date before the review submission. Randomized controlled trials (RCTs) will be included. Two reviewers will independently extract data using a structured data extraction method and assess the risk of bias in the included studies. Data will be synthesized using standardized mean difference (SMD) or risk ratio (RR) with 95% confidence intervals (CI) for continuous and dichotomous data, respectively. The primary outcome will be change in pain and secondary outcomes will include global symptom improvement, functional impairment and disability, impairment of sensation, quality of life, nerve conduction, as well as adverse events. Sensitivity and subgroup analysis will be employed to explore the influence of possible clinical and methodological characteristics. Publication bias will be assessed using funnel plot. We will conduct meta-analysis with RevMan 5.4 and evaluate quality of the evidence using GRADE approach.

Ethics and dissemination: This study does not require ethics approval. Our findings will be disseminated in the peer-reviewed publications.

Systematic review registration: submitted in PROSPERO ID: CRD42021276056

Keywords: low level light therapy, photobiomodulation, diabetic peripheral neuropathy, pain, systematic review

Strengths and limitations of this study

- The systematic review method in the protocol follows standard methodological procedures recommended in the Cochrane Handbook in terms of literature searching and screening, data collecting, risk of bias assessing and data synthesis.
- The reporting of the protocol follows the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols guidelines.
- This study will search eight databases and two trial registries without language restrictions.
- The main expected limitations are variations in light treatments and in outcome measures that may introduce heterogeneity or imprecision, which will influence the reliability of the evidence.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes and affects nearly 50% of adults with diabetes during their lifetime.[1] DPN strongly impacts the patients' quality of life and capacity for work. It leads to foot ulcer in 50% diabetes, and even cause lower limb amputation.[1] People with type 2 diabetes suffered higher risk of DPN than type 1.[1] DPN is recognized by damage to peripheral nerves, commonly occuring in the lower limbs and occasionally affecting the hands. However, up to 50% of patients never experience symptoms, thus diagnosis can only be made in accidental examination or until foot ulcers appear. For patients who have already experienced symptoms, numbness, dryness, burning pain, needle-like pain and some other abnormal sensations are most frequently mentioned. [2]

Significant risk factors for DPN include diabetes duration, age and glycosylated hemoglobin.[3,4] Some other factors, including hypertension, hyperlipidaemia and obesity may also play a role at varying degrees. [5]

Other than improving glycemic control, there is no specific treatment for the underlying nerve damage. Enhanced glucose control can effectively prevent DPN in type 1 diabetes, whereas the evidence for the effect of glycemic control is not strong in type 2 diabetes.[6] Furthermore, enhanced glucose control can increase the risk of severe hypoglycemic episodes.[6] Some symptomatic therapies, such as pregabalin, duloxetine or gabapentin are recommended as first-line pharmacological treatment for relieving painful symptoms. Tricyclic antidepressants, venlafaxine, carbamazepine, opioids and topical capsaicin are also probably effective in relieving pain. [7,8] However, these drugs are accompanied with a variety of adverse events, such as dry mouth, sedation, dizziness, confusion, orthostatic hypotension, headache, nausea, constipation, diarrhea, etc.[9]

Non-pharmacological therapy, such as low level light therapy (LLLT), has also been used to treat DPN due to its function in alleviating pain[10] and improving lower limbs sensation[11,12]. LLLT, also known as photobiomodulation, has been in use from its invention in 1960s. The light used in LLLT is mainly in the red (wavelength of 600-700 nm) and near-infrared (NIR, wavelength of 780-1100 nm) region. [13,14] The red and NIR light is mostly absorbed by the mitochondrial enzyme (i.e., cytochrome-c-oxidase), the key chromophore in the cellular response to LLLT, to increase adenosine triphosphate (ATP) production, modulation of reactive oxygen species (ROS), and the induction of transcription factors. [13,14,15] The mid-IR (infrared) including carbon dioxide laser at wavelength of 10.6 μm and broad band IR source in the 10-50 μm range are also reported as effective LLLT light. Mid-IR light is considered to be absorbed by water in some nanostructured form possibly present in biological membranes.[13] On the tissue level, LLLT has been used to inhibit pain and pathological conditions associated with the nervous system. It exerts potent anti-inflammatory effects in the peripheral nervous system and promotes functional recovery and regeneration of peripheral nerves after

injury, also in DPN. [14,16] The effect of LLLT depends on the type of light, irradiation mode, power density and the properties of irradiated tissue.[13]

Although two systematic reviews [17, 18] have evaluated the effects of LLLT/photobiomudulation for DPN, they both included only a small number of studies in published in English language. Furthermore, one [17] of them only provided qualitative description of the included studies. With some new and larger-sample size RCTs [19-22] published, it is important to conduct an updated systematic review and meta-analysis of LLLT for DPN.

OBJECTIVE

The objective of this review is to determine the benefit and harm of LLLT/photobiomodulation in comparison to sham light, no treatment, other active treatment, or as an additional treatment compared with another treatment alone in patients with DPN. The benefit will include its effect in relieving pain and global symptoms, as well as improving nerve function as well as quality of life.

METHODS AND ANALYSIS

We will use standard methodological procedures following the Cochrane Handbook. The planned start date of the study is July 2021 and end dates is December 2022.

Eligibility criteria for included studies

Types of studies

We will include randomized controlled trials assessing the benefits and harms of LLLT/photobiomodulation for DPN. Trials with randomization of interventions taking place within individuals to different body parts (e.g., to the two legs) will also be included.

Types of population

We will include participants of any age and sex, with either form of diabetes, that were diagnosed as DPN. Although many light therapies are focused on DPN with type 2 diabetes, there are also studies involving patients with type 1 diabetes. We believe the mechanisms of DPN from both types of diabetes are similar. Thus, we include patients with either form of diabetes.

Types of intervention

LLLT/photobiomodulation utilizes non-ionizing forms of light sources, including lasers, LEDs, and broadband light, in the visible and infrared spectrum.[23] The commonly used lights in DPN may include red (wavelength of 780-1100 nm), NIR (wavelength of 780-

1100 nm), mid-IR (e.g., 10.6μm) and broad band IR light in the 10-50 μm.[13] We will compare true LLLT versus sham LLLT, LLLT versus no specific treatment, LLLT versus other specific treatment, or LLLT plus another treatment (usually conventional treatment) versus another treatment only. In order to eliminate confounding effects, we will only include RCTs that used the same co-intervention in each group.

Types of outcome measures

Main outcome

The main outcome will be change in pain measured using a validated scale including visual analogue scale (VAS), numeric rating scale (NRS), Likert scale, or verbal description scale (VDS), etc.

Additional outcomes

1. Global symptom improvement measured by a validated instrument such as neuropathy symptom score (NSS), neuropathy total symptom score (NTSS), or total neuropathy score (TNS). [24-26], The DPN examintion scales such as Michigan neuropathy screening instrument (MNSI), Michigan diabetic neuropathy score (MDNS) and Toronto clinical scoring system (TCSS) will not be considered as validated instruments in evaluating DPN symtoms. Where this continuous outcome was not available, the primary outcome will be an improvement of 30% or more in a validated clinical global symptom score.[27]

2. Change in functional impairment and disability by neuropathy impairment score (NIS) or neuropathy defects score (NDS) in the lower limbs.

3. Change in impairment of sensation in quantitative sensory testing (e.g., vibration perception threshold, thermal threshold and Semmes-Weinstein Monofilaments (SWM)).

4. Change in quality of life by SF-36 or NeurQol, etc.

5. Change in nerve conduction function measured by motor or sensory nerve conduction velocity (NCV), sensory nerve action potential (SNAP) or compound muscle action potential (CMAP).

6. Number of participants experiencing adverse events.

7. Serious adverse events.

The time point of follow-up will be at equal or less than 3 months (closest to 2 months) after randomization for short term and at more than 3 months (closest to 6 months) after randomization for long term.

Search methods for identification of studies

We will search, with no time and language restrictions, the following databases for relevant literature: PubMed (MEDLINE), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science, as well as Chinese language databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database (VIP) and SinoMed. Furthermore, the search will also include the two trial registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) . The electronic database search will be supplemented by a manual search of the reference lists of included articles. The search strategy is illustrated in Appendix 1. The last search date will be the date before the submission of the full review. The studies in Chinese language will be translated by JYW and checked by KC.

Study selection

At least one author (JYW or ZQH) will screen the title and abstract of all records identified by searching. We will obtain the full text of potentially relevant reports and two authors (JYW and ZQH) will independently review the full text to assess its eligibility. We will resolve disagreements by discussion. In case of disagreement, a third author (KC) will make the final decision on the study selection.

Data extraction and management

Two review authors (JYW and ZQH) will independently extract data concerning details of study population, intervention, and outcomes using a structured data extraction form and enter it into a Microsoft excel spreadsheet following section 7.7 of Cochrane Handbook.[28] We will consult the other review author (KC) if there is any conflict.

If the publication did not report outcome data or the data was reported ambiguously, we will request the corresponding authors of the study to provide additional information or clarification by email.

Assessment of treatment adequacy

Two experts, who have a clinical or research experience of more than 5 years in LLLT/photobiomodulation therapy or in DPN treatment, and who have previously worked on RCTs or systematic reviews, will independently assess the adequacy of the light therapy and the control therapy in the trials. Five aspects of the light treatment will be assessed for adequacy: 1) selection of light (including wavelength, power density and energy density) 2) choice of irradiation location; 3) total number of sessions; 4) treatment duration; 5) treatment frequency. The validity of the sham intervention will also be assessed using an open-ended question. The experts will be provided with only the part of each publication that describes the light and control procedures, so that their assessments cannot be influenced by the results of the trials. Discrepancies between the

two experts will achieve consensus by discussion.

Assessment of risk of bias

Two review authors (JYW and ZQH) independently will assess the risk of bias in the studies that were included in this review according to the criteria described in the section 8.2.3 of Cochrane Handbook for Systematic Reviews of Interventions. [29] We will resolve conflicts by consulting the other review author (KC).

The items involve the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

Mean difference or standards mean difference with 95% CI will be used for continuous outcome and relative ratios (RR) with 95% CI will be used for dichotomous data. Data of studies that are sufficiently similar in terms of their comparisons and outcome measurements will be pooled. The data will be pooled by using random-effects model when studies are heterogeneous on clinical and methodological characteristics, and by using fixed-effect model when they are homogeneous. We will report the data separately if the study cannot be combined. We will use mean difference (MD) for single trial comparisons and for RCTs that used the same instrument to measure the same outcome. For the RCTs that assessed the same outcome by various instruments, we will use standard mean difference (SMD). Analyses will be performed by intention to treat, where possible.

Unit of analysis issues

We will also include data from trials with different interventions being applied to different body parts, if the information is available. The analysis will be account for the pairing of parts within individuals in the same way that pairing of intervention periods in the crossover trial.[30] Continuous data from this kind of trial will be analyzed using one of the two approaches: use the results from paired analyses if reported in the original article; treat the study as a parallel trial and pool the interventional parts and compare these to the pooled control parts. Dichotomous outcomes for this kind of trial require more complicated analysis methods and we will consult with a statistician. [31]

Dealing with missing data

For the missing data, we will contact the original author. If we fail to obtain the missing data, we will discuss the potential impact of the dropout for the conclusion of the review.

Assessment of heterogeneity

We will use I^2 statistic to assess statistical heterogeneity. If the I^2 value is greater than 50%, we will conduct subgroups to explore the sources of heterogeneity.

Reporting bias

We will make a funnel plot to assess publication bias if the number of studies is more than 10.

Sensitivity analysis

We will perform sensitivity analysis excluding the trials with high risk of bias when data are adequate. For pooled analyses with continuous data, we will consider analyses based on change scores to be the primary analysis, and analyses based on post-treatment scores to be sensitivity analysis.

Subgroup analysis

If we find sufficient number of RCTs, we will perform subgroup analyses according to:

1. Type of diabetes (type 1 or type 2 diabetes mellitus)

2. Type of light (red, infrared, or other)

3. Dosage of light treatment: including power density, energy density, as well as duration and frequency of the treatment according to the assessment results of treatment adequacy by the experts.

Confidence in cumulative evidence

We will use GRADE system to assess the confidence of our evidence considering five criteria: study limitations, consistency of effect, imprecision, indirectness, and publication bias. We will conduct the assessment in accordance with section 14.2 of the Cochrane Handbook [32] using GRADEpro software.

Patient and public involvement

No patient involved

DISCUSSION

Evidences for LLLT/photobiomudulation in treating diabetic peripheral neuropathy are deficient so far. A 2017 systematic review focused on using infrared light for DPN.[18] A more recent systematic review from 2019 studied LLLT for painful diabetic neuropathy.[17] Both reviews included only six studies each. Among the six studies

included the 2019 review, three were non-RCTs, thus the 2019 review only narratively described the results of the individual study without conducting any meta-analysis or assessing the risk of bias of the included studies. In addition, the conclusions of the two reviews were inconsistent with each other. The 2017 review showed limited evidence of infrared phototherapy resulting in short-term improvement of tactile sensitivity, but not in neuropathic pain relief. In contrast, the 2019 review concluded LLLT is associated with a positive effect in relieving neuropathic pain.

Compared to previous reviews, we will update the search to date to include more recent studies and will expand our search scope to Chinese language databases to collect more evidences. Furthermore, we will include more types of lights, not focusing only on infrared lights as in the 2017 review, since other than infrared light, visible lights are also used in clinic for DPN. In terms of the outcomes, the 2017 review [18] investigated plantar tactile sensitivity and pain; the 2019 review [17] focused on pain and nerve conduction velocity. In additional to the aforementioned outcomes, we will also be concerned about global symptom improvement, functional impairment and disability, quality of life, as well as adverse events due to the therapy. Compared with the 2017 review [18] which performed subgroup analysis according to the type of comparison and length of follow-up, we will carry out subgroup analysis focusing more on the differences in the populations and intervention characteristics (e.g., type of diabetes, type of light and dosage of therapy) according to the suggestion in the Cochrane Handbook.[33]

There are some expected limitations in this review. First, the heterogeneity in light treatment including different types of light, irradiation modes, power densities and sites of irradiation, may result in important heterogeneity in pooled results. Second, the global symptom outcome is usually assessed with composite measures and the measures vary among studies. This may introduce heterogeneity and render pooled estimates difficult to explain. Last, the variations in electrophysiologic measures and quantitative sensory testing among studies may result in only a limited number of studies that can be pooled for a certain outcome. This may influence the reliability of the evidence.

List of abbreviations

CMAP: compound muscle action potential; DPN; diabetic peripheral neuropathy; LLLT: low level light therapy; GRADE: grading of recommendations, assessment, development and evaluations; MDNS: Michigan diabetic neuropathy score; MNSI: Michigan neuropathy screening instrument; NCV: nerve conduction velocity; NDS: neuropathy defects score; NeuQoL: quality of life in neurological disorders; NIR: near- infrared; NIS: neuropathy impairment score; NRS: numeric rating scale; RCT: randomized controlled trial; SF-36: 36-item short-form health survey ; SNAP: sensory nerve action potential; TCSS: Toronto clinical scoring system; VAS: visual analogue scale; VDS: Likert scale, or verbal description scale.

DECLARE

Ethics and dissemination

This study does not require ethics approval. Our findings will be disseminated in peer-reviewed publications.

Contributors

JYW: data acquisition and original draft writing; ZQH: clinical guidance, data acquisition and original draft writing; HPD: clinical guidance and draft revision; LZ: clinical guidance and draft revision; HYD: methodology support and draft revision; JPL: methodology support and revision of protocol and manuscript; XYS: topic conception, clinical guidance and revision of manuscript; KC: topic conception, protocol design, original draft writing and revision of manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author according to the institution guideline on materials and data transfer agreements.

Competing interests

Xueyong Shen and Ke Cheng have had a patent issued for a type of laser therapy apparatus simulating the infrared radiation spectrum of traditional Chinese moxibustion (China Invention Patent ZL 200910056991.4; issued December 1, 2010).

Patient and Public Involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not applicable.

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PubMed search strategy

No	Item
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials as topic [mesh: noexp]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [mh] NOT humans [mh]
#10	#8 NOT #9
#11	diabetes mellitus [mh]
#12	Diabet* [tiab]
#13	#11 OR #12
#14	peripheral nervous system diseases[mh]
#15	#14 OR (neuropath* OR nervous)[tiab]
#16	#13 AND #15
#17	Low-level light therapy [mh]
#18	(Light Therapies OR Light Therapy OR Low Level Light Therapy OR
#19	Low-Level Light Therapies OR Laser Therapy, Low-Level OR Low-Level Laser Therapies OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Low-Power Laser Therapy OR Low Power Laser Therapy OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low Power OR Low-Power Laser OR LLLT OR biostimulation OR phototherapy OR photobiomodulation OR infrared OR photon stimulation) [tiab]
	#10 AND #16 AND #17

[pt] denotes a publication type term;
[ti] denotes a word in the title;
[mh] denotes a Medical Subject Heading (MeSH) term (‘exploded’);
[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (‘exploded’)
[tiab] denotes a word in the title or abstract.

Embase search strategy

#1 ’randomized controlled trial’/exp
#2 ’randomization’/exp
#3 ’double blind procedure’/exp
#4 ’single blind procedure’/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 ’animal’/exp OR ’animal experiment’/exp
#8 ’human’/exp

#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'diabetes mellitus'/exp
#34 Diabet*:ab,ti
#35 #33 OR #34
#36 'peripheral nervous system diseases'/exp
#37 neuropath*:ab,ti OR nervous:ab,ti
#38 #36 OR #37
#39 #35 AND #38
#40 'Low-Level Light Therapy'/exp
#41 (Light Therapies OR Light Therapy OR Low Level Light Therapy OR Low-Level Light Therapies OR Laser Therapy, Low-Level OR Low-Level Laser Therapies OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Low-Power Laser Therapy OR Low Power Laser Therapy OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low Power OR Low-Power Laser OR LLLT OR biostimulation OR phototherapy OR photobiomodulation OR infrared OR photon stimulation)*:ab,ti
#42 #40 OR #41
#43 #32 AND #39 AND #42

CENTRAL search strategy

#1MeSH descriptor diabetes mellitus explode all trees

#2(diabet*)
#3 (#1 or #2)
#4MeSH descriptor Peripheral Nervous System Diseases explode all trees
#5(neuropath* or nervous)
#6(#4 or #5)
#7(#3 and #6)
#8 MeSH descriptor: [Low-Level Light Therapy] explode all trees
#9 (Light Therapies OR Light Therapy OR Low Level Light Therapy OR Low-Level Light Therapies OR Laser Therapy, Low-Level OR Low-Level Laser Therapies OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Low-Power Laser Therapy OR Low Power Laser Therapy OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low Power OR Low-Power Laser OR LLLT OR biostimulation OR phototherapy OR photobiomodulation OR infrared OR photon stimulation)
#10 #8 and #9
#11 #7 and #10

Web of Science search strategy
#1 TS=(diabetes mellitus) OR TS=(diabet*)
#2 TS=(neuropath*) OR TS=(nervous)
#3 #2 AND #1
#4 TS=(Light Therapies OR Light Therapy OR Low Level Light Therapy OR Low-Level Light Therapies OR Laser Therapy, Low-Level OR Low-Level Laser Therapies OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Low-Power Laser Therapy OR Low Power Laser Therapy OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low Power OR Low-Power Laser OR LLLT OR biostimulation OR phototherapy OR photobiomodulation OR infrared OR photon stimulation)
#6 #4 AND #3

China National Knowledge Infrastructure (CNKI)
(((TKA='糖尿病') AND (TKA='周围神经病变'+'神经病变')) OR TKA='DPN') AND (TKA='激光'+'光疗'+'光调节'+'低能量激光'+'低强度激光'+'红外'+'红光'+'红外线')
TKA means title, keywod and abstract

WanFang databases
主题:(激光 or 光疗 or 光调节 or 低能量激光 or 低强度激光 or 红外 or 红光 or 红外线) and((主题:(糖尿病) and 主题:(周围神经病变 or 神经病变)) or 主题:(DPN))

Chinese Scientific Journal Database (VIP)
M=(激光 OR 光疗 OR 光调节 OR 低能量激光 OR 低强度激光 OR 红外 OR 红光 OR 红外线) AND((M=(糖尿病) AND M=(周围神经病变 OR 神经病变)) OR M=(DPN))

M means title or keyword

SinoMed

("激光"[常用字段:智能] OR "光疗"[常用字段:智能] OR "光调节"[常用字段:智能] OR "低能量激光"[常用字段:智能] OR "低强度激光"[常用字段:智能] OR "红外"[常用字段:智能] OR "红光"[常用字段:智能] OR "红外线"[常用字段:智能]) AND(("糖尿病"[常用字段:智能] AND("神经病变"[常用字段:智能] OR "周围神经病变"[常用字段:智能])) OR ("DPN"[常用字段:智能]))

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

(diabetic OR diabetes OR diabete) AND (Neuropathies OR Neuropathy) AND (Light Therapies OR Photobiomodulation OR laser OR LLLT)

World Health Organization International Clinical Trials Registry Platform

(diabetic OR diabetes) AND (neuropath)AND (Light Therapies OR Photobiomodulation OR OR laser OR LLLT)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not amendments
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.