

Lymphovenous Bypass as an Adjunct to Standard Care for Diabetic Peripheral Neuropathy: Protocol for a Randomized, Assessor-Blinded Superiority Trial

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is a length-dependent, symmetric sensorimotor polyneuropathy with substantial global and regional burden. Current pharmacologic options are largely symptomatic and do not modify disease. Lymphovenous bypass (LVB), a supermicrosurgical procedure established for lymphedema, may modulate lymphatic-immune-microvascular dysfunction relevant to DPN

Objective: The primary objective is to determine whether lymphovenous bypass (LVB) combined with standard of care (SOC) improves small-fiber and autonomic function compared with SOC alone at 6 months. Secondary objectives are to evaluate the effects of LVB on large-fiber function, neuropathic pain, ulcer healing, quality of life, and relevant biomarkers, as well as to characterize its safety profile.

Methods: SPIRIT-aligned, single-center, randomized, controlled, parallel-group superiority trial with 2:1 allocation (LVB+SOC:SOC), stratified by ulcer status. Outcome assessors and statisticians are blinded. Primary endpoint is change in pain (DN4) and DPN burden (MNSI), at 6 and 12 months. Key secondary endpoints include foot electrochemical skin conductance (ESC, μ S; Sudoscan), nerve conduction studies (NCS), and ulcer outcomes (time to epithelialization; proportion healed by 20 weeks; infection; reoperation; amputation). Exploratory endpoints include oxidative stress/antioxidant indices, inflammatory cytokines, and intraepidermal nerve fiber density (IENFD). N = 60 (LVB n = 40; SOC n = 20) provides 80% power ($\alpha = 0.05$) to detect a conservative between-group ESC effect (Cohen's $d \geq 0.70$).

Results: Recruitment is planned for September 1, 2025–July 31, 2026; follow-up through July 31, 2027. No outcome data are included.

Conclusions: This trial tests a mechanism-based, non-pharmacologic adjunct targeting lymphatic-immune-microvascular dysfunction in DPN. If effective, LVB could inform phenotype-directed treatment algorithms and motivate multicenter evaluation and health-economic analyses. Clinical Trial: NCT07126197

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Original Manuscript

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Keywords: diabetic peripheral neuropathy; diabetic foot ulcer; lymphovenous bypass; diabetic peripheral neuropathy pain

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is a length-dependent, symmetric sensorimotor polyneuropathy with substantial global and regional burden. Current pharmacologic options are largely symptomatic and do not modify disease. Lymphovenous bypass (LVB), a supermicrosurgical procedure established for lymphedema, may modulate lymphatic-immune-microvascular dysfunction relevant to DPN.

Objective: The primary objective is to determine whether lymphovenous bypass (LVB) combined with standard of care (SOC) improves small-fiber and autonomic function compared with SOC alone at 6 months. Secondary objectives are to evaluate the effects of LVB on large-fiber function, neuropathic pain, ulcer healing, quality of life, and relevant biomarkers, as well as to characterize its safety profile.

Methods: SPIRIT-aligned, single-center, randomized, controlled, parallel-group superiority trial with 2:1 allocation (LVB+SOC:SOC), stratified by ulcer status. Outcome assessors and statisticians are blinded. Primary endpoint is change in pain (DN4) and DPN burden (MNSI), at 6 and 12 months. Key secondary endpoints include foot electrochemical skin conductance (ESC, μS ; SudoScan), nerve conduction studies (NCS), and ulcer outcomes (time to epithelialization; proportion healed by 20 weeks; infection; reoperation; amputation). Exploratory endpoints include oxidative stress/antioxidant indices, inflammatory cytokines, and intraepidermal nerve fiber density (IENFD). $N = 60$ (LVB $n = 40$; SOC $n = 20$) provides 80% power ($\alpha = 0.05$) to detect a conservative between-group ESC effect (Cohen's $d \approx 0.70$).

Results: Recruitment is planned for September 1, 2025–July 31, 2026; follow-up through July 31, 2027. No outcome data are included.

Conclusions: This trial tests a mechanism-based, non-pharmacologic adjunct targeting lymphatic-immune-microvascular dysfunction in DPN. If effective, LVB could inform phenotype-directed treatment algorithms and motivate multicenter evaluation and health-economic analyses.

Trial Registration: NCT07126197

1 Introduction

1.1 Background

Diabetic peripheral neuropathy (DPN) is a pervasive and debilitating complication of diabetes, causing significant morbidity and a heightened risk of foot ulcers and amputation.[1–5] Its prevalence in Taiwan and regionally is estimated to be between 28.5% and 36.3%.[6–8] Consensus frameworks integrate staged clinical definitions with multimodal diagnostics: symptom scales (DN4, ID-Pain, BPI-DPN), bedside sensory testing, autonomic/small-fiber assessments (Sudocan ESC, Neuropad/QSART), corneal confocal microscopy, quantitative sensory testing, and electrodiagnostics (NCV/EMG).[9–12] Despite optimized metabolic care, above 40% of patients may progress over 5 years.[5] Analgesics (e.g., pregabalin, duloxetine) alleviate painful DPN but do not reverse neuropathy; TCAs warrant caution and opioids are not first-line.[13,14] Emerging agents such as GLP-1 receptor agonists show preliminary structural neural benefits but require validation.[15]

Beyond fluid homeostasis, the lymphatic system regulates immune trafficking and inflammatory signaling, with lymphatic-cardiovascular cross-talk implicated in metabolic disease and tissue repair.[16,17] Lymphovenous bypass (LVB) (≤ 0.8 -mm anastomoses) is established for lymphedema and has been associated with immunologic rebalancing, reduced oxidative stress, transcriptomic normalization, and improved wound states.[18–23] Our preliminary case (Charcot neuro-osteoarthropathy with chronic plantar ulcer) treated with LVB plus wound care demonstrated durable healing without amputation and limb-specific neurophysiologic improvement despite suboptimal glycemic control, supporting a mechanistic and clinical rationale for trial testing.

1.2 Aim of the study

The aim of this study is to evaluate whether lymphovenous bypass (LVB) combined with standard of care (SOC) provides superior outcomes compared with SOC alone in patients with diabetic peripheral neuropathy (DPN). We hypothesize that restoration of lymphatic–venous drainage and modulation of inflammatory and oxidative pathways will enhance small-fiber and autonomic function, reduce neuropathic pain, and accelerate ulcer healing when present. To test this hypothesis, changes in neuropathic pain and overall neuropathy burden will be assessed at 6 and 12 months, supported by physiologic measures of small- and large-fiber function and autonomic integrity. In participants with ulcers, the impact on wound repair will be examined through time to complete epithelialization, healing rates, and complication profiles. Mechanistic insights will be explored through biomarkers of oxidative stress, immune modulation, and intraepidermal nerve fiber density (IENFD), while safety assessments will ensure the tolerability of the intervention.

2 Methods

2.1 Design and Setting

This study is a SPIRIT-compliant, single-center, randomized, controlled, parallel-group superiority trial with a 2:1 allocation ratio (LVB plus standard of care [SOC] vs SOC alone), stratified by ulcer status. Outcome assessors, including Sudoscan and nerve conduction study technicians, as well as statisticians, will remain blinded to group assignment. The trial will be conducted within the National Taiwan University Hospital (NTUH) system, encompassing both outpatient and inpatient wound care and diabetes clinics.

2.2 Recruitment and Eligibility

Participant recruitment will take place from September 1, 2025, to July 31, 2026, with each participant followed for 12 months. Eligible individuals will be adults aged 20–80 years with clinically and electrodiagnostically confirmed diabetic peripheral neuropathy (DPN) after exclusion of non-diabetic causes, with or without diabetic foot ulcers as defined by the International Working Group on the Diabetic Foot (IWGDF) and Infectious Diseases Society of America (IDSA). Participants must be able to comply with study procedures and provide written informed consent, with optional consent for biospecimen collection. Key exclusion criteria include autoimmune disease or systemic immunosuppression; clinically significant organ failure (cardiac, pulmonary, renal, or hepatic); Ankle-Brachial Index less than 0.9; baseline infection requiring at least forefoot amputation; significant cognitive impairment; pregnancy; contraindications to anesthesia or surgery; and known hypersensitivity to blue dyes, including Patent Blue V or Indocyanine green. Recruitment will be conducted through endocrinology, neurology, and wound care clinics, as well as inpatient services. Screening procedures include medical history, DPN staging, validated symptom scales, bedside sensory testing, electrochemical skin conductance measurement using Sudoscan, and nerve conduction studies/electromyography as indicated. Written informed consent, available in Mandarin and English, will be obtained before initiation of any study-related procedures.

2.3 Randomization, Allocation Concealment, and Blinding

Participants will be randomized using a computer-generated permuted block design with variable block sizes of 3 and 6, stratified by ulcer status. Allocation will be implemented through a central web-based system, with assignment disclosed solely to the surgical team. Neither participants nor surgeons will be blinded due to the nature of the intervention; however, outcome assessors and statisticians will remain blinded to group allocation. To minimize the risk of unblinding, standardized dressings will be used across groups, and independent assessors will conduct outcome evaluations. The enrollment, randomization, intervention, and follow-up process is summarized in **Figure 1**.

2.4 Intervention

Experimental Intervention (LVB + SOC): Participants allocated to the experimental arm will undergo lymphovenous bypass (LVB) in addition to standard of care (SOC). Lymphatic mapping will be performed with intradermal blue dye injection, followed by a 2–3 cm dorsal foot incision and supermicrosurgical lymphatic–venous anastomosis (end-to-end or end-to-side) to adjacent venules ≤ 0.8 mm in diameter under microscopy, using 11-0 or 12-0 nylon sutures. At least one anastomosis will be completed according to anatomical and flow characteristics, with minimal expected blood loss (<5 mL). In participants with ulcers, concomitant debridement with or without grafting will be undertaken per IWGDF/IDSA guidelines, followed by standardized postoperative wound care and offloading. Postoperative management will include 24 hours of limb elevation, early mobilization, standard analgesia, and antibiotics if grafting is performed. Treatment fidelity will be maintained by single one credentialed plastic microsurgeons following standardized operating procedures, with intraoperative documentation of anastomosis number and type, venous backflow, and confirmation of dye transit.

Control Intervention (SOC Alone): Participants assigned to the control arm will receive SOC only, consisting of guideline-based glycemic and cardiovascular risk-factor management, neuropathic pain control, footwear/offloading, and standardized wound care for those with ulcers. No sham procedure will be performed, owing to ethical considerations.

2.5 Outcome

The primary objective is to compare lymphovenous bypass (LVB) plus standard of care (SOC) with SOC alone in terms of change in neuropathic pain, assessed by the Douleur Neuropathique 4 (DN4) questionnaire, and diabetic peripheral neuropathy (DPN) burden, measured by the Michigan Neuropathy Screening Instrument (MNSI) at 6 and 12 months. Secondary objectives are to evaluate foot electrochemical skin conductance (ESC, μS ; Sudoscan), large-fiber nerve conduction parameters, and, in participants with ulcers, time to complete epithelialization adjudicated by blinded review, proportion of ulcers healed by 20 weeks, infection episodes, reoperations, and rates of minor or major amputation. Exploratory objectives include assessment of serum oxidative stress and antioxidant indices, inflammatory cytokine profiles, and intraepidermal nerve fiber density (IENFD). The safety objective is to characterize adverse events (AEs), serious adverse events (SAEs), surgical site complications, and hypersensitivity reactions to intraoperative mapping dyes.[24]

2.6 Schedule of Assessments

Baseline Assessments: At trial inclusion, demographic and clinical variables will be collected, including age, sex, and relevant past medical history (diabetes mellitus, hypertension, chronic kidney disease, and diabetic retinopathy) from the electronic medical record. Physical examination parameters will include body mass index (BMI) and waist circumference. Laboratory assessments will comprise fasting plasma glucose, glycated hemoglobin (HbA1c), triglycerides (TG), blood urea nitrogen (BUN), and serum creatinine (Cr). Baseline severity of diabetic neuropathy will be evaluated through nerve conduction studies (NCS), quantitative sensory testing (QST), heart rate variability (HRV), electrochemical skin conductance (Sudscan, if not performed within the preceding 3 months), and symptom scoring with the Michigan Neuropathy Screening Instrument (MNSI) and Douleur Neuropathique 4 (DN4). Ulcer status will be documented and photographed when present, and IENFD from ulcer biopsy will be evaluated by a neurologist.

Follow-up Assessments: At 6 months, participants will undergo repeat assessments including Sudscan, HRV, QST, MNSI, DN4 with testing supported by self-payment arrangements. At 12 months, similar assessments (Sudscan, HRV, QST, MNSI, DN4) and biopsy-proven IENF will be performed, with reimbursement provided under the National Health Insurance (NHI) framework. These follow-up evaluations are intended to capture both the primary endpoint at 6 months and the durability of outcomes at 12 months.

2.7 Statistical Analysis

The primary analysis will follow the intention-to-treat principle, with per-protocol analyses conducted as sensitivity checks. The primary endpoint, change in electrochemical skin conductance (ESC), will be analyzed using a mixed-effects model for repeated measures (MMRM) including fixed effects for treatment group, time, group-by-time interaction, ulcer stratum, and prespecified covariates (age, sex, diabetes duration, HbA1c), with a random intercept for each subject. Results will be reported as adjusted mean differences with 95% confidence intervals and P values. Secondary endpoints will be analyzed using similar MMRM models for nerve conduction studies, generalized mixed models for ordinal and binary outcomes, Kaplan–Meier estimates and Cox regression for ulcer healing, and log-binomial or Poisson regression with robust variance for the proportion of ulcers healed at 20 weeks. Exploratory biomarker analyses will use analysis of covariance or mixed models, with multiple testing controlled by the Benjamini–Hochberg false discovery rate. Missing data will be assumed missing at random, with MMRM inherently accommodating missingness and multiple imputation applied for sensitivity analyses. Prespecified subgroup analyses will evaluate outcomes by ulcer status, baseline DPN stage, HbA1c tertiles, dyslipidemia, and chronic kidney disease. Interim analyses will be restricted to safety reviews by the Data and Safety Monitoring Board (DSMB) after approximately 20 and 40 participants, with no efficacy-based stopping rules.

2.8 Data Management and Ethics

Study data will be collected using electronic case report forms (eCRFs) in REDCap with full audit

trials, employing pseudonymized participant identifiers, and records will be retained for at least 5–10 years. Risk-based monitoring will be performed, with 100% source data verification for the primary endpoint and informed consent. The protocol has been approved by the National Taiwan University Hospital (NTUH) Research Ethics Committee, and written informed consent will be obtained from all participants prior to enrollment. Lymphovenous bypass (LVB) is considered a low-risk microsurgical procedure, and participant safety will be overseen by an independent Data and Safety Monitoring Board (DSMB).

3 Results

This study is currently in the pre-initiation phase, during which standard operating procedures have been finalized, assessor training has been completed, and device calibration has been performed. Recruitment is scheduled to begin on September 1, 2025, and will continue through July 31, 2026. Each participant will be followed for 12 months, with final follow-up expected by July 31, 2027. Data lock and analysis are planned for the third to fourth quarters of 2027, and primary reporting of study outcomes is anticipated between the fourth quarter of 2027 and the first quarter of 2028. No outcome data are available at this time.

4 Discussion

This trial evaluates lymphovenous bypass (LVB) as a mechanism-based adjunctive therapy for diabetic peripheral neuropathy (DPN). By recruiting lymphatic outflow, LVB has the potential to reduce endoneurial edema, clear pro-inflammatory mediators, and normalize microvascular exchange, thereby improving small-fiber function, alleviating neuropathic pain, and accelerating ulcer healing. These hypothesized benefits parallel clinical improvements observed in lymphedema and venous ulcer populations. The study addresses a critical gap in DPN management by testing a novel, pathophysiology-targeted surgical intervention. If successful, LVB may emerge as a disease-modifying adjunct to standard diabetes care, complementing metabolic optimization and symptomatic pharmacologic therapies.

Reduced IENFD density is a critical histopathological marker of diabetic neuropathy that significantly contributes to the pathogenesis and impaired healing of diabetic foot ulcers. The progressive loss of these small nerve fibers, driven by metabolic and microvascular injury, leads to a diminished protective sensation and a disruption of neurotrophic and neurovascular support. This lack of sensory feedback allows minor foot injuries to go unnoticed, while the absence of key neuropeptides, such as CGRP and substance P, impairs local blood flow and tissue regeneration. The combination of compromised sensation and a blunted healing response creates a vicious cycle that contributes to the chronicity and high morbidity of these ulcers.[25,26] Therefore, the assessment of IENF density, often through skin biopsies, serves as a valuable diagnostic and prognostic tool, offering insight into the neural contributions to ulcer pathogenesis and serving as a sensitive endpoint for evaluating therapeutic efficacy.

Diabetic autonomic neuropathy is a key factor in the development and poor healing of diabetic foot ulcers. Assessments such as HRV and SSR are essential for evaluating this condition. A decrease in HRV indicates parasympathetic dysfunction, increasing cardiovascular risk, while an absent or reduced SSR points to sympathetic nerve failure, causing dry, cracked skin. This dual impairment—loss of protective sensation from somatic neuropathy and compromised skin integrity from autonomic dysfunction—creates a cycle where minor injuries go unnoticed and the body's natural healing processes are hindered, leading to chronic, non-healing ulcers.[27,28] Therefore, a comprehensive assessment of both somatic and autonomic neuropathy is vital for effective management and risk stratification in patients with diabetic foot ulcers. We will evaluate how effective LVB is at easing diabetic autonomic neuropathy.

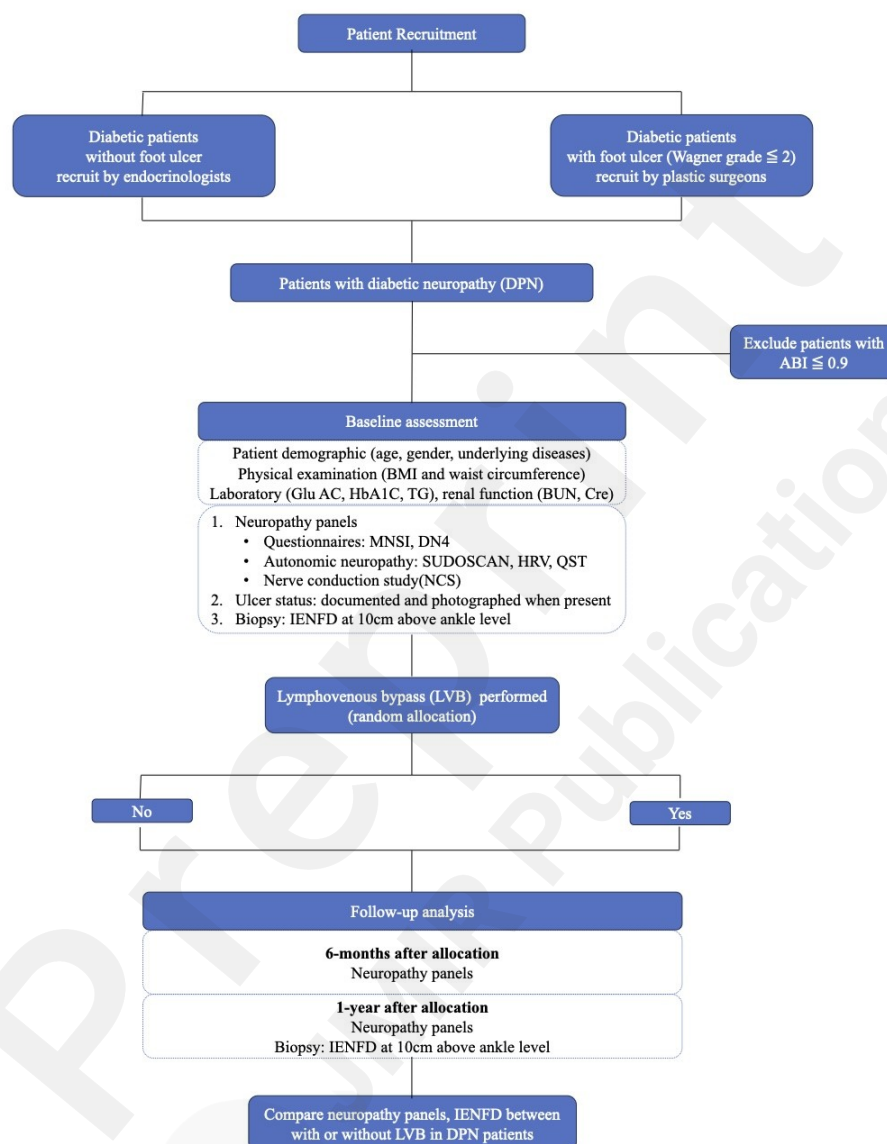
The strengths of this study include its randomized, assessor-blinded design, the incorporation of

objective autonomic and electrophysiologic endpoints, and the integration of biomarker and histological sub-studies to provide mechanistic insight. The inclusion of ulcer-related outcomes further enhances the clinical relevance, as foot ulcers remain a major cause of morbidity and amputation in DPN. Positive findings, particularly improvements in small-fiber function and ulcer healing, could inform future treatment algorithms tailored to specific DPN phenotypes, thereby advancing precision care in diabetic neuropathy.

Several limitations must be acknowledged. The single-center design may constrain generalizability, and the inability to blind participants and surgeons introduces a risk of performance bias, although this is mitigated by the use of objective, assessor-blinded measures such as electrochemical skin conductance and nerve conduction studies. The heterogeneity of DPN phenotypes presents additional challenges in interpreting subgroup responses. While the sample size is adequately powered for the primary endpoint, it may be underpowered to detect smaller effects across secondary and exploratory outcomes. Future research should include multicenter replication to validate findings, cost-effectiveness analyses to assess feasibility in routine practice, and refinement of indications such as early autonomic DPN or refractory ulcer phenotypes. Comparative effectiveness studies, including evaluation alongside emerging pharmacologic agents such as GLP-1 receptor agonists, are also warranted. Taken together, this trial has the potential to establish LVB as a paradigm-shifting intervention that redefines the therapeutic landscape of DPN.

Figure 1: Flowchart

Flowchart of study design showing participant screening, randomization, and allocation to intervention (lymphovenous bypass plus standard care) or control (standard care alone). The diagram also illustrates follow-up and analysis with outcome assessors and statisticians remaining blinded.



Abbreviation: Glu Ac, fasting plasma glucose; HbA1c, glycated hemoglobin; TG, triglycerides; BUN, blood urea nitrogen; Cre, serum creatinine; NCS, nerve conduction studies; QST, quantitative sensory testing; HRV, heart rate variability; Sudoscan, electrochemical skin conductance; MNSI, symptom scoring with the Michigan Neuropathy Screening Instrument; DN4, Douleur Neuropathique 4

5 Conflict of Interest

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

6 Author Contributions

SC, CC, ST, CY, and TC conceived the study and developed the methodology, with SC performing the LVB surgeries. CY and TC managed participant recruitment, and HY was responsible for patient follow-up, data curation, statistical analyses, and drafting of the manuscript. CC, ST, NC and SC contributed to review and editing. All authors approved the final manuscript and are accountable for the work.

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9 Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Supplementary Files

Figures

Flowchart of study design showing participant screening, randomization, and allocation to intervention (lymphovenous bypass plus standard care) or control (standard care alone). The diagram also illustrates follow-up and analysis with outcome assessors and statisticians remaining blinded.

