Electronic Journal of General Medicine
2026, 23(3), em740
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Original Article

OPEN ACCESS

Efficacy and tolerability of alpha-lipoic acid and B vitamins in the management of diabetic patients with symptomatic distal symmetric polyneuropathy: A randomized-placebo controlled trial

Che Nur Ain Che Abdullah [1], Noraini Mohamad [2,3]*, Nani Draman [1,3], Zainab Mat Yudin [2,3], Wan Muhamad Amir W Ahmad [2], Ritzzaleena Rosli Mohd Rosli [1,3], Chee Yong Chuan [4], Najib Majdi Yaacob [5]

[1] Department of Family Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, MALAYSIA
[2] Medical and Basic Dental Sciences Unit, School of Dental Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, MALAYSIA
[3] Outpatient Family Health Clinic, Universiti Sains Malaysia Specialist Hospital, Kelantan, MALAYSIA
[4] Neurology Unit, Department of Internal Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, MALAYSIA
[5] Biostatistics and Research Methodology Unit, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, MALAYSIA
***Corresponding Author:** mnoraini@usm.my

Citation: Che Abdullah CNA, Mohamad N, Draman N, Mat Yudin Z, W Ahmad WMA, Mohd Rosli RR, Chuan CY, Yaacob NM. Efficacy and tolerability of alpha-lipoic acid and B vitamins in the management of diabetic patients with symptomatic distal symmetric polyneuropathy: A randomized-placebo controlled trial. Electron J Gen Med. 2026;23(3):em740. https://doi.org/10.29333/ejgm/18705

ARTICLE INFO

Received: 23 Dec. 2025

Accepted: 19 May 2026

ABSTRACT

Background: Distal symmetric polyneuropathy (DSPN) is a microvascular complication of type 2 diabetes mellitus (T2DM) that significantly impairs quality of life. However, effective treatment remains a challenge. This study evaluates the efficacy and tolerability of a fixed-dose combination of alpha-lipoic acid (ALA) and B vitamins in T2DM patients with symptomatic DSPN.

Methods: A single-center, randomized, double-blind, placebo-controlled trial enrolled 80 T2DM patients with DSPN into two groups. The intervention group (n = 40) received two tablets daily of ALA (300 mg), vitamin B12 (500 mcg), B6 (8 mg), and B1 (39 mg), i.e., Bionerv®, and the control group (n = 40) received a placebo in the same dosage for 12 weeks from June to December 2024. Efficacy was assessed using the total symptom score (TSS) and neuropathy symptom score (NSS) at baseline, 6 weeks, and 12 weeks, while the neuropathy disability score (NDS) and safety parameters, including renal function tests (RFT) and liver function tests (LFT), were measured at baseline and at week 12.

Results: The intervention group showed a significant reduction in TSS mean (M) score from baseline (6.72 ± 2.82) to weeks 6 (3.53 ± 2.50) and 12 (2.49 ± 1.88), compared to the placebo group, with a significant improvement in stabbing pain, paranesthesia, and numbness. NSS M score also decreased significantly in the intervention group from 7.45 ± 1.15 at baseline to 4.18 ± 2.39 in week 12. The NDS M score in the intervention group significantly decreased from 8.28 ± 1.63 at baseline to 7.11 ± 1.95 in 12 weeks, but the between-group difference was not significant (p = 0.057). There are no significant changes in RFT and LFT after 12 weeks of treatment.

Conclusion: The 12-week oral treatment with a fixed-dose combination of ALA and B vitamins is effective in reducing symptoms of DSPN with a favorable safety profile.

Keywords: alpha-lipoic acid, B vitamins, distal symmetric polyneuropathy, neuropathy symptom score, neuropathy disability score, total symptoms score

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus (T2DM) attributed to chronic hyperglycemia [1, 2]. DPN may be focal or diffuse, with distal symmetric polyneuropathy (DSPN) being the most common diffuse type [2]. DSPN can be diagnosed by using various clinical scoring, including the neuropathy symptom score (NSS) and neuropathy disability score (NDS) [3] or Michigan neuropathy screening instrument [4].

Globally, the prevalence of DSPN varies widely, ranging from 30% to 40% among T2DM patients, depending on diagnostic criteria and the population studied [5, 6]. The significant burden of DSPN contributes heavily to morbidity and disability among diabetic patients [5]. DSPN causes chronic pain that reduces the quality of life and impairs balance, consequently increasing the risk of falls [7], foot ulceration, and lower-limb amputation [8]. In addition to these physical complications, the chronic pain associated with DSPN often leads to sleep disruption, anxiety, and depression, further reducing patients' overall quality of life [9].

Despite numerous complications that may arise from DSPN, the effective treatment of symptomatic DSPN remains challenging. First-line pharmacotherapy options for painful DSPN include several antidepressants (e.g., duloxetine,

venlafaxine, amitriptyline, and other tricyclic drugs) and the gabapentinoid antiseizure medications (e.g., pregabalin and gabapentin) [10, 11].

Although these medications are generally more effective than a placebo in relieving pain, they are associated with several adverse side effects, including nausea, somnolence, dizziness, decreased appetite, constipation, diaphoresis, and sexual dysfunction [10]. Therefore, for patients who are intolerant of first-line pharmacotherapies, the 2022 guidelines of the International Diabetes Federation recommend treatment with oral pathogenetically oriented pharmacotherapy of alpha-lipoic acid (ALA) and benfotiamine (vitamin B1) [11].

ALA, also known as thioctic acid, is a potent antioxidant that mitigates oxidative stress, a major contributor to DSPN pathophysiology [12]. Several randomized controlled trials have shown that ALA is effective in treating DSPN [13-16]. However, the evidence supporting the efficacy of ALA in the treatment of diabetic neuropathy remains inconclusive [17]. A systematic review reported inconsistent findings, with four trials demonstrating significant improvement in neuropathic symptoms [18-21], and three showing no notable effect [22-24]. Furthermore, a meta-analysis and systematic review reported that ALA improved sensory symptoms in DSPN patients [25]. In contrast, another review found no significant differences for pain reduction or functional outcomes [26].

Similarly, B vitamins, including B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin), are essential for nerve health by enhancing nerve cell metabolism and myelin sheath formation [27]. A systematic review reported that B vitamin supplementation may improve several symptoms and signs of DPN [28]. However, another review article concluded that the overall efficacy of B vitamins in treating diabetic neuropathy remains uncertain and requires further study [29].

Given the inconsistent evidence on the individual efficacy of ALA and B vitamins in alleviating DSPN symptoms among T2DM patients, further investigation is warranted. Therefore, this study aims to evaluate the efficacy of a fixed-dose combination of ALA and B vitamins in reducing DSPN symptoms among patients with T2DM through potential synergistic effects. Furthermore, evidence regarding these combinations within the Malaysian population remains limited, highlighting the need for further research among local populations.

METHODS

Study Design

This study employed a single-center, randomized, double-blind, placebo-controlled trial design. It was conducted in accordance with the Declaration of Helsinki [30] and following the approval granted by Human Research Ethics Committee at Universiti Sains Malaysia (USM/JEPeM/KK/23110893). The protocol for this study was registered with ClinicalTrials.gov (Identifier: NCT06568185).To ensure that the study meets the recommended standards, this study was conducted and reported in accordance with the consolidated standards of reporting trials statement guidelines [31].

Population and Sample

Participants were recruited between 1 June 2024 and 1 December 2024 from the outpatient clinic and diabetes clinic at Universiti Sains Malaysia Specialist Hospital. Adults aged 18 years and older, with underlying T2DM and diagnosed with clinical DSPN based on the neurological symptom score (NSS) and the neuropathy disability score (NDS) criteria, were eligible for inclusion in this study [3]. Nerve conduction study (NCS) was not performed for the diagnosis of DSPN, in accordance with the 2017 American Diabetes Association (ADA) recommendations, which stated that DSPN is primarily diagnosed based on clinical presentation, while electrophysiological testing is reserved for atypical or uncertain cases, or when another underlying cause is suspected [2].

The exclusion criteria consisted of the following: participants with a documented mental impairment, peripheral vascular disease (non-palpable foot pulses, and intermittent claudication), amputated foot or leg, aspartate aminotransferase or alanine aminotransferase levels more than three times the normal levels, renal impairment (chronic kidney disease stage IV and V), and individuals using medications that could potentially influence the study results, such as antidepressants, anticonvulsants, opiates, neuroleptics, antioxidants, and particularly methylcobalamin, pyridoxine and other B complex preparations. Individuals who were pregnant, lactating, or had a history of allergy to vitamin B complex preparations (i.e., vitamin B12, B6, and B1) and ALA were also excluded.

The sample size was calculated using G*power software version 3.1.9.7. The sample size for this study was determined based on the primary study endpoint, namely the change in total symptoms score (TSS) from baseline to week 12. Since the intended statistical analysis is a A repeated-measures analysis of variance (RM-ANOVA) that investigates both between-group and within-group effects, the sample sizes were calculated based on two options. The largest sample size was based on the calculation of between-group effects (35 participants per group) with 80% statistical power to detect a medium effect size of 0.25, at a 5% type I error, and assuming a correlation of 0.3 among repeated measures. To account for an anticipated 10% dropout rate, the final sample size was increased to 40 participants per group, resulting in a total sample size of 80 participants.

Study Enrolment

Patients with T2DM attending the outpatient and diabetes clinic were approached individually for study participation. Individuals who agreed to participate in this study were provided with a detailed explanation of the study's significance, objectives, and procedures. Then, the participants were brought to the research room for eligibility screening. NSS and NDS assessments were also carried out to establish a clinical diagnosis of DSPN. The sensitivity, specificity, and diagnostic efficacy of NSS and NDS scores were evaluated in [32], using NCS as the gold standard. The study reported sensitivity values of 82.05% and 92.31%, and specificity values of 66.67% and 47.62% for the NSS and NDS, respectively, with an overall diagnostic efficacy of 77% [32].

NSS consists of four symptom components: type, location, timing, and relief by maneuver. For symptom type, burning, numbness, or tingling sensations are scored as 2 points, while

fatigue or cramping is scored as 1 point; absence of symptoms is scored as 0. For symptom location, symptoms confined to the feet are scored as 2 points, symptoms in the calves as 1 point, and symptoms elsewhere as 0. The third symptom component is timing: 2 points for nocturnal exacerbation; 1 point if symptoms persist day and night; 0 if only during the day. An additional point is added if symptoms wake the patient from sleep. The fourth symptom component is relief by manoeuvre: symptoms are reduced by walking (2 points), standing (1 point), or sitting or lying down (0 points). The total score ranges from 0 to 9, categorizing DSPN as mild (3-4), moderate (5-6), or severe (7-9) [3, 6].

In addition to the NSS, NDS is used to assess neurological deficits through clinical examination, including vibration, temperature, pinprick, and the Achilles tendon reflex on both feet. Vibration perception was evaluated using a 128 Hz tuning fork on the hallux of the big toe. A score of 0 was assigned for normal vibration perception and 1 for reduced or absent sensation on each side [33]. Vibration perception was considered normal when the patient perceived vibration at the hallux of the big toe, similar to the reference sensation elicited by applying the tuning fork to the sternum or forehead. Temperature perception was assessed with a cold tuning fork on the dorsum of the foot, following the same scoring method [34]. Pain perception was evaluated using a pinprick test at the proximal end of the big toenail. The ability to distinguish sharp and blunt for each side was scored as 0 when sharpness was present and 1 when absent [33]. The Achilles tendon reflex was assessed bilaterally with a tendon hammer and scored 0 for normal, 1 for reflex present with reinforcement, and 2 for absent reflex [3, 6]. The total NDS score ranges from 0 to 10, with severity scores classified as mild (3-5), moderate (6-8), or severe (9-10) [3]. In this study, the diagnosis of DSPN was established based on the presence of moderate symptoms (NSS > 5) with mild neurological signs (NDS > 3) [3].

All neurological assessments were performed by two researchers who had been undergone training and standardization under the supervision of a neurologist to ensure consistency and reliability in the assessment procedures.

Randomization and Blinding

Participants who fulfilled all the inclusion and exclusion criteria were invited to participate, and written informed consent was obtained prior to enrolment. Eligible participants were randomized into the trial in a 1:1 ratio into either the intervention group or the control group. To ensure balanced group allocation, mixed block randomization was performed by independent statisticians using IBM SPSS software to assign patients to intervention and placebo groups randomly. Given the nature of the double-blind study, both participants and clinical staff were also blinded to the treatment allocation throughout the study period. In the event of a serious adverse reaction, an unblinding procedure was implemented to disclose the treatment allocation, enabling appropriate management of the participant's condition.

Study Medication

Participants in the intervention group received a fixed-dose combination of ALA and B vitamins (Bionerv®). Each tablet contained 300 mg ALA, 500 mcg methylcobalamin (vitamin B12), 8 mg pyridoxine (vitamin B6), and 39 mg thiamine (vitamin B1). They were instructed to take two tablets once daily after breakfast for 12 weeks, resulting in a total daily intake of 600 mg ALA, 1,000 mcg vitamin B12, 16 mg vitamin B6, and 78 mg vitamin B1. The control group was administered placebo tablets containing croscarmellose sodium, microcrystalline cellulose, silicon dioxide, and magnesium stearate, formulated with the same excipients as the active medication. The placebo was identical in appearance, color, and texture to the intervention tablets, ensuring effective blinding. Participants in both groups adhered to the same dosing schedule throughout the study. The 12-week treatment duration was selected based on prior clinical evidence, the timeline of nerve repair, safety considerations, and practical trial design constraints [35].

Table 1. A scoring approach for the neuropathic symptoms included in the TSS score (stabbing pain, burning pain, paranesthesia, and numbness)

Symptoms frequency	Symptom intensity			
	Absent	Slight	Moderate	Severe
Occasional	0	1.00	2.00	3.00
Frequent	0	1.33	2.33	3.33
Almost	0	1.66	2.66	3.66

Data Collection and Follow-Up Visit

Data were collected at three time points: baseline (prior to initiating study medications), week 6, and week 12. At baseline, neurological assessments, including the NSS and NDS, were conducted as part of the screening process to confirm the diagnosis of DSPN, as previously described. In addition, participants' sociodemographic information including age, gender, race, education level, occupation, monthly income, and marital status were recorded. Relevant medical history including duration and treatment of diabetes, presence of retinopathy, and comorbidities such as hypertension and dyslipidemia were also documented.

The total symptom score (TSS) was assessed to evaluate the severity of neuropathic symptom burden. TSS is a comprehensive assessment that quantifies neuropathic symptom burden by summing scores for four core symptoms: stabbing pain, burning pain, paraesthesia, and numbness. Each symptom is rated based on its frequency (occasional, frequent, or continuous) and intensity (absent, slight, moderate, or severe). The combined score ranges from 0 to 14.64, with higher TSS scores indicating greater frequency and intensity of neuropathic symptoms and reflecting a more severe symptom burden [35, 36]. The scoring method for TSS is presented in **Table 1**.

At the baseline visit, 6 mL of venous blood was collected to assess safety parameters, including a renal function test (RFT), which measures serum creatinine, and a liver function test (LFT), which assesses aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). Baseline haemoglobin A1c (HbA1c) levels were also measured.

During the week-6 follow-up visit, NSS and TSS were reassessed. At the final follow-up visit at week 12, participants underwent repeat evaluations of NSS, NDS, and TSS, as well LFT and RFT to monitor treatment safety and changes in clinical outcomes. Treatment adherence and adverse events were also assessed and documented throughout the study period.

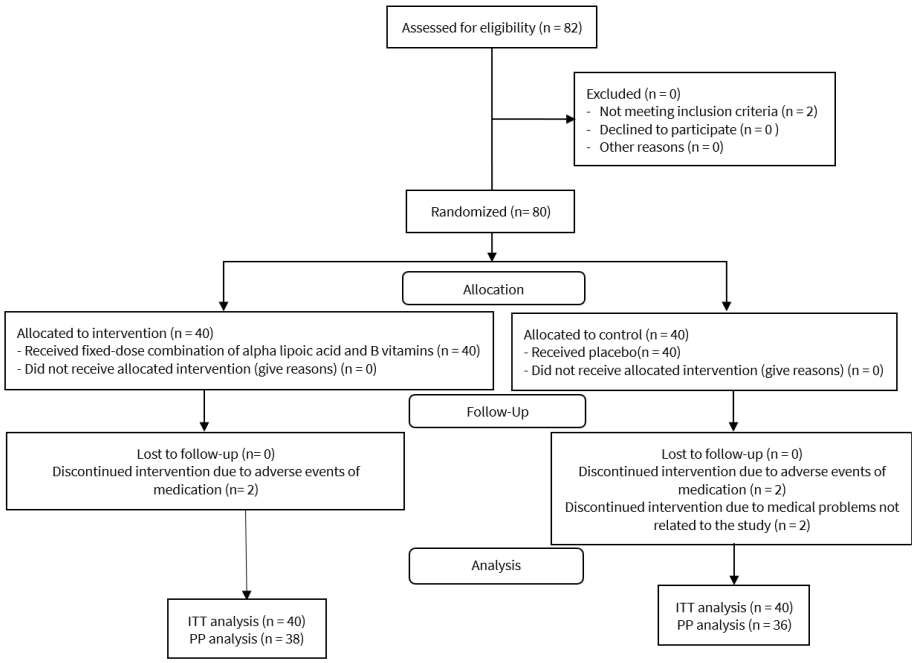

Figure 1. CONSORT diagram of the study participants [Figure 1 was reprinted from Research Methods and Reporting, 2025; 388, Hopewell S, Chan AW, Collins GS, et al, CONSORT 2025 statement: updated guideline for reporting randomised trials, Pages No 5., Copyright (2025), with permission from https://creativecommons.org/licenses/by/4.0/]

Study Outcomes

The primary outcome was the change in NSS, NDS, and TSS scores over the 12-week intervention period. Secondary outcomes included changes in safety parameters, namely LFT and RFT, as well as the incidence of treatment-related adverse effects among participants with DSPN.

Compliance and Safety Measures

A daily checklist form was provided to the participants to monitor their compliance with the study medication. Participants were instructed to complete the checklist after taking the fixed-dose combination of ALA and B vitamins or a placebo. Treatment compliance was defined as consuming at least 80% of the assigned medication throughout the study period. Participants who failed to meet compliance criterion were withdrawn from the study and were not replaced.

Safety measures included monitoring serious adverse events (SAEs) and adverse events throughout the study period. Participants were instructed to report any adverse effects experienced during the intervention. All reported events were documented using a standardized adverse effect reporting sheet. Any adverse events related to the study intervention were reported to the clinic and attended by a medical doctor from the research team when necessary. Participants who developed SAEs were withdrawn from the study and were not replaced.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 29 (IBM Corp., Armonk, NY, USA) [37] and R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) [38]. All analyses were conducted according to intention-to-treat (ITT) principle, which included all randomized participants who received at least one dose of the study medication. Missing outcome data were addressed using non-parametric, random forest-based multiple imputation implemented via the missRanger package in R. This approach applies chained random forests with predictive mean (M) matching to maintain the original data structure and distribution [39]. Diagnostic plots comparing observed and imputed values confirmed that the imputation procedure adequately preserved the underlying variable distributions.

For categorical variables, group differences were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were assessed for normality using the Shapiro-Wilk test and summarized as M ± standard deviation (SD). Baseline between-group comparisons were performed using independent t-tests. An RM-ANOVA was performed to evaluate significant changes in primary and secondary outcomes. The analysis aimed at examining:

(1) within-group changes over time (time effect), and

(2) overall differences between treatment groups (group effect).

The interaction between time and treatment (time x group effect) was also examined. Model results were presented as M (SD) and 95% confidence intervals (CIs). When Mauchly's test indicated sphericity violations, the Greenhouse-Geisser correction was applied. Two-tailed p-values of less than 0.05 were considered statistically significant.

Ethical Approvals

The study protocol was reviewed and approved by the Human Research Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/KK/23110893) on 31 March 2024. Written informed consent was obtained from all participants prior to their enrolment in the study.

RESULTS

The distribution of subjects throughout the trial is shown in **Figure 1**. Of the 82 participants initially screened for this study, 80 were eligible for randomisation, and two did not meet the inclusion criteria due to high serum creatinine levels.

Table 2. Baseline sociodemographic data and medical profile of the participants (n = 80)

Variables	Intervention (n = 40): n (%)	Placebo (n = 40): n (%)	Total (n = 80): n (%)	p-value
Age (year)	65.40 (7.05)*	62.95 (10.77)*	64.18 (9.13)*	0.233[a]
Gender				
Male	17 (43.6)	22 (56.4)	39 (48.8)	0.423[b]
Female	23 (56.1)	18 (43.9)	41 (51.2)	0.435[b]
Race				
Malay	36 (49.3)	37 (50.7)	73 (91.2)	0.907[b]
Others	4 (57.1)	3 (42.9)	7 (8.8)	0.705[b]
Education				
No/primary school	3 (42.9)	4 (57.1)	7 (8.8)	0.705[b]
Secondary school	29 (59.2)	20 (40.8)	49 (61.2)	0.199[b]
Tertiary level	8 (33.3)	16 (66.7)	24 (30.0)	0.102[b]
Occupation				
Employed	5 (38.5)	8 (61.5)	13 (16.2)	0.405[b]
Unemployed	35 (52.2)	32 (47.8)	67 (83.8)	0.714[b]
Monthly income (MYR)	2,424.48* (1,890.75)	2,935.75* (1,743.25)	2,680.11* (1,825.17)	0.212[a]
Marital status				
Single/widow	7 (50.0)	7 (50.0)	14 (17.5)	> 0.999[b]
Married	33 (50.0)	33 (50.0)	66 (82.5)	> 0.999[b]
Duration of DM (years)	16.18 (6.40)*	15.68 (7.98)*	15.93 (7.19)*	0.758[a]
Medication				
Metformin	30 (44.8)	37 (55.2)	67 (83.8)	0.392[b]
Gliclazide	8 (38.1)	13 (61.9)	21 (26.3)	0.275[b]
SGLT2 inhibitors	16 (57.1)	12 (42.9)	28 (35.0)	0.450[b]
DPP-4 inhibitors	3 (60.0)	2 (40.0)	5 (6.3)	0..655[b]
Insulin	32 (53.3)	28 (46.7)	60 (75.0)	0.606[b]
Hypertension	37 (51.4)	35 (48.6)	72 (90.0)	0.814[b]
Hyperlipidemia	39 (49.4)	40 (50.6)	79 (98.8)	0.910[b]
Retinopathy	14 (56.0)	11 (44.0)	25 (31.3)	0.549[b]

Note. *M (SD); [a]Independent t-test; [b]Chi-square test

Table 3. Baseline clinical characteristics and blood parameters of participants (n = 80)

Variable	M (SD)		Mean difference (95%CI)	t-statistics (df)	p-value*
	Intervention (n = 40)	Placebo (n = 40)			
TSS score	6.72 (2.82)	6.73 (2.82)	-0.01 (-1.26,1.25)	-0.01 (78)	0.991
Stabbing pain	1.65 (1.09)	1.69 (1.10)	-0.04 (0.53,0.45)	-0.17 (78)	0.866
Burning pain	0.96 (1.09)	0.85 (1.07)	0.11 (-0.37,0.59)	0.45 (78)	0.655
Paraesthesia	1.57 (1.10)	1.64 (1.15)	-0.07 (-0.58,0.43)	-0.29 (78)	0.767
Numbness	2.59 (0.74)	2.54 (0.66)	0.05 (-0.26,0.36)	0.32 (78)	0.749
NSS score	7.45 (1.15)	7.22 (1.25)	0.23 (-0.31, 0.76)	0.84 (78)	0.405
NDS score	8.28 (1.63)	8.45 (1.52)	-0.17 (-0.87,0.53)	-0.49 (78)	0.621
HbA1c (%)	9.18 (2.05)	9.87 (2.52)	-0.69 (-1.72,0.33)	-1.35 (78)	0.180
Creatinine (μmol/L)	90.17 (31.84)	85.93 (25.73)	4.24 (-8.64,17.14)	0.66 (78)	0.513
AST (U/L)	26.42 (11.31)	26.45 (11.79)	-0.03 (-5.17,5.12)	-0.01 (78)	0.992
ALT (U/L)	27.80 (17.64)	30.08 (17.31)	-2.28 (-10.05,5.50)	-0.58 (78)	0.562
ALP (U/L)	92.35 (28.52)	88.45 (25.63)	3.90 (-8.17,15.97)	0.64 (78)	0.522

Note. *Independent t-test

A total of 80 participants entered the run-in phase. During the intervention period, 74 participants completed the trial, whereas 6 (7.5%) discontinued participation at week 6 due to mild adverse events. Specifically, two participants (5%) from the intervention group and four (10%) participants from the control group (**Figure 1**). Following random forest-based imputation of missing values for the ITT analysis, diagnostic assessments demonstrated close alignment between observed and imputed datasets, indicating that the imputation did not materially alter the variable distributions. Therefore, the ITT dataset (n = 80) was used for the primary analysis, while the per-protocol (PP) dataset (n = 74) was analyzed for sensitivity comparison.

Participants Characteristics

At baseline, the sociodemographic characteristics and medical profiles of the participants were comparable between groups, with no significant differences observed, indicating homogeneity of the study population (**Table 2**). Similarly, no significant between-groups differences were found for baseline clinical characteristics and blood parameters. The M scores for TSS, stabbing pain, burning pain, paraesthesia, numbness, NSS, NDS, HbA1c, serum creatinine, ALT, AST and ALP were comparable between the intervention and control groups with $p > 0.05$ (**Table 3**).

Primary Outcomes

The comparison between TSS, NSS, and NDS scores between the intervention and placebo groups at baseline, 6 weeks and 12 weeks after treatment is shown in **Table 4**. An RM- ANOVA revealed two main effects: within-group effects and between-group effects. For the within-group effect which compared scores across baseline, 6 weeks, and 12 weeks within the intervention group, significant change were observed in the M TSS score (F [df] = 87.11 [2, 156], $p < 0.001$)

Table 4. Comparison of TSS, NSS, and NDS scores between intervention and placebo groups at baseline, 6 and 12 weeks after treatment (n = 80)

Variables/visit	M (SD)		Mean difference (95% CI)[a]	F-statistics (df)[a]	p-value[a]
	Intervention: (n = 40)	Placebo: (n = 40)			
TSS score (TSS within visit: F-statistics (df) = 87.11 [2, 156]; p < 0.001)					
Baseline	6.72 (2.82)	6.73 (2.82)	-0.01 (-1.26, 1.25)		
6 weeks	3.53 (2.50)	5.42 (2.83)	-1.89 (-3.08, -0.69)	14.89 (2, 156)	< 0.001
12 weeks	2.49 (1.88)	4.98 (2.99)	-2.49 (-3.59, -1.36)		
Stabbing pain (stabbing pain within visit: F-statistics [df] = 37.43 [2, 156]; p < 0.001)					
Baseline	1.65 (1.09)	1.69 (1.10)	-0.04 (-0.53, 0.45)		
6 weeks	0.80 (0.84)	1.33 (1.02)	-0.53 (-0.94, -0.11)	6.35 (2, 156)	0.002
12 weeks	0.53 (0.77)	1.23 (1.09)	-0.70 (-1.12, -0.28)		
Burning pain (burning pain within visit: F-statistics [df] = 27.01 [2, 156]; p < 0.001)					
Baseline	0.96 (1.09)	0.85 (1.07)	0.11 (-0.37, 0.59)		
6 weeks	0.36 (0.69)	0.47 (0.86)	-0.11 (-0.46, 0.24)	1.19 (2, 156)	0.306
12 weeks	0.26 (0.54)	0.39 (0.70)	-0.13 (-0.41, 0.15)		
Paraesthesia (paraesthesia within visit: F-statistics [df] = 41.49 [2, 156]; p < 0.001)					
Baseline	1.57 (1.10)	1.65 (1.15)	-0.07 (-0.58, 0.43)		
6 weeks	0.71 (0.77)	1.29 (1.08)	-0.58 (-1.00,-0.17)	7.73 (2, 156)	< 0.001
12 weeks	0.33 (0.46)	1.16 (1.16)	-0.83 (-1.22, -0.43)		
Numbness (numbness within visit: F-statistics [df] = 66.69 [2, 156]; p < 0.001)					
Baseline	2.59 (0.75)	2.54 (0.66)	0.05 (-0.26, 0.36)		
6 weeks	1.66 (0.96)	2.32 (0.85)	-0.66 (-1.06, -0.26)	22.68 (2, 156)	< 0.001
12 weeks	1.36 (0.86)	2.21 (0.84)	-0.85 (-1.23, -0.47)		
NSS score (NSS within visit: F-statistics [df] = 44.56 [2, 156]; p < 0.001)					
Baseline	7.45 (1.15)	7.22 (1.25)	0.23 (-0.31, 0.76)		
6 weeks	5.33 (2.41)	6.37 (1.63)	-1.04 (-1.96, -0.13)	15.80 (2, 156)	< 0.001
12 weeks	4.18 (2.39)	6.45 (1.78)	-2.27 (-3.21, -1.33)		
NDS score (NDS within visit: F-statistics [df] = 11.20 [2, 78]; p < 0.001)					
Baseline	8.28 (1.63)	8.45 (1.52)	-0.17 (-0.87, 0.53)	3.73 (2, 78)	0.057
12 weeks	7.11 (1.95)	8.14 (1.83)	-1.03 (-1.87, -0.19)		

Note. [a]RM-ANOVA

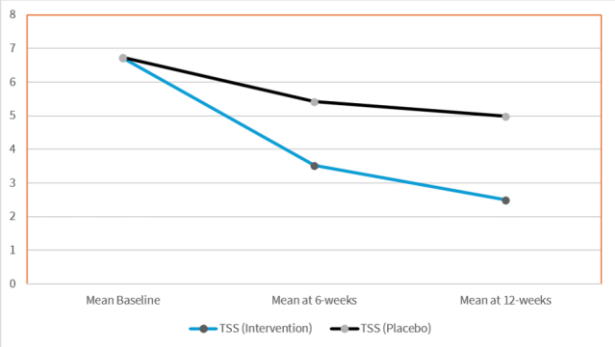

Figure 2. TSS M scores of the intervention and placebo group after 12 weeks of treatment (Figure created by the authors based on data obtained from this study)

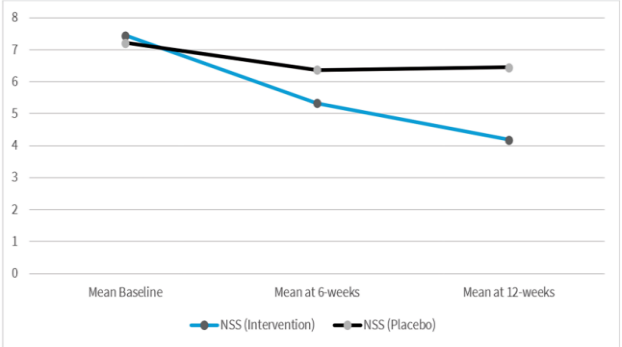

Figure 3. NSS M scores of the intervention and placebo group after 12 weeks of treatment (Figure created by the authors based on data obtained from this study)

and TSS components, NSS (F [df] = 44.56 [2, 156]; p < 0.001) and NDS score (F [df] = 11.20 [2, 78]; p < 0.001).

For the between-group effect, significant reductions in the M score of TSS, stabbing pain, paraesthesia, numbness, and NSS were observed in the intervention group compared to the placebo group over the 12-week treatment period. In the intervention group, the M TSS score significantly decreased from 6.72 ± 2.82 at baseline to 3.53 ± 2.50 in 6 weeks and 2.49 ± 1.88 at 12 weeks, compared to the placebo group (p < 0.001) (**Figure 2**).

Similarly, significant reductions were observed in several TSS components within the intervention group. Stabbing pain scores significantly decreased from 1.65 ± 1.09 at baseline to 0.80 ± 0.84 in 6 weeks and 0.53 ± 0.77 in 12 weeks compared with the placebo group (p < 0.001). Paraesthesia scores also decreased significantly from baseline 1.57 ± 1.10 to 0.71 ± 0.77 in 6 weeks and 0.33 ± 0.46 in 12 weeks compared to the placebo group (p < 0.001). For numbness, the scores also reduced significantly from baseline 2.59 ± 0.75 to 1.66 ± 0.96 in 6 weeks and 1.36 ± 0.86 in 12 weeks compared to the placebo group (p < 0.001). Although not significant, the M changes in TSS components for burning pain decreased when compared with the placebo group. The score reduced from 0.96 ± 1.09 at baseline to 0.36 ± 0.69 in 6 weeks and 0.26 ± 0.54 in 12 weeks (p = 0.107).

Meanwhile, the NSS M scores in the intervention group showed a significant decrease over the 12-week period from 7.45 ± 1.15 at baseline to 5.33 ± 2.41 in 6 weeks and 4.18 ± 2.39 in 12 weeks, compared with the placebo group (p < 0.001) (**Figure 3**).

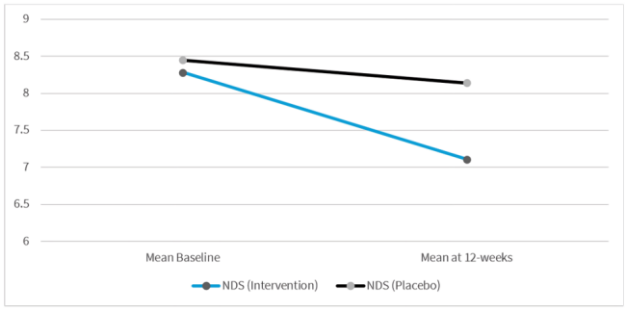

Figure 4. NDS M scores of the intervention and placebo group after 12 weeks of treatment (Figure created by the authors based on data obtained from this study)

The M NDS score in the intervention group also decreased from 8.28 ± 1.63 at baseline to 7.11 ± 1.95 in 12 weeks, although not significant as compared to the placebo group (p = 0.057) (**Figure 4**).

Secondary Outcomes

Safety parameter outcomes over the 12-weeks study period is shown in **Table 5**. Renal and hepatic parameters showed no significant differences within or between groups over the study period. Serum creatinine levels remained stable in both the intervention and placebo groups, with no significant changes (p = 0.784). Similarly, liver enzymes (AST, ALT, and ALP) showed no significant changes after 12 weeks of treatment (p > 0.05).

Adverse Event

The most frequently reported adverse event in the intervention group during the second visit was nausea (15%), followed by itchiness (5%), dizziness (5%), and light-headedness (5%). A similar adverse event profile was observed in the placebo group, with nausea reported in 5%, itchiness in 2.5%, dizziness in 2.5%, and light-headedness in 2.5%. During the 12-week follow-up, the incidence of adverse events declined, with only 2 participants reporting mild but tolerable nausea: 1 participant (2.5%) from the intervention group and 1 participant (2.5%) from the placebo group (**Table 6**).

Two participants (5%) in the intervention group discontinued the study treatment due to nausea and itchiness. In the placebo group, four participants (10%) withdrew from the study; two of them discontinued due to unrelated medical conditions (one reported femur pain post-plating, and another experienced an acute exacerbation of bronchial asthma).

Table 6. Side effects of medication (n = 80)

Side effects	Intervention (n = 40): n (%)	Placebo (n = 40): n (%)
Visit 2		
Nausea	6 (15.0)	2 (5.0)
Itchiness	2 (5.0)	1 (2.5)
Dizziness	2 (5.0)	1 (2.5)
Light-headedness	2 (5.0)	1 (2.5)
Visit 3		
Nausea	1 (2.5)	1 (2.5)

All adverse events were assessed by the investigator and determined to have an “unlikely” causal relationship with the study medication. The remaining two participants in the placebo group discontinued due to nausea. No SAEs were reported during this study period.

DISCUSSION

Symptomatic DSPN significantly impacts the quality of life for patients with T2DM [11]. Therefore, effective treatment strategies are essential to alleviate symptoms and improve functional outcomes. In this study, the intervention group that received a fixed-dose combination of ALA and B vitamins (B12, B6, and B1) (Bionerv®) demonstrated significant improvements across all key neuropathy-related outcomes, including TSS score, TSS score components (stabbing pain, paraesthesia, numbness) and NSS score over a 12-week treatment period compared to the placebo group. A previous Korean study investigating the efficacy of oral ALA (600 mg/day) in patients with painful DPN (n = 52) reported a significant decrease in M TSS score from 5.15 ± 3.57 at baseline to 3.52 ± 3.39 at 12 weeks of treatment. Significant decreases were also observed in M sub-scores of stabbing pain (baseline 1.62 ± 1.26 to 12-weeks 1.04 ± 0.93), paraesthesia (baseline 1.27 ± 1.29 to 12-weeks 0.74 ± 1.04), and numbness (baseline 1.03 ± 1.16 to 12-weeks 0.65 ± 0.97) [35].

Similarly, a study conducted in Mexico among patients with DPN (n = 45) evaluated the efficacy of ALA (600 mg/day) over 20 weeks. The M score of TSS decreased from 8.9 ± 1.8 at baseline to 3.46 ± 2.0 after 4 weeks in phase I and further improved from 3.7 ± 1.9 to 2.5 ± 2.5 at 16 weeks during phase II of treatment [40]. In Pakistan, treatment with ALA 600 mg/day among diabetic patients with a baseline TSS of ≥ 4.0 (n = 110), reported an M TSS reduction of 2.38 ± 1.99, compared with 0.53 ± 1.32 in the control group [15].

Table 5. Comparison of safety parameters of intervention and placebo groups at baseline and 12 weeks after treatment (n = 80)

Variables/visit	M (SD)		Mean difference (95% CI) [a]	F-statistics (df)[a]	p-value[a]
	Intervention: (n = 40)	Placebo: (n = 40)			
Creatinine (µmol/L) (creatinine within visit: F-statistics [df] = 1.01 [1, 78]; p = 0.319)					
Baseline	90.17 (31.84)	85.93(25.73)	4.24 (-8.64, 17.14)	0.07 (1, 78)	0.784
12 weeks	91.16 (33.39)	87.65 (23.75)	-3.51 (-16.41, 9.39)		
AST (U/L) (AST within visit: F-statistics [df] = 1.16 [1, 78]; p = 0.285)					
Baseline	26.42(11.31)	26.45(11.79)	-0.03 (-5.17, 5.12)	0.02 (1, 78)	0.885
12 weeks	25.36 (11.77)	25.64(11.52)	-0.28 (-5.46, 4.91)		
ALT (U/L) [ALT within visit: F-statistics [df] =0.01 [1,78]; p = 0.943)					
Baseline	27.80 (17.64)	30.08(17.31)	-2.28 (-10.05, 5.50)	0.08 (1, 78)	0.772
12 weeks	28.03(16.96)	29.70(18.63)	-1.67 (-9.61, 6.25)		
ALP (U/L) [ALP within visit: F-statistics [df] = 2.52 [1,78]; p = 0.117)					
Baseline	92.35(28.52)	88.45(25.63)	3.90 (-8.17, 15.97)	0.25 (1, 78)	0.617
12 weeks	94.44(27.73)	92.47(27.87)	1.97 (-10.41, 14.34		

Note. [a]RM-ANOVA

Earlier clinical trials also supported the efficacy of ALA in the management of DSPN. The SYDNEY 2 trial conducted in 2006 evaluated the effects of ALA (600 mg/day) among diabetes patients with symptomatic DSPN (n = 45) for 5 weeks. The study demonstrated a reduction in the TSS M score from 9.44 ± 1.86 at baseline to 4.85 ± 3.035 in 5 weeks, compared with the placebo group. Significant decrease was also observed across all TSS components, including stabbing pain, burning pain, paraesthesia, and numbness ($p < 0.05$) [13]. Subsequently, the NATHAN 1 trial conducted in 2011 to evaluate the long-term efficacy and safety of ALA (600 mg/day) over a 4-year period in patients with mild to moderate diabetic distal symmetric sensorimotor polyneuropathy (n = 460) concluded that long-term ALA treatment resulted in a clinically meaningful improvement and prevention of progression of neuropathic impairments and was well tolerated [14].

In addition to improvements in TSS scores, our study also demonstrated significant reductions in NSS and NDS scores among patients receiving the fixed-dose ALA and B vitamins, although the between-group difference for NDS did not reach statistical significance ($p = 0.057$). These findings are consistent with previous studies. An Egyptian study investigating the efficacy of oral ALA 600 mg twice daily over 6 months among DPN patients (n = 200) reported significantly greater improvements in NSS and NDS scores in the ALA-treated patients [21]. Likewise, a study from Greece to evaluate the effect of ALA (600 mg/day) on patients with painful diabetic neuropathy (n = 72) found that the M of NSS reduced from baseline (7.9, range 4-10) to 5.3 (range 2-10) at day 40 of treatment [41]. Earlier work from Germany also demonstrated significant reductions in NDS following treatment with ALA (600 mg/day) for 3 weeks in patients with symptomatic diabetic polyneuropathy (n = 24) [42].

The beneficial effects of ALA may be attributed to its antioxidant and anti-inflammatory properties. A systematic review and meta-analysis on the effect of ALA on oxidative stress parameters found that ALA supplementation may reduce lipid peroxidation and enhance antioxidant defence, thereby contributing to a reduction of reactive oxygen species [43]. Consequently, ALA has been proposed as an effective intervention for treating DSPN due to its anti-inflammatory, anti-hyperglycemic, and antioxidant properties, as well as its function in the endothelial activation and lipid metabolism parameters [44]. For patients who are unable to tolerate first-line pharmacotherapies for painful DSPN due to their side effects and who prefer a nutritional supplement approach, ALA 600 mg daily is recommended, as it is a potent antioxidant that may alleviate oxidative stress, while targeting the underlying pathophysiology of neuropathy, and mitigate neuropathic pain [10].

Neurotropic B vitamins, specifically B1, B6, and B12, consistently protect nerves from detrimental environmental factors. Vitamin B1 functions as a site-specific antioxidant, vitamin B6 regulates nerve metabolism, and vitamin B12 preserves myelin sheaths. Adequate levels of vitamins B1, B6, and B12 facilitates crucial nerve regeneration by promoting the formation of new cellular structures. Conversely, deficiencies in these vitamins may accelerate irreversible nerve deterioration and discomfort, ultimately resulting in peripheral neuropathy [45]. Vitamin B12 deficiency is prevalent among patients with T2DM, particularly among those receiving metformin therapy, which interferes with calcium-dependent absorption of the vitamin B12 intrinsic factor complex in the terminal ileum [46]. Prevalence of vitamin B12 deficiency after metformin use has been reported to be 22.2% and concurrent supplementation of B vitamins may potentially protect against the deficiency [47].

Regarding safety outcomes, our study found no significant differences between the intervention and placebo groups in renal and hepatic parameters. Serum creatinine, ALT, AST, and ALP remained stable and unchanged throughout the study period. These findings are consistent with a study conducted in Greece after 12 months of treatment with ALA and vitamin B12 [48], in Egypt after 3 months of ALA [16], and the NATHAN 1 trial, a long-term ALA supplementation of 600 mg/day for over 4 years [14]. This indicates a favorable safety profile for the ALA and B vitamins combination, supported by previous studies [16, 48].

In this study, side effects were reported more frequently in the intervention group, with nausea being the most common (15%) at six weeks. This observation is consistent with previous ALA studies in which nausea, vomiting, and vertigo were reported as common side effects [13, 21]. The placebo group reported fewer side effects, consistent with expectations for inactive control. Overall, the adverse effects observed were mild and self-limiting, supporting the potential suitability of ALA and B vitamins in long-term management when accompanied by appropriate patient counselling.

Despite the findings, several limitations should be acknowledged. First, although the 2010 ADA statement recommended that a diagnosis of DSPN requires both abnormal NCS and the presence of symptoms or signs of neuropathy [49], the 2017 ADA statement emphasized that the diagnosis of DSPN is primarily clinical, based on typical symptoms and signs of symmetrical distal sensory loss [2]. Electrophysiological testing is reserved for atypical cases or diagnostic uncertainty, or when an alternative etiology is suspected [2, 50]. In the present study, the diagnosis of DSPN was established using validated clinical tools, namely the NSS and NDS scores, which have been widely applied to establish the diagnosis of DSPN in previous studies conducted in Brazil, Germany, and Malaysia [6, 51, 52]. Nevertheless, future studies should incorporate NCS as both a diagnostic and an outcome measure to improve diagnostic precision and strengthen evaluation of treatment effects.

Second, baseline serum B vitamin levels were not assessed in this study. Given that deficiencies in vitamins B1, B6, and B12 are recognized contributors to the pathogenesis and progression of DSPN [45], this omission makes it unclear whether the observed benefits resulted from correcting deficiencies or from the pharmacological effects of supplementation. Future studies should therefore include these measurements to better clarify their role.

Third, this is a single-center study, which may limit the generalizability of the findings, as the study population may not fully represent the broader, more diverse population of patients with T2DM. Multi-center trials with larger, more diverse populations are needed to improve external validity.

Fourth, the relatively short follow-up duration limits conclusions regarding the long-term efficacy and sustainability of treatment benefits. Although improvements in neuropathy symptoms were observed over 12 weeks, DSPN is a chronic condition requiring long-term management. Extended follow-up studies are necessary to assess sustained outcomes and disease progression.

CONCLUSIONS

This study highlights the significant benefits of a fixed-dose combination of ALA and B vitamins in reducing DSPN symptoms among patients with T2DM. Over 12 weeks of treatment, the intervention group demonstrated improvements in symptom relief and overall neuropathy scores, including TSS, NSS, and NDS, compared with the placebo group. The intervention group demonstrated acceptable short-term tolerability over 12 weeks, with mild and self-limiting adverse events and no clinically significant changes in renal or hepatic parameters. Nevertheless, while the results are promising, further research involving multi-center trials, longer follow-up periods, and diverse populations is necessary to confirm these benefits for DSPN management.

Author contributions: CNACA: conceptualization, data curation, formal analysis, writing – original draft; **NM:** conceptualization, data curation, formal analysis, supervision, funding acquisition, writing – original draft, writing – review & editing; **ND:** supervision, writing – original draft, writing – review & editing; **ZMY:** writing – review & editing; **WMAWA:** writing – review & editing; **RRMR:** writing – review & editing; **CYC:** writing – review & editing; **NMY:** writing – review & editing. All authors agreed with the results and conclusions.

Funding: This study was supported by an educational grant from BREGO Life Sciences Sdn. Bhd. (R504-LR-GAL007-0000000133-B152).

Acknowledgments: The authors would like to thank all participants and contributors who facilitated the successful completion of this study. The authors would also like to thank Dr. Anna Misyail Abdul Rashid, neurologist from Universiti Putra Malaysia, for her invaluable assistance in the preparation of the research proposal.

Ethical statement: This study was approved by the Human Research Ethics Committee at Universiti Sains Malaysia on 31 March 2024 with approval number USM/JEPeM/KK/23110893.

AI statement: The authors acknowledge the use of AI-based language tools, including Copilot and Grammarly, to enhance grammar, sentence structure, and overall readability of the manuscript. All AI-assisted outputs were critically reviewed by the authors to ensure accuracy, integrity, and reliability. Final interpretations and conclusions presented in this article were exclusively determined by the authors.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. Darivemula S, Nagoor K, Patan S, Reddy N, Deepthi C, Chittooru C. Prevalence and its associated determinants of diabetic peripheral neuropathy (DPN) in individuals having type-2 diabetes mellitus in rural south India. Indian J Community Med. 2019;44(2):88-91.
2. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136-54. https://doi.org/10.2337/dc16-2042 PMid:27999003
3. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36:150-54. https://doi.org/10.1007/BF00400697 PMid:8458529
4. Feldman EL, Stevens M, Thomas P, Brown M, Canal N, Greene D. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care. 1994;17(11):1281-89. https://doi.org/10.2337/diacare.17.11.1281 PMid:7821168
5. Sendi R, Mahrus A, Saeed R, Mohammed M, Al-Dubai S. Diabetic peripheral neuropathy among Saudi diabetic patients: A multicenter cross-sectional study at primary health care setting. J Family Med Prim Care. 2020;9(1):197-201. https://doi.org/10.4103/jfmpc.jfmpc_927_19 PMid:32110590
6. Pfannkuche A, Alhajjar A, Ming A, Walter I, Piehler C, Mertens PR. Prevalence and risk factors of diabetic peripheral neuropathy in a diabetics cohort: Register initiative diabetes and nerves. Endocr Metab Sci. 2020;1(1-2):100053. https://doi.org/10.1016/j.endmts.2020.100053
7. Khan KS, Christensen DH, Nicolaisen SK, et al. Falls and fractures associated with type 2 diabetic polyneuropathy: A cross-sectional nationwide questionnaire study. J Diabetes Investig. 2021;12(10):1827-34. https://doi.org/10.1111/jdi.13542 PMid:33686761
8. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes Care. 2023;46(1):209-21. https://doi.org/10.2337/dci22-0043 PMid:36548709
9. Pouwer F, Mizokami SK, Reeves ND, et al. Psychosocial care for people with diabetic neuropathy: Time for action. Diabetes Care. 2024;47(1):17-25. https://doi.org/10.2337/dci23-0033 PMid:38117989
10. Feldman EL. Management of diabetic neuropathy. UpToDate; 2024. Available at: https://www.uptodate.com/contents/management-of-diabetic-neuropathy (Accessed: 20 January 2025).
11. Ziegler D, Tesfaye S, Spallone V, et al. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations. Diabetes Res Clin Pract. 2022;186:1-23. https://doi.org/10.1016/j.diabres.2021.109063 PMid:34547367
12. Viana MDM, Lauria PSS, Lima AAd, Opretzka LCF, Marcelino HR, Villarreal CF. Alpha-lipoic acid as an antioxidant strategy for managing neuropathic pain. Antioxidants. 2022;11(12):1-19. https://doi.org/10.3390/antiox11122420 PMid:36552628
13. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: The SYDNEY 2 trial. Diabetes Care. 2006;29(11):2365-70. https://doi.org/10.2337/dc06-1216 PMid:17065669
14. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: The NATHAN 1 trial. Diabetes Care. 2011;34(9):2054-60. https://doi.org/10.2337/dc11-0503 PMid:21775755
15. Siddique N, Awais F, Shakil M, Sarwar S, Kakar NH, Ullah MI. Effect of anti-oxidant (α-lipoic acid) treatment on improvement of diabetic neuropathic pain. Rawal Med J. 2021;46(1):33-6.
16. Elbadawy AM, Abd Elmoniem RO, Elsayed AM. Alpha lipoic acid and diabetes mellitus: Potential effects on peripheral neuropathy and different metabolic parameters. Alex J Med. 2021;57(1):113-20. https://doi.org/10.1080/20905068.2021.1907961

17. Abubaker SA, Alonazy AM, Abdulrahman A. Effect of alpha-lipoic acid in the treatment of diabetic neuropathy: A systematic review. Cureus. 2022;14(6):1-7. https://doi.org/10.7759/cureus.25750 PMid:35812639
18. Ziegler D, GriesFA. α-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. Diabetologia. 1997;46(2):62-6. https://doi.org/10.2337/diab.46.2.S62 PMid:9285502
19. Liu F, Zhang Y, Yang M, et al. Curative effect of alpha-lipoic acid on peripheral neuropathy in type 2 diabetes: A clinical study. J Chin Med Assoc. 2007;87(38):2706-9.
20. Tankova T, Koev D, Dakovska L. Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study). Rom J Intern Med. 2004;42(2):457-64.
21. El-Nahas MR, Elkannishy G, Abdelhafez H, Elkhamisy ET, El-Sehrawy AA. Oral alpha lipoic acid treatment for symptomatic diabetic peripheral neuropathy: A randomized double-blinded placebo-controlled study. Endocr Metab Immune Disord Drug Targets. 2020;20(9):1531-34. https://doi.org/10.2174/1871530320666200506081407 PMid:32370731
22. Gilron I, Robb S, Tu D, et al. Double-blind, randomized, placebo-controlled crossover trial of alpha-lipoic acid for the treatment of fibromyalgia pain: The IMPALA trial. Pain. 2021;162(2):561-68. https://doi.org/10.1097/j.pain.0000000000002028 PMid:32773602
23. Reljanovic M, Reichel G, Rett K, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (α-lipoic acid): A two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Free Radic Res. 1999;31(3):171-9. https://doi.org/10.1080/10715769900300721 PMid:10499773
24. Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A 7-month multicenter randomized controlled trial (ALADIN III study). Diabetes Care. 1999;22(8):1296-01. https://doi.org/10.2337/diacare.22.8.1296 PMid:10480774
25. Hsieh RY, Huang I, Chen C, Sung JY. Effects of oral alpha-lipoic acid treatment on diabetic polyneuropathy: A meta-analysis and systematic review. Nutrients. 2023;15(16):1-14. https://doi.org/10.3390/nu15163634 PMid:37630823
26. Orellana DM, Lopez CM, Barahona VM, et al. Effectiveness of alpha-lipoic acid in patients with neuropathic pain associated with type I and type II diabetes mellitus: A systematic review and meta-analysis. Medicine. 2023;102(44):1-9. https://doi.org/10.1097/MD.0000000000035368 PMid:37933068
27. Fillah AM, Waafi AK, d'Arqom A, Qorib MF, Rimbun, Sharifah ZSA. Vitamins supplementation for nerve regeneration: A systematic review of clinical evidence. Trends Sci. 2025;22(4):1-21. https://doi.org/10.48048/tis.2025.9421
28. Farah S, Yammine K. A systematic review on the efficacy of vitamin B supplementation on diabetic peripheral neuropathy. Nutr Rev. 2022;80(5):1340-55. https://doi.org/10.1093/nutrit/nuab116 PMid:34990506
29. Karaganis S, Song XJ. B vitamins as a treatment for diabetic pain and neuropathy. J Clin Pharm Ther. 2021;46(5):1199-12. https://doi.org/10.1111/jcpt.13375 PMid:33565138
30. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects.JAMA. 2013;310(20):2191-94. https://doi.org/10.1001/jama.2013.281053 PMid:24141714
31. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: Updated guideline for reporting randomised trials. BMJ. 2025;388:1-9. https://doi.org/10.12771/emj.2025.00409 PMid:40739975
32. Asad A, Hameed MA, Khan UA, Ahmed N, Butt MU. Reliability of the neurological scores for assessment of sensorimotor neuropathy in type 2 diabetics. J Pak Med Assoc. 2010;60(3):166-70.
33. Kisozi T, Mutebi E, Kisekka M, et al. Prevalence, severity and factors associated with peripheral neuropathy among newly diagnosed diabetic patients attending Mulago Hospital: A cross-sectional study. Afr Health Sci. 2017;17(2):463-73. https://doi.org/10.4314/ahs.v17i2.21 PMid:29062342
34. Kamel SR, Hamdy M, Abo Omar HA, Kamal A, Ali LH, Abd Elkarim AH. Clinical diagnosis of distal diabetic polyneuropathy using neurological examination scores: Correlation with nerve conduction studies. Egypt Rheumatol Rehabil. 2015;42:128-36. https://doi.org/10.4103/1110-161X.163945
35. Won JC, Kwon HS, Moon SS, et al. Gamma-linolenic acid versus alpha-lipoic acid for treating painful diabetic neuropathy in adults: A 12-week, double-placebo, randomized, noninferiority trial. Diabetes Metab J. 2020;44(4):542-54. https://doi.org/10.4093/dmj.2019.0099 PMid:31701699
36. Ziegler D, Hanefeld M, Ruhnau K, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN study). Diabetologia. 1995;38(12):1425-33. https://doi.org/10.1007/BF00400603 PMid:8786016
37. IBM Corp. IBM SPSS statistics for Windows, version 29. Armonk, NY: IBM Corp; 2024. Available at: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-29 (Accessed: 22 August 2024).
38. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2023. Available at: https://www.R-project.org (Accessed: 2 August 2025).
39. Mayer M. missRanger: Fast imputation of missing values. R package version 2.6.2. 2025. Available at: https://mayer79.github.io/missRanger (Accessed: 2 August 2025).
40. Garcia-Alcala H, Santos Vichido CI, Islas Macedo S, et al. Treatment with α-lipoic acid over 16 weeks in type 2 diabetic patients with symptomatic polyneuropathy who responded to initial 4-week high-dose loading. J Diabetes Res. 2015;2015:189857. https://doi.org/10.1155/2015/189857 PMid:26345602
41. Agathos E, Tentolouris A, Eleftheriadou I, et al. Effect of α-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. J Int Med Res. 2018;46(5):1779-90. https://doi.org/10.1177/0300060518756540 PMid:29517942
42. Ruhnau KJ, Meissner H, Finn JR, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (α-lipoic acid) in symptomatic diabetic polyneuropathy. Diabet Med. 1999;16(12):1040-43. https://doi.org/10.1046/j.1464-5491.1999.00190.x PMid:10656234

43. Zonooz SR, Hasani M, Morvaridzadeh M, et al. Effect of alpha-lipoic acid on oxidative stress parameters: A systematic review and meta-analysis. J Funct Foods. 2021;87:1-12. https://doi.org/10.1016/j.jff.2021.104774
44. Sementina A, Cierzniakowski M, Rogalska J, Piechowiak I, Spichalski M, Araszkiewicz A. A novel approach to alpha-lipoic acid therapy in the treatment of diabetic peripheral neuropathy. J Med Sci. 2022;91(3):181-91. https://doi.org/10.20883/medical.e714
45. Baltrusch S. The role of neurotropic B vitamins in nerve regeneration. Biomed Res Int. 2021;1:1-9. https://doi.org/10.1155/2021/9968228 PMid:34337067
46. Malla D, Bajracharya MR, Karki BB, Rajouria AD, Shrestha PS. Prevalence of vitamin B12 deficiency in patients with type II diabetes mellitus on metformin. J Diabet Endocrinol Assoc Nepal. 2021;5(1):39-43. https://doi.org/10.3126/jdean.v5i1.38916
47. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine. 2019;98(46):1-8. https://doi.org/10.1097/MD.0000000000017918 PMid:31725641
48. Didangelos T, Karlafti E, Kotzakioulafi E, et al. Efficacy and safety of the combination of superoxide dismutase, alpha lipoic acid, vitamin B12, and carnitine for 12 months in patients with diabetic neuropathy. Nutrients. 2020;12(11):3254-65. https://doi.org/10.3390/nu12113254 PMid:33114210
49. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-93. https://doi.org/10.2337/dc10-1303 PMid:20876709
50. American Diabetes Association Professional Practice Committee for Diabetes. Retinopathy, neuropathy, and foot care: Standards of care in diabetes 2026. Diabetes Care. 2026;49(1):261-76. https://doi.org/10.2337/dc26-S012
51. Reis de Matos M, Santos-Bezerra DP, Dias Cavalcante CDG, et al. Distal symmetric and cardiovascular autonomic neuropathies in Brazilian individuals with type 2 diabetes followed in a primary health care unit: A cross-sectional study. Int J Environ Res Public Health. 2020;17(9):1-9. https://doi.org/10.3390/ijerph17093232 PMid:32384735
52. Ali H, May JM, Yein LP, Rashid AA. Prevalence of diabetic peripheral neuropathy among type 2 diabetes mellitus and its associated factors in a primary care clinic in Malacca: A cross-sectional study. Mal J Med Health Sci. 2024;20(5):219-25. https://doi.org/10.47836/mjmhs20.5.28