Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

STUDY PROTOCOL

Investigating the Effectiveness of Electroacupuncture for Diabetic Peripheral Neuropathy and Exploring the Feasibility of Infrared Thermography as an Efficacy Assessment Tool: Study Protocol for a Randomized Controlled Trial

Ning Luo[1,*], Yi-Chen Zeng[1,*], Bai-Tian Fu[1], Je Wie Low[2], Jian-Qiao Fang[1]

[1]The Third Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [2]Institute of International Education of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jian-Qiao Fang, The Third Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China, Email fangjianqiao7532@163.com

Introduction: Diabetic peripheral neuropathy (DPN) affects patients' quality of life significantly. To date, selecting the appropriate treatment remains challenging. While electroacupuncture (EA) has shown promise as an effective adjunct therapy for DPN, and infrared thermography (IRT) has been considered as a potential predictor of treatment efficacy, the evidence for both remains inconclusive. As such, the objectives of this trial are twofold: to ascertain the efficacy of EA for DPN, and to explore the feasibility of IRT as an adjunctive objective tool for efficacy assessment.

Methods: The study was designed as a randomized, parallel, controlled trial. It spanned over 6 weeks of treatment and an additional 4 weeks of follow-up. 104 eligible participants will be stratified for severity of disease: mild with Toronto clinical scoring system(TCSS) score 6–8, moderate (TCSS score 9–11), and severe (TCSS score 12–19), and each level will be randomised in a 1:1 ratio into a EA group and waiting-list group. The waiting-list group received only the current conventional medication, while the EA group received an additional 12 EA sessions on top of the conventional medication. The primary outcome indicators is nerve conduction velocity (NCV), which will be tested at the baseline and week 6. Total clinical efficiency, TCSS, Clinical symptoms score of Traditional Chinese Medicine (TCM), Patient global impression of change(PGIC), Temperature of regions of interest (ROIs), and Physico chemical examination will be used as secondary outcome indicators. In addition, safety assessment will be determined based on adverse events during the trial.

Conclusion: The expected results of this study will determine whether EA improves efficacy in the treatment of DPN with an acceptable safety profile, and investigating variations in the efficacy of EA across different levels of DPN severity. Furthermore, it will explore the viability of IRT as an objective measure for evaluating treatment effectiveness for DPN.

Clinical Trial Registration: ClinicalTrials.gov identifier, NCT06054087.

Keywords: electroacupuncture, waiting-list, diabetic peripheral neuropathy, clinical trial, infrared thermography

Introduction

Epidemiologic surveys have identified diabetes as a major global health problem, with approximately 700 million people worldwide predicted to have diabetes by 2045,[1] and the prevalence of diabetes has increased significantly in China according to cross-sectional surveys.[2] The global prevalence of T2DM has significantly contributed to a corresponding

Received: 7 April 2024
Accepted: 16 August 2024
Published: 23 August 2024

epidemic of complications. Diabetic peripheral neuropathy (DPN), a prevalent chronic microvascular disorder linked to diabetes, affects over 50% of diabetics.[3] Symptoms include symmetrical numbness and pain resembling a glove and sock pattern, along with sensations of bloating and sweating. DPN also leads to muscle weakness, atrophy, gangrene, and other debilitating effects that significantly reduce the patient's quality of life.[4,5]

Management strategies for DPN currently include glycemic control, lifestyle modifications, and pharmaceutical interventions.[6] Nonetheless, the exact relationship between high blood sugar levels and the onset, advancement, and intensity of neuropathy is not fully understood.[7] Moreover, while tricyclic antidepressants, 5-hydroxytryptamine-norepinephrine reuptake inhibitors, and anticonvulsants are commonly recommended as first-line treatment,[8] they typically induce prolonged drug reliance and adverse reactions such as fatigue, somnolence, dizziness, and peripheral edema.[9,10] These factors contribute to the challenge of managing patients with DPN. Hence, there is an urgent need to pioneer new (combination) therapeutic approaches in order to optimize efficacy and safety.

As an integral component of Traditional Chinese Medicine (TCM), acupuncture has been extensively used internationally for the treatment of neuropathic pain.[11] Acupuncture alone[12,13] or in combination with appropriate adjunctive treatments[14] has demonstrated significant improving the quality of life of patients with DPN, accompanied by a faster onset of action and fewer side effects. However, as documented in meta-analyses, the duration and intensity of acupuncture treatment vary across studies, with many failing to clearly outline its anticipated effects and potential adverse events.[15,16] Moreover, there is a lack of randomized controlled trials (RCTs) examining the differential efficacy of acupuncture for the treatment of DPN across varying severity levels. Electroacupuncture (EA) is a cutting-edge approach that merges traditional acupuncture methods with modern technology to enhance stimulation and maximize therapeutic effects. Earlier studies have evinced that low-frequency EA[17] is more effective in ameliorating peripheral nerve function and local blood circulation, promoting nerve regeneration, and mitigating inflammatory responses.[14,18,19] Therefore, this study aims to evaluate the clinical efficacy of EA as a therapeutic intervention for DPN through a well-designed RCT employing a standardized approach. Moreover, the study also aims to investigate differences in the efficacy of different severity of DPN following EA intervention.

Existing evidence indicates that microangiopathy, metabolic dysfunction, oxidative stress, and a deficiency in nerve growth factor may contribute to the progression of DPN,[20,21] eventually impairing vasodilatory function and disrupting local blood flow in patients. Previous studies have identified that diabetic patients developing neuropathy have increased distal small-vessel blood flow,[22,23] impacting the skin temperature of their extremities.[24] Infrared thermography (IRT) is an innovative medical imaging technique that relies on infrared radiation emitted from the surface of an object to quantify and visualize temperature distribution.[25] It has the advantages of high sensitivity, outstanding visualization, and non-invasiveness and has been widely used in TCM and disease diagnosis.[26] Based on previous findings that epidermal temperature is positively correlated with DPN severity,[27] alterations in the epidermal temperature of extremities of patients with DPN will be examined before and after EA intervention to explore the correlation between temperature changes and efficacy, and to investigate the value of IRT as an objective tool for assessing treatment efficacy for DPN. If validated, this approach could quantify changes in blood flow induced by EA in DPN and offer a more objective and quantitative method of assessing treatment efficacy for DPN.

The primary objectives of this RCT were as follows: 1) To determine the efficacy of EA for the treatment of DPN compared with a waiting list control group while also investigating variations in the efficacy of EA across different levels of DPN severity. 2) To detect changes in the temperature of the extremities of DPN patients before and after EA treatment using IRT and to explore the viability of IRT as an objective measure for evaluating treatment effectiveness for DPN.

Methods and Design

Study Design

This study is a stratified multi-center RCT. The trial period is scheduled to occur between September 2023 and December 2025. Following eligibility verification, participants will be classified into three categories, namely mild DPN (scores 6–8), moderate DPN (scores 9–11), and severe DPN (scores 12–19)29 based on TCSS scores.[28] Subsequently, patients from each category will be randomly assigned to either the EA group or waiting list group at a 1:1 ratio. This study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[29] (as presented in the Supplementary File) and the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[30]

Study Procedure

The study will comprise a 6-week treatment period followed by a 4-week follow-up phase. The flow chart is illustrated in Figure 1, while a detailed schedule of enrollment, intervention, and outcome assessment is outlined in Table 1.

Participant Recruitment and Screening

The primary pool of participants for this study will consist of diabetic patients attending the Third Hospital, the Second Hospital, or the First Hospital affiliated with Zhejiang University of TCM. Additionally, eligible subjects also will be recruited through various channels, including newspapers, social media platforms, and posters.

Patients diagnosed with diabetes who express interest in participating in clinical are invited to undergo a comprehensive screening evaluation and eligibility appraisal. The eligibility of participants will be meticulously assessed by a proficient endocrinologist, utilizing predetermined criteria for inclusion and exclusion. Furthermore, a designated investigator for the recruitment of subjects will comprehensively explain the objectives of the study, as well as the potential risks and benefits, to prospective subjects, guaranteeing their complete comprehension prior to obtaining a signed informed consent form prior to trial initiation.

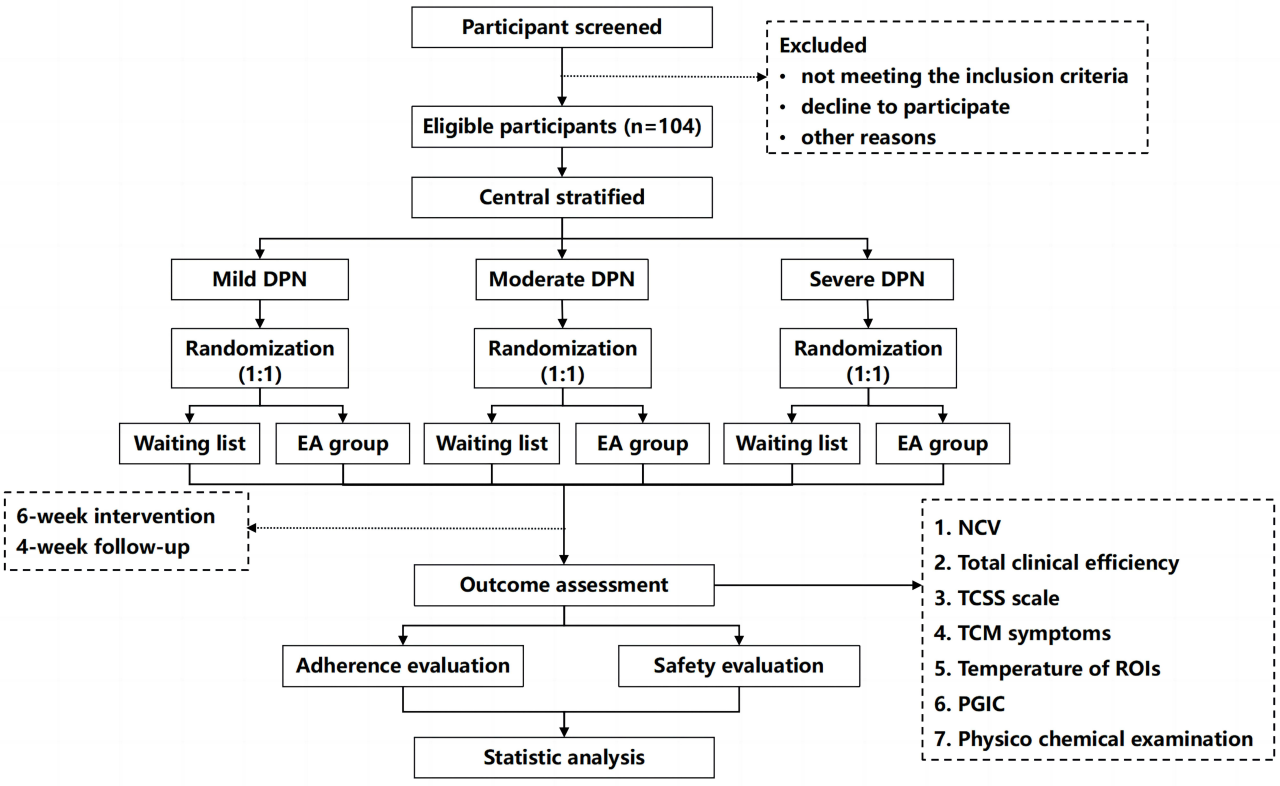

Figure 1 Flow chart of the study process.

Table 1 Schedule of Enrolment, Interventions and Outcome Assessments

	Baseline	Treatment Phase (6 Weeks)		Follow-Up (4 Weeks)
Time Point	**Week 0**	**Week 3 ± 7Days**	**Week 6 ± 7Days**	**Week 10 ± 7days**
Enrollment				
Demographic information	×			
Medical history and treatment history	×			
Determine diagnosis criteria	×			
Determine inclusion criteria	×			
Determine exclusion criteria	×			
Sign informed consents	×			
Interventions				
Waiting list				
EA treatment		×	×	
Outcome assessments				
1. NCV	×		×	
1. Total clinical efficiency		×	×	×
1. TCSS scale	×	×	×	×
1. TCM symptoms	×	×	×	×
1. Temperature of ROIs	×		×	
1. PGIC	×	×	×	×
1. Physico chemical examination				
HbA1c	×		×	
FPG, 2hPG	×	×	×	×
Other work				
Safety evaluation		×	×	
Adherence evaluation			×	
Combined medication	×			
Adverse event	×			
Processing data	×			
Researcher review	×			

Note: ×, required.

Abbreviations: EA, electroacupuncture; NCV, Nerve conduction velocity; TCSS, Toronto clinical neuropathy scoring system scale; TCM, Traditional Chinese Medicine; ROIs, Regions of interests; PGIC, Patient global impression of change; HbA1c, Hemoglobin A1c; FPG, Fasting plasma glucose; 2hPG, 2-hour postprandial blood glucose.

Inclusion Criteria

1. Meet the diagnostic criteria for DPN;[31]
   a. Diagnosed with diabetes according to the American Diabetes Association diagnostic criteria;[32]
   b. Presence of peripheral neuropathy at or after the diagnosis of diabetes mellitus;
   c. The presence of clinical symptoms consistent with DPN, such as pain, numbness, or abnormal sensation;
   d. Abnormalities in at least one of the five tests of ankle reflex, pinprick nociception, vibration sensation, stress sensation, and temperature sensation if clinical symptoms are present; or abnormalities in two or more of these five tests (ankle reflex, pinprick nociception, vibration sensation, stress sensation, and temperature sensation) in the absence of clinical symptoms; or decreased NCV in two or more lower extremity nerves as detected by electromyography;
   e. Rule out other potential causes of peripheral neuropathy.

1. Stable use of antidiabetic medication within the past 1 month;
2. Age between 18 ~ 85 years (regardless of gender);
3. Voluntary participation with a signed informed consent form.

Exclusion Criteria

1. Presence of other causes of peripheral neuropathy (eg hypothyroidism, alcohol, drugs, genetics, etc) and extremity ulcers;
2. Presence of serious physical conditions such as heart failure, myocardial infarction, cerebral infarction, cancer, severe mental illness, etc;
3. A history of lower extremity fracture or surgery within the past 3 months;
4. Receipt of acupuncture treatment for DPN within the past 3 months;
5. Pregnancy and lactation;
6. Presence of scars or hyperpigmentation at the test site that would affect the accuracy of the test;
7. Unwillingness to be randomly assigned to either the waiting list group or the EA group;
8. Chronic abuse of opioids, analgesics, illicit drugs, or alcohol;
9. Concurrent participation in other trials.

Participant Withdrawal Criteria

1. Non-compliance with treatment requirements or incomplete information leading to inability to assess treatment efficacy;
2. Occurrence of adverse events and serious complications necessitating trial suspension;
3. Lack of cooperation during treatment sessions;
4. Voluntary withdrawal from the study during the treatment period due to unwillingness to participate.

Stratified and Randomization

The severity of DPN in eligible participants will be evaluated using the TCSS scale, which categorizes individuals into three groups: mild DPN (score of 6–8), moderate DPN (score of 9–11), and severe DPN (score of 12–19). Patients in each group will then be randomly assigned to either the EA group or the waiting list group in a 1:1 ratio. The randomization process for this study was designed by an independent clinical evaluation center. The allocation of participants at each center will be carried out by an impartial administrator utilizing a designated account and password to access the Electronic Data Capture (EDC) system. This administrator will have no participation in other facets of the research. Upon inputting the patient's demographic details and DPN severity, the system will automatically assign the patient to either the electroacupuncture intervention or the waiting list group.

Blinding Method

This study will not implement blinding for acupuncture practitioners and patients owing to the unique characteristics of acupuncture practice and waiting list control. Nevertheless, to mitigate potential biases in the results, designated individuals will be engaged as outcome assessors and statisticians, ensuring that they remain unaware of group assignments.[33]

Interventions

All the enrolled patients will be randomly assigned to the EA group or the waiting list group through a central randomization system.

EA Group

Patients will undergo treatment with EA in addition to their current treatment regimen. The selected acupoints will include Yanglingquan (GB34), Zusanli (ST36), Xiajuxu (ST39), Xuanzhong (GB39), Yinlingquan (SP9), Sanyinjiao (SP6), Jiexi (ST41), Taichong (LR3), and Zulinqi (GB41) as primary points. Additional points, namely Kunlun (BL60),

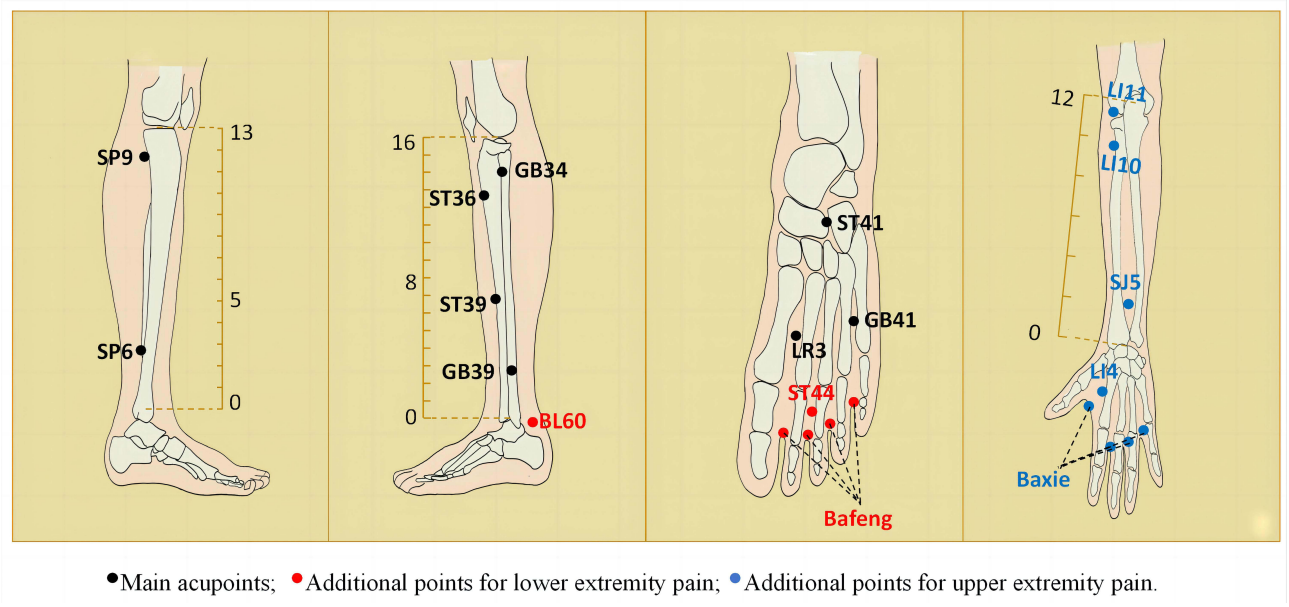

Figure 2 The location of used acupoints in the EA group.

Neiting (ST44), and Bafeng, will be added if pain in the lower limbs is significant. If accompanied by upper limb pain, the Quchi (LI11), Shousanli (LI10), Waiguan (SJ5), Hegu (LI4), and Baxie acupoints will be incorporated within the intervention. All acupoints will be located in accordance with the WHO Standard Acupuncture Locations, as displayed in Figure 2, with detailed information on their precise locations and the corresponding operations summarized in Table 2.

The patient will assume a supine position, and the designated site for needling will be sterilized with a 75% alcohol solution. Sterile, disposable, stainless steel needles of varying lengths and diameters (0.25 mm*40 mm/0.18 mm*25 mm) from Huatuo Medical Instruments Co. Ltd., Suzhou, China, will be utilized in the EA group. The depth of these needles

Table 2 Acupoints Used in the EA Group

Acupoints	Locations	Needle Insertion
Main points		
Yanglingquan (GB34)	The outer side of the calf, in the depression below the anterior aspect of the fibula head	Insert perpendicularly to a depth of 1.5–2 cun with manipulation for the de-qi
Zusanli (ST36)	3 cun below the patella, between the anterior tibia and the extensor digit rum longus muscle	Insert perpendicularly to a depth of 1.5–2 cun with manipulation for the de-qi
Xiajuxu (ST39)	The outer side of the calf, 3 cun below the patella, one transverse finger from the anterior border of the tibia	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Xuanzhong (GB39)	The outer side of the calf, 3 cun above the tip of the lateral ankle, anterior border of the fibula	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Yinlingquan (SP9)	On the medial side of the calf, at the depression between the lower margin of the medial tibial condyle and the medial margin of the tibial condyle	Insert perpendicularly to a depth of 1.5–2 cun with manipulation for the de-qi
Sanyinjiao (SP6)	On the medial side of the leg, 3 cun above the tip of the medial malleolus, posterior to the medial border of the tibia	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Jiexi (ST41)	In the central depression of the transverse stripe at the junction of the dorsum of the foot and the lower leg, between the tendons of the extensor hallucis longus and extensor digitorum longus	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi
Taichong (LR3)	Dorsum of the foot, the depression in front of the metatarsal joint of the first and second toes	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi

(*Continued*)

Table 2 (Continued).

Acupoints	Locations	Needle Insertion
Additional acupoints for lower limb pain		
Kunlun (BL60)	The depression between the tip of the ankle and the Achilles tendon, behind the ankle.	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi
Neiting (ST44)	Between the 2nd and 3rd toes on the dorsum of the foot, the junction of the red and white skin behind the toe web edge	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi
Bafeng	Dorsum of the foot, located between the 1st and 5th toes, the junction of the red and white skin behind the toe web edge, 4 points on one side, 8 points in total	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi
Additional acupoints for upper extremity pain		
Quchi (LI11)	At the elbow, the midpoint of the lateral end of the elbow transverse line and the upper tibia	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Shousanli (LI10)	Radial side of the forearm, 2 cun below the transverse line of the elbow	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Waiguan (SJ5)	Radial side of the forearm, 2 cun above the transverse line of the dorsal wrist, between the ulna and the radius	Insert perpendicularly to a depth of 1–1.5 cun with manipulation for the de-qi
Hegu (LI4)	Dorsum of the hand, between the first and second metacarpals, midpoint of the radial side of the second metacarpal	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi
Baxie	Dorsum of the hand, between the first and fifth fingers, the junction of the red and white skin behind the finger web edge, 4 points on one side, a total of 8 points	Insert perpendicularly to a depth of 0.5–0.8 cun with manipulation for the de-qi

will be adjusted to conform to the standard depth of each acupoint. Next, an even reinforcing-reducing technique, which consists of moderate lifting, jabbing, twisting, and turning, will be applied until the deqi sensation is elicited. Furthermore, EA will be administered to the bilateral ST36 and SP6 acupoints utilizing a Huatuo SDZ-IIB EA apparatus. The EA parameter will entail a dilute wave with 2 Hz, with a treatment duration of 30 minutes and a current intensity adjusted to guarantee the comfort of subjects. Treatment sessions will be performed 2 times per week, with a three to four-day interval between each session, totaling 12 sessions over the span of 6 weeks. A 4-week follow-up assessment will be performed after the completion of treatment.

Waiting List Group

Patients in the waiting-list group will not be subjected to acupuncture treatment during the 10-week observation period. After the end of the follow-up period, these patients will receive 12 EA treatment sessions free of charge, with the same treatment protocol as patients in the EA group, as compensation.

To ensure the integrity of the study, individuals in all the experimental groups will be prohibited from receiving alternative controlled treatments for DPN-related pain, including but not limited to electrical spinal cord stimulation, transcutaneous electrical nerve stimulation, laser therapy, herbal remedies, and psychotherapy, except for their current daily medications. However, participants are allowed to temporarily use pain medications as needed and are required to document their usage in a designated diary.

Infrared Thermography Assessment

The infrared thermography test will be conducted in a controlled environment, isolated from direct sunlight and air movement. The room temperature will be maintained at a comfortable level of approximately 25±1°C, while the air humidity will be maintained between 40% and 50%. Before the test, participants will be instructed to avoid strenuous physical activity for an hour. During the test, subjects will be instructed to relax, breathe naturally, and keep the area being tested still.

IRT Procedures

This study will utilize a NEC R450 infrared thermal imager from NEC AVIO, Japan. Participants will be instructed to expose their limbs and lie down for 15 minutes. The imager will be positioned at an appropriate height to ensure proper visibility and will capture photos of the soles of their feet on the bed, as well as the dorsum of feet, palms, and backs of hands while seated. A total of six images will be captured in each area, with one image captured every 10 seconds for one minute. The InfRec Analyzer NS9500 software will be used to store and analyze the infrared thermograms. The specific areas of filming and the scope of analysis are listed in Table 3.

Outcome Measures

Primary Outcomes

Changes in NCV: Changes in the MNCV and SNCV of the peroneal nerve and tibial nerve will be compared between the two groups prior to and following EA treatment. Measurement will be conducted at baseline and week 6.

Secondary Outcomes

a. Total clinical efficiency: According to the Guidelines for Clinical Research of New Chinese Medicines, changes in the clinical symptoms of the subjects will be comprehensively assessed and categorized into three grades: cured, effective, and invalid. See Supplementary Table 1 for specific scoring criteria. Measurement will be carried out at week 6.

1. Ultimately, the total clinical effectiveness of the two treatment arms will be calculated as follows: [(number of cured cases + number of effective cases)/total number of cases] * 100%.
2. TCSS score: The scale consists of symptom scores, reflex scores, and sensory test scores. The total score ranges from 0 (least severe) to 19 (most severe). The criteria are depicted in Supplementary Table 2. Measurement will be performed at baseline and weeks 3, 6, and 10.
3. Clinical symptoms score of TCM. The scale was developed based on the Guidelines for Clinical Research on New Chinese Medicines for the Treatment of Diabetes Mellitus and the Guide to Evidence-based Clinical Practice in Chinese Medicine for Diabetes Mellitus. The score ranges from 0 (least severe) to 45 (most severe) (see Supplementary Table 3). Measurements will be performed at baseline, followed by weeks 3, 6, and 10.
4. Temperature of ROIs. IRT will be applied to assess the temperature of ROIs, as previously described. The average temperature of the ROIs will be extracted and calculated using IRT and InfRec Analyzer NS9500 software, respectively. Measurements will be performed at baseline, week 6.
5. Patient global impression of change (PGIC). The PGIC scale assesses treatment effectiveness by measuring patients' self-reported recovery, serving as a subjective indicator of treatment efficacy. It consists of a 7-point score, where higher scores indicate poorer outcomes. A score of 1 signifies a significant improvement in treatment efficacy, while a score of 4 indicates no change before or after acupuncture treatment. Conversely, a score of 7 indicates a significant worsening of treatment efficacy. Measurement will be taken at baseline and weeks 3, 6, and 10.
6. Physicochemical examination. These will include changes in HbA1c (week 6), FPG, and 2hPG (weeks 3, 6, and 10) compared to the baseline levels.

Table 3 Specific Ranges Captured by IRT

Filming Area	Specific Scope
Soles	Areas other than toes, includes the anterior metatarsal area, lateral foot area, toe arch area, and heel area.
Dorsum of foot	Area from the toe-metatarsal joint to the transverse line of the ankle joint.
Palms	Area from the wrist stripes to the roots of the 2nd to 5th finger.
Dorsum of hand	Area from the dorsal stripe of the wrist to the root of the 2nd-5th finger.

Evaluation of Acupuncture Expectation and Compliance

A six-point method (0–5 points) will be utilized to assess acupuncture expectations prior to the first intervention. A higher score signifies a greater expectation of efficacy, whereas a lower score indicates a lack of belief in EA. Compliance will be evaluated at the end of week 6 using the following formula: Compliance Rate = (actual treatment times/total treatment times) * 100%.

Safety Evaluation

The safety assessment will rely on treatment-related adverse events, including information on their type, onset, duration, intensity, and outcome, which will be recorded in the CRF. Prompt and appropriate management will be provided to patients experiencing adverse events. Serious adverse events will be reported to the ethics committee.

Quality Control and Data Management

The study protocol underwent a thorough review and revision process by experts in the fields of acupuncture, endocrinology, and statistics. All relevant personnel will undergo comprehensive training on the study protocol and standard operating procedures. Acupuncture treatments will be administered by licensed acupuncturists with a minimum of 3 years of clinical experience.

To ensure consistency of the data, outcome assessors from each center will receive specialized training prior to data recording. The accuracy and consistency of the data will be verified by a quality control committee, which will address any inconsistencies through queries with researchers. Participant data will be securely stored in the EDC system, with exclusive access granted to data monitors. Additionally, the principal investigator and research team will address trial-related matters on a quarterly basis to discuss and determine optimal solutions.

Sample Size Estimation

The sample size was calculated based on the results of our preliminary study. Following 6 weeks of intervention, the SCV of the superficial peroneal nerve was 43.47±5.01 m/s in the EA group and 36.81±6.37 m/s in the waiting list group. Assuming a 10% increase in SCV after 6 weeks of EA intervention, EA was considered more effective than the waiting list group. By inputting the given values into the PASS 15, assuming anαof 0.05 and aβof 0.80, a sample size of 47 patients is needed for each group. Taking into account a 10% dropout rate, 52 patients will be finally included in each group, totaling 104 patients for the study.

Statistical Analysis Plan

Statistical analyses will be performed using SPSS 27.0 software, following the intention-to-treat (ITT) principle. Missing data resulting from participant dropout will be imputed with the last observed values before discontinuation.

Continuous variables following a normal distribution will be expressed as mean ± standard deviation. Differences in primary outcome indicators will be compared using the 2-tailed Student's *t*-test for independent samples. Data from repeated measures will be analyzed using repeated-measures analysis of variance (repeated measures ANOVA) to assess and compare changes in continuous variables within and between groups before and after the intervention and interactions between groups and time points. Additionally, adjusted analyses will be conducted, accounting for potential confounders such as age, gender, duration of diabetes, baseline severity of DPN, and treatment. Furthermore, subsequent to the classification of patients based on TCSS scores at baseline, subgroup analyses or logistic regression analyses will be conducted for all outcomes.

Variables following a non-normal distribution will be presented in medians and quartiles, and between- and within-group comparisons will be made using the Mann–Whitney *U*-test. Categorical variables will be expressed as frequencies and percentages and compared using the chi-square ($\chi 2$) test or Fisher's exact test, as appropriate.

Moreover, the correlation between alterations in the epidermal temperature of ROIs and the efficacy will be scrutinized using Spearman correlation or Partial correlation analysis. Adverse events will be compared between groups

using the $\chi 2$ test or Fisher's exact test. All statistical examinations will be implemented using a two-sided test, where a P value of ≤ 0.05 is regarded as indicative of a statistically significant variation.

Discussion

The prevalence of DPN has progressively increased along with the global prevalence of diabetes, posing a major health threat and socioeconomic burden in the 21st century. Clinical research positioned EA as a promising treatment option that has been shown to improve insulin sensitivity[34,35] and C-peptide levels, as well as lipid metabolism,[36] by modulating metabolic disorders, such as hyperglycemia,[37,38] obesity,[39] and inflammation.[40] Likewise, systematic reviews have corroborated the benefits of acupuncture in diabetic patients.[41,42] Indeed, most preclinical studies have shown that peripheral neuropathy function improves with electrical stimulation. However, there is insufficient research on this topic in humans to draw definitive conclusions.[43] Therefore, conducting evidence-based, high-quality RCTs is essential for assessing the effectiveness and safety of EA for the treatment of DPN.

The objective of this research is to assess the effectiveness of EA for managing DPN and to investigate the feasibility of IRT as an objective tool for assessing treatment efficacy for DPN. Various strategies will be employed to mitigate potential biases and imprecisions that could impact the accuracy of the results.

Firstly, complex interventions and methodological shortcomings observed in previous sham-controlled trials may have led to insufficient evidence regarding the effectiveness of acupuncture for treating DPN, thereby compromising its clinical application.[16,44] Therefore, it is reasonable to prioritize comparing the efficacy of EA in combination with conventional drug therapy versus conventional drug therapy alone to elucidate the effect of EA on DPN. Secondly, participants will be recruited from multiple centers and randomly assigned to the EA or waiting list group at a 1:1 ratio, thus mitigating selection bias. Furthermore, the implementation of stratified randomization techniques will be applied for the first time in a clinical study on the therapeutic efficacy of EA for DPN. Indeed, this approach guarantees that both cohorts will exhibit comparable characteristics at baseline, thus avoiding any potential bias in the study results that might arise from the use of a completely randomized allocation method. Finally, a standardized outcome assessment will be implemented to enhance imprecision. For instance, this study will include a higher number of objective outcome indicators such as NCV, the temperature of ROIs, and related physicochemical indicators, while the use of TCM evidence scales, which integrates TCM evidence with modern medicine, enhances the objectivity of TCM evidence quantification. The use of other scales, including the TCSS score, PGIC, and overall effectiveness, reduces the likelihood of measurement error associated with a single scale. Outcome assessors will undergo uniform training prior to the trial and will remain blinded to subgroup allocation, which minimizes inter-assessor variation.

Moreover, to the best of our knowledge, this clinical trial constitutes the first study utilizing IRT as an outcome measure in research focused on EA for DPN, distinguishing it from previous trials. The onset of DPN frequently results in altered blood circulation in the extremities, which may drive changes in ROIs. Notably, regional temperature collected by IRT has been identified as an early predictor of DPN. Specifically, foot regional temperature in DPN patients is higher than that in diabetic patients and healthy volunteers and is positively correlated with DPN severity.[45,46] Based on the previous findings, the present study hypothesizes a strong correlation between regional temperature and the severity of DPN and that IRT is a valuable tool for objectively evaluating the efficacy of EA for the treatment of DPN. Consequently, the use of regional temperature data collected via IRT as an objective outcome indicator in this study not only validates the possibility of IRT as an early prediction tool for DPN but may also further offer an objective strategy to evaluate treatment efficacy.

Taken together, the aforementioned measures in this study design will assist in minimizing the risk of bias and imprecision, resulting in a more reliable assessment of the efficacy of EA for DPN. However, it is crucial to acknowledge that bias cannot be completely eliminated from any study. Therefore, the findings of this study should be interpreted with caution and corroborated by future research.

This trial has several unavoidable limitations. Firstly, due to constraints in research time and funding, a sham EA group will not be established, potentially allowing for the placebo effect of EA to influence outcomes. However, it is universally recognized that placebo effects contribute to the overall therapeutic efficacy of EA. Secondly, while this study attempted to limit the effects of exogenous and endogenous factors on epidermal temperature by controlling the ambient

conditions and requiring patients to rest sufficiently before the test, the possibility of errors using this testing technique cannot be excluded. Notwithstanding, to mitigate potential measurement inaccuracies, rigorous training will be provided to testers prior to formal testing. Lastly, as an open-label trial, the inability to implement double-blinding may introduce bias and compromise our results. Nonetheless, the use of NCV as the primary objective outcome indicator will partially limit this bias.

Conclusions

In summary, this study will provide high-quality clinical evidence for the use of EA in the treatment of DPN, clarifies the actual efficacy of EA, and promote its clinical application. In addition, the correlation between regional temperature and efficacy will be explored, to determine whether IRT can be used as an objective tool for assessing treatment efficacy. These findings will serve as a valuable reference for future studies in this field.

Trial Status

The study is ongoing. Patient recruitment began in October 2023 and is expected to be completed by the end of 2025.

Data Sharing Statement

The results of this clinical trial will be shared through scientific articles and academic conferences. All data are available by contacting the corresponding author.

Ethics Approval and Consent to Participate

This clinical trial will adhere to the Declaration of Helsinki guidelines during its implementation and ethics approval has been obtained from the Institutional Ethical Review Board of the Third Affiliated Hospital of Zhejiang University of TCM (number ZSLL-KY-2023-004-02-01), the Second Affiliated Hospital of Zhejiang University of TCM (number 2023-061-01), and the First Affiliated Hospital of Zhejiang University of TCM (number 2023-KL-337-01). The participants provided their written informed consent to participate in this study. The findings will be disseminated in a peer-reviewed journal.

Acknowledgments

The authors would like to thank all participants for their collaboration. All the claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The trial was supported by the Major Project of Science and Technology Plan between the Department of Science and Technology of the State Administration of TCM and the Zhejiang Provincial Administration of TCM (No. GZY-ZJ-KJ -23021).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

References

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9(th) edition. *Diabet Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843
2. Li Y, Teng D, Shi X, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American diabetes association: national cross sectional study. *BMJ*. 2020;369:m997. doi:10.1136/bmj.m997
3. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American diabetes association. *Diabetes Care*. 2017;40(1):136–154. doi:10.2337/dc16-2042
4. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol*. 2012;11(6):521–534. doi:10.1016/S1474-4422(12)70065-0
5. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5(1):42. doi:10.1038/s41572-019-0097-9
6. Ang L, Cowdin N, Mizokami-Stout K, Pop-Busui R. Update on the management of diabetic neuropathy. *Diabetes Spectr*. 2018;31(3):224–233. doi:10.2337/ds18-0036
7. Calcutt NA. Diabetic neuropathy and neuropathic pain: a (con)fusion of pathogenic mechanisms? *Pain*. 2020;161(Suppl 1):S65–86. doi:10.1097/j.pain.0000000000001922
8. Khdour MR. Treatment of diabetic peripheral neuropathy: a review. *J Pharm Pharmacol*. 2020;72(7):863–872. doi:10.1111/jphp.13241
9. Hor CP, Fung WY, Ang HA, et al. Efficacy of oral mixed tocotrienols in diabetic peripheral neuropathy: a randomized clinical trial. *JAMA Neurol*. 2018;75(4):444–452. doi:10.1001/jamaneurol.2017.4609
10. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care*. 2012;35(12):2451–2458. doi:10.2337/dc12-0656
11. Kim S, Zhang X, O'Buckley SC, Cooter M, Park JJ, Nackley AG. Acupuncture resolves persistent pain and neuroinflammation in a mouse model of chronic overlapping pain conditions. *J Pain*. 2018;19(12):1381–1384. doi:10.1016/j.jpain.2018.05.013
12. Cho E, Kim W. Effect of acupuncture on diabetic neuropathy: a narrative review. *Int J Mol Sci*. 2021;22(16). doi:10.3390/ijms22168575
13. Lin T, Huang F, Zhao S, Qiu M, Wen J, Liu M. Acupuncture for diabetic peripheral neuropathy: an overview of systematic reviews. *Complement Ther Clin Pract*. 2021;43:101375. doi:10.1016/j.ctcp.2021.101375
14. Wang Z, Hou Y, Huang Y, Ju F, Liang Z, Li S. Clinical efficacy and safety of electro-acupuncture combined with beraprost sodium and α-lipoic acid for diabetic peripheral neuropathy. *Am J Transl Res*. 2022;14(1):612–622.
15. Zhou L, Wu T, Zhong Z, Yi L, Li Y. Acupuncture for painful diabetic peripheral neuropathy: a systematic review and meta-analysis. *Front Neurol*. 2023;14:1281485. doi:10.3389/fneur.2023.1281485
16. Yu B, Li M, Huang H, et al. Acupuncture treatment of diabetic peripheral neuropathy: an overview of systematic reviews. *J Clin Pharm Ther*. 2021;46(3):585–598. doi:10.1111/jcpt.13351
17. He XF, Wei JJ, Shou SY, Fang JQ, Jiang YL. Effects of electroacupuncture at 2 and 100 hz on rat type 2 diabetic neuropathic pain and hyperalgesia-related protein expression in the dorsal root ganglion. *J Zhejiang Univ Sci B*. 2017;18(3):239–248. doi:10.1631/jzus.B1600247
18. Wang X, Li Q, Han X, Gong M, Yu Z, Xu B. Electroacupuncture alleviates diabetic peripheral neuropathy by regulating glycolipid-related glo/ages/rage axis. *Front Endocrinol*. 2021;12:655591. doi:10.3389/fendo.2021.655591
19. Yu X, Chen X, Liu W, Jiang M, Wang Z, Tao J. Proteomics analysis of the spinal dorsal horn in diabetic painful neuropathy rats with electroacupuncture treatment. *Front Endocrinol*. 2021;12:608183. doi:10.3389/fendo.2021.608183
20. Tentolouris A, Eleftheriadou I, Tzeravini E, et al. Endothelium as a therapeutic target in diabetes mellitus: from basic mechanisms to clinical practice. *Curr Med Chem*. 2020;27(7):1089–1131. doi:10.2174/0929867326666190119154152
21. Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia*. 2001;44(11):1973–1988. doi:10.1007/s001250100001
22. Kim SW, Kim SC, Nam KC, Kang ES, Im JJ, Kim DW. A new method of screening for diabetic neuropathy using laser Doppler and photoplethysmography. *Med Biol Eng Comput*. 2008;46(1):61–67. doi:10.1007/s11517-007-0257-z
23. Zhou Q, Qian Z, Yang M, et al. Alterations in plantar vessel blood flow in patients with mild diabetic peripheral neuropathy. *BMJ Open Diabetes Res Care*. 2022;10(1):e002492. doi:10.1136/bmjdrc-2021-002492
24. Zhou Q, Qian Z, Wu J, Liu J, Ren L, Ren L. Early diagnosis of diabetic peripheral neuropathy based on infrared thermal imaging technology. *Diabetes Metab Res Rev*. 2021;37(7):e3429. doi:10.1002/dmrr.3429
25. Tattersall GJ. Infrared thermography: a non-invasive window into thermal physiology. *Comp Biochem Physiol a Mol Integr Physiol*. 2016;202:78–98. doi:10.1016/j.cbpa.2016.02.022
26. Li X, Jiang Y, Hu H, et al. The moxibustion-induced thermal transport effect between the heart and lung meridians with infrared thermography. *Front Cardiovasc Med*. 2022;9:817901. doi:10.3389/fcvm.2022.817901
27. Deng F, Tang Q, Jiang M, Zhong N, Liu G. Infrared thermal imaging and Doppler vessel pressurization ultrasonography to detect lower extremity deep vein thrombosis: diagnostic accuracy study. *Clin Respir J*. 2018;12(3):1118–1124. doi:10.1111/crj.12639
28. Dyck PJ, Albers JW, Andersen H, et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab Res Rev*. 2011;27(7):620–628. doi:10.1002/dmrr.1226
29. Chan AW, Tetzlaff JM, Altman DG, et al. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200–207. doi:10.7326/0003-4819-158-3-201302050-00583
30. Macpherson H, Altman DG, Hammerschlag R, et al. Revised standards for reporting interventions in clinical trials of acupuncture (stricta): extending the consort statement. *Plos Med*. 2010;7(6):e1000261. doi:10.1371/journal.pmed.1000261
31. Iqbal Z, Azmi S, Yadav R, et al. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. *Clin Ther*. 2018;40(6):828–849. doi:10.1016/j.clinthera.2018.04.001
32. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15–33. doi:10.2337/dc21-S002
33. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can J Surg*. 2010;53(5):345–348.

34. Firouzjaei A, Li GC, Wang N, Liu WX, Zhu BM. Comparative evaluation of the therapeutic effect of metformin monotherapy with metformin and acupuncture combined therapy on weight loss and insulin sensitivity in diabetic patients. *Nutr Diabetes*. 2016;6(5):e209. doi:10.1038/nutd.2016.16
35. Chang SL, Lin KJ, Lin RT, Hung PH, Lin JG, Cheng JT. Enhanced insulin sensitivity using electroacupuncture on bilateral zusanli acupoints (st 36) in rats. *Life Sci*. 2006;79(10):967–971. doi:10.1016/j.lfs.2006.05.005
36. Liang F, Koya D. Acupuncture: is it effective for treatment of insulin resistance? *Diabetes Obes Metab*. 2010;12(7):555–569. doi:10.1111/j.1463-1326.2009.01192.x
37. Cheok YC, Mohd SZ, Chan YM, Ng OC, Lee PY. Effectiveness of acupuncture as adjunctive therapy in type 2 diabetic: study protocol for a randomized controlled trial. *PLoS One*. 2023;18(9):e284337. doi:10.1371/journal.pone.0284337
38. Peplow PV, Baxter GD. Electroacupuncture for control of blood glucose in diabetes: literature review. *J Acupunct Meridian Stud*. 2012;5(1):1–10. doi:10.1016/j.jams.2011.11.018
39. Zhang K, Zhou S, Wang C, Xu H, Zhang L. Acupuncture on obesity: clinical evidence and possible neuroendocrine mechanisms. *Evid Based Complement Alternat Med*. 2018;2018:6409389. doi:10.1155/2018/6409389
40. Wei Y, Dong M, Zhang H, et al. Acupuncture attenuated inflammation and inhibited th17 and treg activity in experimental asthma. *Evid Based Complement Alternat Med*. 2015;2015:340126. doi:10.1155/2015/340126
41. Dimitrova A, Murchison C, Oken B. Acupuncture for the treatment of peripheral neuropathy: a systematic review and meta-analysis. *J Altern Complement Med*. 2017;23(3):164–179. doi:10.1089/acm.2016.0155
42. Yang M, Li X, Liu S, et al. Meta-analysis of acupuncture for relieving non-organic dyspeptic symptoms suggestive of diabetic gastroparesis. *Bmc Complement Altern Med*. 2013;13:311. doi:10.1186/1472-6882-13-311
43. Chiaramonte R, Pavone V, Testa G, et al. The role of physical exercise and rehabilitative implications in the process of nerve repair in peripheral neuropathies: a systematic review. *Diagnostics (Basel)*. 2023;13(3). doi:10.3390/diagnostics13030364
44. Ju ZY, Wang K, Cui HS, et al. Acupuncture for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;12(12):CD12057. doi:10.1002/14651858.CD012057.pub2
45. Papanas N, Papatheodorou K, Papazoglou D, Monastiriotis C, Maltezos E. Foot temperature in type 2 diabetic patients with or without peripheral neuropathy. *Exp Clin Endocrinol Diabetes*. 2009;117(1):44–47. doi:10.1055/s-2008-1081498
46. Balbinot LF, Canani LH, Robinson CC, Achaval M, Zaro MA. Plantar thermography is useful in the early diagnosis of diabetic neuropathy. *Clinics*. 2012;67(12):1419–1425. doi:10.6061/clinics/2012(12)12