Original Article

The effectiveness of neurodynamic techniques in patients with diabetic peripheral neuropathy: Study protocol for a randomized sham-controlled trial

Mahdi Ashoori[1], Mohammadreza Pourahmadi[1], Seyed Ebrahim Hashemi[2], Mehdi Dadgoo[1], Mahboobeh Sadat Hosseini[3]

[1]Iranian Center of Excellence in Physiotherapy, Rehabilitation Research Center, Department of Physiotherapy, School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran, [2]Exercise Physiology Research Center, Life Style Institute, Baqiyatallah al-Azam Hospital, Baqiyatallah University of Medical Science, Tehran, Islamic Republic of Iran, [3]Health Research Center, Life Style Institute, Baqiyatallah al-Azam Hospital, Baqiyatallah University of Medical Science, Tehran, Islamic Republic of Iran

Abstract

Background: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus (DM). DPN is the primary risk factor for diabetic foot ulcers that can cause amputation. Although several observational studies have investigated the morphological and biomechanical characteristics of peripheral nerves in DPN, interventional studies regarding the effectiveness of neurodynamic techniques (NDT) in DPN patients are confined to a handful. The effects of NDT on neuropathy severity, nerve conduction parameters, quality of life (QoL), and mechanosensitivity have not been explored yet in this population.

Materials and Methods: Forty type 2 DPN (T2DPN) patients, diagnosed based on an electrodiagnosis study, will be recruited into two groups. The experimental group will receive the tibial nerve's real proximal and distal slider techniques in addition to DPN standard treatment as a basic treatment, and the control group will receive the tibial nerve's sham proximal and distal slider techniques along with the basic treatment for eight sessions twice a week. Baseline and post-intervention assessments will be based on the Michigan diabetic neuropathy score (MDNS) (primary outcome), tibial nerve conduction parameters, neuropathy-specific quality of life (Neuro QoL) questionnaire, and straight leg raising range of motion (SLR ROM) (secondary outcomes).

Results: This study is expected to last approximately seven months, depending on recruitment. The results of the study will be published in a peer-reviewed journal.

Conclusions: The present study will evaluate the efficacy of NDT on the primary and secondary outcome measurements in DPN patients.

Keywords: Diabetic neuropathy, peripheral nerves, neurodynamic techniques, nerve mobilization, nerve conduction studies, electromyography, range of motion

Address for correspondence: Dr. Mohammadreza Pourahmadi, Department of Physical Therapy, Rehabilitation Research Center, School of Rehabilitation Science, Iran University of Medical Science, Madadkaran All., Shahnazari St., Madar Sq., Mirdamad Blvd., Tehran, Islamic Republic of Iran.
E-mail: pourahmadipt@gmail.com
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Introduction

Diabetes mellitus (DM) is one of the most common heterogeneous metabolic disorders recognized with chronic hyperglycemia.[1] In 2017, the global prevalence, deaths, and disability-adjusted life-years of DM were reported at 476 million, 1.37 million, and 67.9 million, respectively.[2] According to the Global Burden of Disease Study, DM was the eleventh most common cause of death in 2009, while this disease was reported as the fifth leading cause of death in Iran

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in 2019.[3] Diabetic peripheral neuropathy (DPN) is defined as the presence of any signs and/or symptoms of peripheral nerve dysfunction in a person with DM after excluding other reasons.[4] DPN is the most common complication in DM and usually affects 50% of type 2 diabetes mellitus (T2DM) patients.[5,6] DPN is the leading cause of diabetic foot ulcers, which can get infected and lead to amputation.[7,8]

Hyperglycemia and dyslipidemia result in several intracellular pathological alterations that can cause endoplasmic reticulum stress, DNA damage, mitochondrial dysfunction, and apoptosis that eventually lead to DPN.[9-11] Chronic hyperglycemia can also affect peripheral nerves' Schwann cells.[12-15] In this situation, cytoskeletal properties of axons will change, and Schwann cell-axon ribosome transfer, that is responsible for intra-axonal mRNA translation will also be affected.[16] Moreover, extracellular matrix gene expression will be altered due to hyperglycemia.[17] Changes in protein expression in dorsal root ganglia (DRG), such as reduction in neurofilament polymers,[18] growth-associated protein 43 (GAP43), β-tubulin synthesis, and increased heat shock proteins (HSPs);[10,19] and poly (ADP-ribose) polymerase (PARP) expression[20,21] could occur after persistent hyperglycemia.

Boyd *et al*. demonstrated that diabetic patients have abnormal tibial nerve biomechanics.[22] During ankle dorsiflexion with the lower extremity in 20° hip flexion and knee extension in the side-lying position, the DM group demonstrated significantly reduced distal mobility at the ankle and knee sites, as well as increased transverse excursion of the tibial nerve in the posterior direction at the ankle site, compared to a healthy control group.[22] Therefore, it seems that neural mobilization (NM) can be considered as a technique to promote peripheral nerves' mobility in diabetic peripheral neuropathic patients. Santos *et al*. showed that NM reduced allodynia and lowered neural growth factor (NGF) and glial fibrillary acidic protein (GFAP) expression in the ipsilateral DRG which can reverse pain symptoms in constriction-injured rats.[23] Zhu *et al*. investigated the impact of NM on the levels of inflammatory cytokines and mechanical allodynia in rats with DPN.[24] They discovered that NM significantly reduced tumor necrosis factor α (TNFα), and interleukin 1β (IL-1β) which is related to the alleviation of the mechanical allodynia.[24] Carta *et al*. perused the biological effects of neurodynamic techniques (NDT) on sensory and motor neurons *in vitro*.[25] However, NDT did not cause Bax expression (a pro-apoptotic protein), it indicated anti-apoptotic Bcl2 expression in motor neurons. The sensory neuron protein PIEZO1, which is responsible for mechanical pain suppression, was also found to be upregulated after NDT.[25] According to these findings, NDT can facilitate nerve regeneration procedures and lead to pain reduction.

NDT is a term to describe the integration of morphology, biomechanics, and physiology of the nervous system. This technique integrates neural structure, innervated tissue, and mechanical interface.[26] According to Butler *et al*., NDT is a method of NM in which forces are applied to nerve structures through postures and multi-joint movements.[27]

Boyd *et al*. showed that neurodynamic slider exercises are safe in mild to moderate DPN patients and immediately affect straight leg raising range of motion (SLR ROM).[28] Manu *et al*. revealed that passive NM, nerve massage, and transcutaneous electrical nerve stimulation (TENS), together, improved pain, quality of life (QoL), range of motion, and radiological magnetic resonance diffusion tensor imaging outcomes following six sessions of intervention in a 63-year-old man diagnosed with DPN.[29]

Despite several observational studies investigating the morphological and biomechanical characteristics of peripheral nerves in DPN patients, interventional studies are confined to only a few ones.[28-31] Moreover, neurodynamic slider exercises were considered safe for patients with mild to moderate DPN.[28] To the best of the authors' knowledge, this study aims to investigate the effectiveness of NDT on neuropathy severity, nerve conduction parameters, QoL, and mechanosensitivity in type 2 DPN (T2DPN) patients for the first time. The primary objective of the present study is to investigate the effectiveness of NDT on neuropathy severity in T2DPN patients. Secondary objectives include exploring the effects of NDT on nerve conduction parameters, QoL, and mechanosensitivity in the intended population.

The present study is a two-arm parallel-group, double-blinded, randomized, sham-controlled superiority trial. The allocation ratio will be 1:1. A CONSORT diagram illustrating the flow of the participants through this trial is depicted in Figure 1.

Materials and Methods

Participants

The study will involve patients referred to the Physical Medicine and Rehabilitation clinic at Baqiyatallah Hospital, Tehran, Iran. Included participants have to fulfill the following criteria: 1. Adults (40-70 years old) who have been diagnosed with T2DPN based on their most recent laboratory test (within the last three months);[32] and electrodiagnostic study[33] by an experienced endocrinologist (MSH) and physiatrist (SEH), 2. To be eligible, participants must have at least 90° hip flexion, full knee extension, and 0° dorsiflexion to 30° plantarflexion in the ankle.[22] The exclusion criteria are as follows: 1. Persistent low back pain, neck pain, radiculopathy, and sciatalgia (for at least three days) in the previous six months (based on four limbs electrodiagnosis study), 2. Chemical or alcohol dependency, 3. Syphilis, Guillain-Barré syndrome, rheumatoid arthritis, complex regional pain syndrome, and tarsal tunnel syndrome, 4. Lower extremity open wound and infection, 5. Amputation proximal to the metatarsophalangeal joint, 6. History of chemotherapy or spinal surgery in the last year, 7. Previous peripheral nerve injury or surgery, 8. Pregnancy, 9. Severe DPN (The Michigan diabetic neuropathy score (MDNS) >30),[28] and 10. Personal reluctance to participate in the study. The assessor will be the third author (SEH), a physiatrist with ten years of experience in diagnosing and treating DPN patients. This trial's therapist will be the first author (MA), a

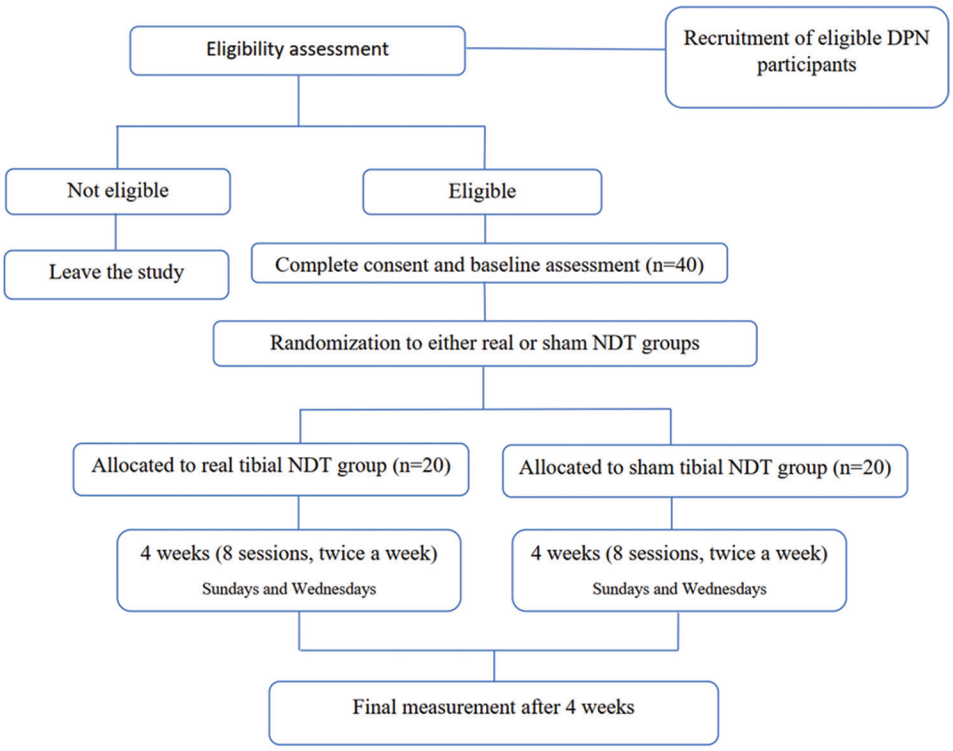

Figure 1: Trial design

physical therapist with three years of experience and adequate training in NDT.

Intervention description

Participants in experimental group will receive real tibial nerve's diastal and proximal slider techniques. Real tibial nerve's distal slider technique will be performed in a side-lying position on the intended side. Enough pillows will support the patient's head and neck in a comfortable and neutral position and will also ensure that the thoracolumbar spine is in neutral alignment. In this position, the therapist will flex the patient's hip to 80° and keep the knee in full extension [Figure 2a]. The therapist will move the ankle into dorsiflexion, eversion combined with toe extension, and the patient will be asked to extend their head and neck simultaneously [Figure 2b].[26,34] Real tibial nerve's proximal slider technique will be applied in the same starting position as explained previously [Figure 2a]. In this position, the therapist will move the ankle toward plantarflexion, inversion combined with toe flexion, and ask the patient to flex the head and neck simultaneously [Figure 2c].[26,34]

Patients in control group will receive sham tibial nerve's distal and proximal slider techniques.In order to perform sham tibial nerve's distal slider technique, participant will be asked to lie on their intended side, and the therapist will move the patient's hip toward abduction, flex the hip to 20°, and keep the knee extended [Figure 3a]. The sham tibial neurodynamic distal slider technique will follow the same sequence as the real tibial neurodynamic distal slider technique [Figure 3b].[26,34]

In the starting position [Figure 3a], to perform sham tibial nerve's proximal slider technique, the participant will be asked to flex the head and neck while the therapist is moving the ankle into plantarflexion, inversion, and the toes into flexion [Figure 3c].[26,34] These techniques will be applied for 10 repetitions in five sets.[25,35] The slider techniques will be performed with large amplitude to let the intended nerve move a great deal toward its resting position.[26] Basic standard treatments: Both groups will receive TENS (frequency = 80 Hz, duration = 0.2 mS, 2 to 3 times sensory threshold) for 20 min. One electrode will be placed at the popliteal fossa and the other at the medial tarsal tunnel.[36,37] In addition, a 4-min longitudinal and transverse tibial nerve massage will be applied at the medial tarsal tunnel and the popliteal fossa [Figure 4].[26,31] These treatments will continue for eight sessions over four weeks (twice a week).[35]

To control bias in reporting subjective outcomes and contamination bias, this double-blinded randomized sham-controlled trial was designed. Consequently, sham tibial NDT will be performed in 20° hip flexion, abduction, and knee extension. González *et al*. demonstrated that sham NDT in this position is a believable sham treatment and can provide a suitable blinded comparison.[34] Therefore, this sham NDT was chosen as a comparator for the control group in this study. On the other hand, both groups will receive standard treatment based on the evidence-based guidelines by Bril *et al*.[36]

This study aims to explore the efficacy of NDT in conjunction with basic standard treatment. Consequently, the researchers

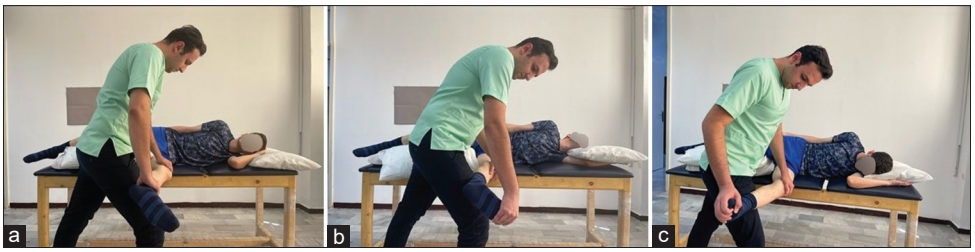

Figure 2: Real tibial nerve neurodynamic technique, (a) Starting position (b) Real distal slider technique (c) Real proximal slider technique

Figure 3: Sham tibial nerve neurodynamic technique, (a) Starting position (b) Sham distal slider technique (c) Sham proximal slider technique

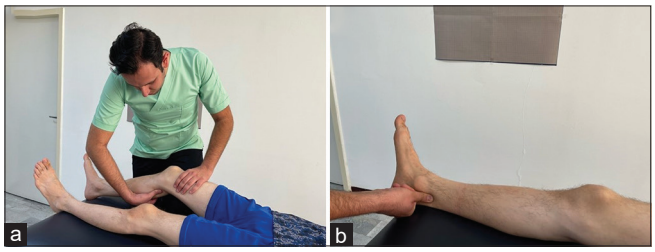

Figure 4: Tibial nerve massage, (a) At the popliteal fossa (b) At the medial tarsal tunnel

of this study will not alter the standard treatment protocols, which include pharmaceutical remedies. However, additional rehabilitation procedures that may affect outcomes are prohibited.

If a patient misses two sessions in a row or three sessions in total, or if they are reluctant to engage in the study, the interventions will be ended. These participants will be followed to check their symptoms.

Before each session, the first author (MA) will contact all participants to remind them of the session. Participants will be informed about the potential efficacy of treatment approaches. Participants will be encouraged to attend all sessions. All treatments and assessments will be offered at no cost. After the completion of the sessions, the participants will receive a complimentary endocrinology consultation with the fifth author (MSH).

Outcomes

Primary outcome measure: The primary outcome of this study is MDNS, which is a scoring system for DPN severity.[38] *Secondary outcome measures:* The secondary outcomes include tibial nerve conduction velocity, tibial nerve distal latency, amplitude of tibial motor nerve action potential (MNAP), tibial nerve F-wave latency, neuropathy-specific quality of life questionnaire (Neuro QoL), plantarflexion SLR ROM, and dorsiflexion SLR ROM.[39-41]

Participant timeline

Participants will be made aware of the study's procedure and aims. The participants will sign a written informed consent form at the beginning of the study. In addition, patients will be examined during the initial appointment to determine whether they meet the eligibility criteria. Demographic information, including age, weight, height, body mass index (BMI), fasting blood sugar (FBS), HbA1c, 2-h oral glucose tolerance test, vit B12 and vit D3, calcium, phosphor us, serum albumin, and thyroid-stimulating hormone (TSH) will be documented as a form. Randomization will be performed using the block-balanced randomization method with four-character blocks containing letters A and B. Patients will be randomly admitted to one of the two groups of real (group A) or sham (group B) tibial nerve NDT. In the same session, outcomes will be measured by the blind assessor. After completing the baseline evaluation, the treatment program will initiate and proceed for eight sessions over four weeks.[35] Outcomes will be measured at the baseline and the last session. The study duration for each participant will take approximately four weeks. The present study's timeframe is depicted in Table 1. DPN patients will be recruited from the Endocrinology and the Physical Medicine and Rehabilitation Clinics of Baqiyatallah Hospital, Tehran, Iran.

Assignment of interventions allocation

DPN participants will be randomized into a real or a sham NDT group with a 1:1 ratio. A block-balanced randomization technique will be used for randomization with four-character blocks containing letters A and B. Allocation instructions will be written and placed in sequentially numbered, opaque, sealed envelopes. DPN participants will be blinded to the allocation schedule until the end of the study. The procedure will be performed by the secretary of the clinic, who will not

Table 1: Participant timeline

TIMEPOINT	Enrollment	Allocation	Study period								Close-out
			Post-allocation								
	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	T_8
ENROLLMENT:											
Eligibility screen	X										
Informed consent	X										
Demographic questionnaire	X										
Allocation		X									
INTERVENTIONS:											
Group A (real neurodynamic)											
Group B (sham neurodynamic)											
ASSESSMENTS:											
MDNS			X								X
Tibial NCV			X								X
Tibial nerve's distal latency			X								X
Tibial nerve's amplitude of MNAP			X								X
Tibial nerve's F-wave latency			X								X
Persian version of neuropathy-specific quality of life questionnaire			X								X
Plantarflexion/SLR and Dorsiflexion/SLR ROM			X								X

be involved in the assessment, allocation, or treatment. The randomization schedule is known only to the therapist of this study.

Participants will receive numbered, opaque, and sealed envelopes. The therapist who is not in charge of outcomes assessment will open these sealed envelopes and discover the participants' treatment procedure. Members of the research team in charge of data collection and analysis will not be informed of the groups' allocation. The clinic's secretary, who is not part of the study, will come up with allocation outcomes, sign up patients, and put them in the right intervention group based on the randomization schedule.

Participants and the outcome assessor are blinded regarding the allocation throughout the study. The therapist will be asked not to reveal the participants' allocation status during the trial. The therapist is encouraged to maintain the blindness as far as possible. Because of how the study is set up, all participants and members of the research team responsible for evaluation and data collection must remain blinded during the study period.

Data collection, management, analysis

The third author (SEH) is the outcomes assessor of this trial.

Primary outcome

MDNS consists of 46 points for both limbs in three separate items. The sensory item of MDNS includes vibration perception threshold (VPT), light touch, and pinprick sensation assessment. The VPT will be assessed with a 128-Hz tuning fork over the dorsum of the great toe on the bony prominence of the distal interphalangeal (DIP) joint. A 10-gr monofilament that is applied over the dorsum of the great toe midway between the nail fold and the DIP joint will be used for light touch assessment. Moreover, a standard pin on the dorsum of the great toe will be utilized to assess pinprick sensation. The next item, muscle strength, consists of a strength assessment of toe abductors, great toe extensors, and ankle dorsiflexor muscles. The last item, deep tendon reflexes (DTR) of biceps brachii, triceps brachii, quadriceps femoris, and Achilles, will be evaluated by a standard reflex hammer.[42]

Secondary outcomes

The electrodiagnostic study is the best way to evaluate peripheral nerves' function in DPN.[43] An NCS unit (Neuropack®, s1 MEB-9400, Nihon Kohden, Japan) will be used to measure NCS parameters. Owing to the motor nature of the tibial nerve, orthodromic supramaximal (20-50 mA) stimulation (duration = 200 mS) will be applied over the popliteal fossa for proximal stimulation, and slightly proximal and posterior to the medial malleolus for distal stimulation. The recording site is the abductor hallucis brevis (AHB) muscle. NCV of the tibial nerve, distal latency, and MNAP amplitude will be reported in m/s, mS, and mV, respectively.[39] To measure F-wave latency, despite gain and sweep increment, the setup would be the same as the tibial nerve's routine motor conduction study. However, due to the anodal block, the stimulator's cathode should be more proximal than the anode.[39] F-wave latency will be reported in mS.[39]

QoL will be assessed by the localized Persian version of Neuro QoL.[40] This outcome is a patient-reported questionnaire with 27 questions and 5 options for each question (Cronbach alpha = 0.87, reliability of subscales = 0.86-0.95).[40] This questionnaire has six subscales that measure problems with DPN patients' physical and emotional lives.[40]

SLR ROM will be evaluated by a manual goniometer, to assess mechanosensitivity.[44] This outcome will be assessed in the supine position. The goniometer's axis, moving arm, and

stable arm will be placed on the greater trochanter of the femur, parallel to the femur, and parallel to the trunk, respectively.[45] In this position, the patient will be instructed to actively raise their leg with an extended knee, once with ankle plantarflexion and then with ankle dorsiflexion, until the first onset of symptoms (p_1) and maximally tolerated symptoms (p_2).[41,44,45]

Participants will complete an informed consent form and a demographic information form. Based on the randomization approach, all primary and secondary outcomes are printed on prefabricated paper forms for each participant. The participants will complete the Neuro QoL questionnaire, while the assessor will complete the remaining forms related to all other outcomes. In addition, all data is reviewed by a second assessor, and if unreasonable associations are detected, another evaluation will be conducted, and the corrected data will be kept. Each participant's data will be stored in a separate file on a personal computer, including the individual's information. Finally, each participant's confidential data will be stored in an Excel (Microsoft) file with a unique identifier prepared for statistical analysis.

Statistical methods

Statistical analysis will be performed on a personal computer using STATA software for Windows release version 14.2 (StataCorp LLC) and SPSS version 21.0 (IBM Corp). To investigate the normal distribution of data, P-P plot analysis, mean and median similarity, Shapiro-Wilk statistical test, analysis of histogram, and the skewness and kurtosis analysis of the data distribution will be used. If the data distribution is normal, parametric tests will be used for statistical analysis of the data before and after the intervention. The variable transformation will be used first if the data distribution is not normal, especially for primary outcome measurement. In abnormal data distribution, when the variable transformation is not possible, non-parametric statistical tests will be used. If Levene's test validates the data, the ANCOVA test will be used. The covariance variable in this test is the baseline data values before the intervention. The significance level of the tests will be set at 0.05. In addition to the significance value, Cohen's *d* effect size will be utilized to compare the two treatment groups to determine the effects of the intervention on every dependent variable, regardless of the sample size. According to the newly discovered interpretation, the effect size can be divided and interpreted as follows: 0.2 = no/trivial effect; 0.2 to 0.5 = small effect; 0.5 to 0.8 = medium effect; 0.8 to 1.2 = large effect; and 1.2 to 2 = very large effect.[46] G Power 3.1 was utilized to calculate the required sample size. As a family test, the F-test was utilized. Analysis of covariance (ANCOVA) was used as a statistical test. Required sample size was estimated by given α, power, and effect size. Based on the results of the primary pilot study with 10 patients (attrition rate = 30%, α =0.05, power = 80%, and effect size F = 0.53), 40 participants (20 patients in each group) will be recruited. There are no plans to do any extra or subgroup analyses in the current investigation. The trial's non-adherence and attrition will be managed by conducting an intention-to-treat analysis. Also, there is no interim analysis in the present study.

Discussion

DPN, the most common complication in T2DM, causes several disabilities for patients.[5-7] NDT can be considered as one of the possible rehabilitation techniques for these patients. Observational studies have shown decreased mobility in peripheral nerves due to DPN.[22,47] These techniques can improve peripheral nerves' mobility during movements.[48] Besides the potential effects of NDT on the biomechanical and morphological characteristics of peripheral nerves,[49] recent studies have shown the effectiveness of NDT on peripheral nerves' conduction parameters in other populations, like carpal tunnel syndrome.[50,51] To the best of the authors' knowledge, this is the first time an investigation aims to determine the effectiveness of NDT on neuropathy severity, tibial nerve conduction parameters, QoL, and mechanosensitivity in T2DPN.

This study is expected to have the following limitations. DPN is considered a polyneuropathy by nature, but this study will only investigate the effectiveness of NDT on the tibial nerve's conduction parameters. Although long-term follow-up will not be possible for this trial, studies with sufficient follow-up design will be required in the future. Nevertheless, it is approved that NDT is a dose-dependent technique, but the best dose-response analysis for NDT has not been investigated yet, so future studies should explore this issue in DPN.

Acknowledgement

We are grateful to the patients for donating their time and enthusiasm to partaking in our study. We would also like to thank Amirhossein Shamsi for his contributions to protocol development, and Mahdi Akhgari for his assistance in taking and editing the figures. We also appreciate Dr. Khadijeh Nemati for her contributions to participants' recruitment.

Ethics approval and consent to participate

This study is the MSc thesis of the first author (MA). Ethical approval was obtained from the Research Ethics Committee of the Iran University of Medical Science on July 10, 2022 (approval ID: IR.IUMS.REC.1401.316). This trial was registered at https://www.irct.ir/, (IRCT20220401054379N1) on October 13, 2022. The authors are responsible for informing the Iran University of Medical Science about any deviation from the approved protocol. Also, all the amended protocols will be updated on https://www.irct.ir/.

As far as the authors know, no harm has been reported for the evaluation and treatment techniques mentioned earlier.

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Informed consent forms and also other prefabricated forms that are given to participants are in Persian, so these forms are not attached in the protocol. The informed consent form was approved by the Ethics Committee of Iran University of Medical Sciences.

Financial support and sponsorship

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If data access were required, the individual-level dataset would be available by sending a valid email to the first corresponding author (MRP).

Conflicts of interest

There are no conflicts of interest.

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