Effect of α-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy

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Abstract

Objective: To examine the effect of α-lipoic acid on neuropathic symptoms in patients with diabetic neuropathy (DN).

Methods: Patients with painful DN were treated with 600 mg/day α-lipoic acid, orally, for 40 days. Neuropathy Symptom Score (NSS), Subjective Peripheral Neuropathy Screen Questionnaire (SPNSQ) and douleur neuropathique (DN)4 questionnaire scores were assessed at baseline and day 40. Quality-of-life treatment effects were assessed by Brief Pain Inventory (BPI), Neuropathic Pain Symptom Inventory (NPSI) and Sheehan Disability Scale (SDS). Changes in body weight, arterial blood pressure, fasting serum glucose and lipids were also assessed.

Results: Out of 72 patients included, significant reductions in neuropathic symptoms were shown by reduced NSS, SPNSQ and DN4 scores at day 40 versus baseline. BPI, NPSI, and SDS in terms of work disability, social life disability, and family life disability scores were also significantly reduced. Moreover, 50% of patients rated their health condition as 'very much better' or 'much better' following α-lipoic acid administration. Fasting triglyceride levels were reduced,

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but no difference was found in body weight, blood pressure, fasting glucose, or other lipids at day 40 versus baseline.

Conclusions: A-lipoic acid administration was associated with reduced neuropathic symptoms and triglycerides, and improved quality of life.

Introduction

Diabetes mellitus is a major public health problem, reaching epidemic proportions globally. Approximately 9% of adults are estimated to be affected by diabetes worldwide, however, around half of the cases remain undiagnosed.[1] Peripheral neuropathy is a common complication in patients with diabetes, with population and clinic-based studies suggesting prevalence rates of 5.3–47.6% for peripheral sensorimotor neuropathy.[2–6] Diabetic peripheral neuropathy is associated with older age, long duration of diabetes mellitus, poor glycemic control, increased lipid levels and high blood pressure.[2] In addition to sensory loss and motor deficits, diabetic neuropathy may be associated with intractable neuropathic pain. Significant improvements have been made in therapeutic options that target mainly neuropathic symptoms, but not in those that target pathogenetic mechanisms.[2] Despite therapeutic advances, diabetic neuropathy is still associated with substantial morbidity, increased mortality, and impaired quality of life (QoL) compared with patients who have diabetes but no neuropathy.

Oxidative stress is thought to possess a significant role in the pathogenesis of diabetic neuropathy.[7] A-lipoic acid, a very potent antioxidative agent, has been shown to improve nerve blood flow, reduce oxidative stress and improve distal nerve conduction in a rat model of diabetic neuropathy.[8] Clinical studies investigating the effect of α-lipoic acid on diabetic neuropathy have revealed promising results in terms of neuropathic symptoms.[9–12] In addition, a recent meta-analysis revealed that treatment with 300–600 mg/day α-lipoic acid, intravenously (i.v.) for 2–4 weeks, was safe and significantly improved nerve conduction velocity and neuropathic symptoms.[13]

The aim of the current study was to prospectively investigate the effect of 600 mg/day α-lipoic acid (Nevralip Retard®, Medical Pharmaquality, Athens, Greece) administered orally for 40 days, on symptoms, laboratory parameters, QoL, and overall health status of patients with painful diabetic neuropathy.

Patients and methods

Study population and setting

This prospective, interventional study was conducted at Laiko General Hospital, Athens, Greece, between September 2015 and May 2016. Patients with type 1 or type 2 diabetes mellitus, who were followed at the outpatient Diabetes Clinic of Laiko General Hospital and were eligible to

participate, were consecutively enrolled into the study. Inclusion criteria comprised the following: (1) patient's agreement to participate; (2) aged 18–75 years; (3) diabetic peripheral neuropathy diagnosis and $\geq$ one typical painful neuropathic symptom such as burning, shooting pain, paraesthesia, muscle cramps or allodynia, in the feet, for $\geq$ 6 months, that interfered with daily life or sleep; and (4) if treated with medications for painful diabetic neuropathy, treatment had to be stable for $\geq$ 3 months before recruitment into the study. Exclusion criteria comprised: (1) causes of neuropathy other than diabetes (such as chronic alcohol misuse, vitamin B12 deficiency, drug-induced neuropathy), truncal neuropathy or severe neurological diseases (such as Parkinson's disease and multiple sclerosis); (2) severe renal disease defined as estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 using the Modification of Diet in Renal Disease formula,[14] or severe liver disease; (3) recent treatment for cancer or haematological malignancies; (4) presence of foot ulcers; (5) peripheral arterial disease defined as non-palpable pulses at the feet arteries and/or intermittent claudication; (6) use of agents in the previous 3 months that could interfere with the interpretation of results, such as opiates, vitamin B compounds or antioxidants; and (7) pregnancy, lactation, or childbearing age without use of safe contraception.

Participants were prescribed 600 mg/day α-lipoic acid (Nevralip Retard®), orally, for 40 days, and were advised not to discontinue any medications for managing painful diabetic neuropathy, antidiabetic drugs, or medications used for managing arterial hypertension or dyslipidaemia during the study.

The study was approved by the Ethics Committee of Laiko General Hospital, and was conducted in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all participants.

Definition of neuropathy

Diabetic peripheral neuropathy was defined as the presence of signs and/or symptoms of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes.[2] In the current study, assessment of diabetic peripheral neuropathy included examination of symptoms and signs, and quantitative sensory testing. Symptoms of somatic neuropathy were assessed using the Neuropathy Symptom Score (NSS), as described previously,[2] and the Neuropathy Disability Score (NDS) was used, as described previously,[15] to quantify signs of diabetic peripheral neuropathy. The criteria for diagnosing diabetic peripheral neuropathy were NDS $\geq$ 6 irrespective of the NSS values, or NDS = 3–5 with NSS $\geq$ 5.[2]

Data collection and patient follow-up

Two visits were scheduled for data collection, physical examination and laboratory testing of participating patients: the first prior to initiation of α-lipoic acid administration (baseline visit) and the second at day 40 following initiation of α-lipoic acid (2nd visit). The following data were collected from participants' medical records and through personal interviews by one trained healthcare professional (E.A.): age, gender, type of diabetes mellitus, history of other underling diseases, diabetes medications, other medications, and alcohol consumption. Height and weight were measured in light clothing and body mass index (BMI) was calculated. Systolic and diastolic blood pressure was measured twice, 2 min apart, with the patient in a sitting position and the mean of the two measurements was recorded. All measurements were performed at the baseline visit (by E.A.) and at the end of the study (2nd visit at day 40 [by C.P.]).

Assessment of neuropathic symptoms and QoL measures

Data regarding patients' neuropathy symptoms, QoL, and patients' perception of overall health status were collected by one trained healthcare professional (E.A) during the baseline (E.A.) and 2nd visit (C.P.) using specific questionnaires. All questionnaires were administered via face to face interview with the healthcare professional and without any time limit.

Neuropathy symptom scores were calculated for both visits using the following questionnaires.

1. Neuropathy Symptoms Score (NSS),[16] comprising five questions about neuropathy symptoms, with a score ranging from '0' (no neuropathic symptoms) to '10' (the most severe neuropathic symptoms).
2. Subjective Peripheral Neuropathy Screen Questionnaire (SPNSQ),[17] comprising 15 'yes/no' questions regarding symptoms of neuropathy, with the score calculated by summing the 'yes' answers, and ranging from '0' (no neuropathic symptoms) to '15' (the most severe neuropathic symptoms).
3. Douleur neuropathique (DN)4 Questionnaire,[18] comprising 10 'yes/no' items regarding neuropathic pain, with the score calculated by summing the 'yes' answers, and ranging from '0' (no neuropathic pain) to '10' (the most severe neuropathic pain).

Quality of life was assessed using the following questionnaires.

1. Brief Pain Inventory (BPI)-modified short form (SF),[19] comprising 11 items (the first four concerned the severity of patients' pain, and the remaining seven concerned the degree to which pain interferes with the common dimensions of feeling and function). The answers to all items ranged from '0' ('no pain' in the case of the first four and 'no interference' in the case of the other seven) to '10' ('pain as bad as you can imagine' in the case of the first four and 'interferes completely' in the case of the other seven). Two scores were calculated: the BPI severity score (mean number of correct answers to the first four items) and the BPI interference score (mean number of the correct answers to the last seven items).
2. Neuropathic Pain Symptom Inventory (NPSI),[20] comprising six scores: Total Intensity Score, ranging from '0' (none) to '100' (worst imaginable); and five scores corresponding to dimensions of pain, namely, burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paraesthesia/dysesthesia (all ranging from '0' [none] to '10' [worst imaginable]).
3. Sheehan Disability Scale (SDS),[21] which included three self-rated items that measured functional impairment, and generated three scores: work-disability score, social life-disability score, and family-life disability score, ranging from '0' (no disability) to '10' (worst imaginable disability).

Patient Global Impression-Improvement (PGI-I) was also estimated during the 2nd visit. In particular, the patient described his/her condition, compared with how it was before the initiation of treatment with α-lipoic acid, using the following descriptors: 'very much better', 'much better', 'a little better', 'no change', 'a little worse', 'much worse', or 'very much worse'. The physician who administered the questionnaires at the 2nd visit (C.P.) was not aware of the baseline visit responses.

Laboratory assays

Blood samples (approximately 15 ml per sample) were collected following a 12-h overnight fast, via venepuncture of the

forearm vein. Blood samples were left for 10 min at room temperature to allow clotting and then centrifuged at 4042 g for 15 min at 4°C. Measurements were performed immediately following centrifugation. Fasting serum glucose, creatinine and lipids were measured using an automated Technicon RA-XT clinical chemistry analyser and reagents (Technicon Instruments, Tarrytown, NY, USA) according to the manufacturer's instructions. The Friedewald formula[22] was used to calculate low-density lipoprotein cholesterol (LDL-C). Glycosylated haemoglobin (HbA_{1c}) was measured using high-performance liquid chromatography, and eGFR was calculated using the Modification of Diet in Renal Disease formula. All measurements were performed at the baseline and 2nd visit, except for serum creatinine which was measured only at baseline.

Statistical analyses

Data were analysed using SPSS software, version 22.0 (IBM, Armonk, NY, USA) for Windows. Continuous variables are presented as mean ± SD, or median, minimum and maximum values. Nominal variables are presented as n (%) prevalence or frequencies. A 95% confidence interval (CI) was calculated to assess the difference in mean NSS between the baseline and 2nd Visit. Student's *t*-test was used to compare total scores/measurements between the baseline and 2nd visit. McNemar's test was used to compare the percentage of 'yes' responses for the DN4 questionnaire and SPNSQ between the baseline and 2nd visit. Multivariate linear regression was used to investigated any statistical associations between changes in NSS, DN4 questionnaire and SPNSQ scores from the baseline and 2nd visit (dependent variables) and the following parameters (independent variables): age, sex, BMI, comorbidities, arterial blood pressure and heart rate. All

tests were two sided with α = 0.05. A *P* value < 0.05 was considered statistically significant.

Sample size

The sample size was determined by the number of patients with diabetes that could be recruited within one year. The sample size of 72 patients gave a very high precision regarding the CI estimation of the difference in NSS between the baseline and 2nd visit. Specifically, the precision was 0.5 units and the corresponding CI for the NSS difference (improvement) was 2.6 ± 0.5 (95% CI 2.1, 3.1).

Results

During the study period 96 patients with neuropathy were invited to participate; 10 patients failed to meet the study inclusion criteria and 14 patients were not eligible due to exclusion criteria. Of these, 72 patients were eligible and all completed the study successfully. Baseline characteristics and medications are shown in Tables 1 and 2, respectively.

Statistically significant reductions in neuropathic symptoms were noted by patients following the 40-day administration of α-lipoic acid, indicated by changes in NSS, SPNSQ and DN4 scores. Mean NSS score was 7.9 (range, 4–10) at the baseline visit compared with 5.3 (range, 2–10) at day 40 of treatment (*P* < 0.001). Results of the SPNSQ by visit revealed a statistically significant decrease in 14 out of the 15 questions for neuropathy symptoms at day 40 compared with baseline (Table 3), while mean SPNSQ score decreased from 8.8 (range, 3–15) at baseline to 4.4 (range, 0–14) at the end of α-lipoic acid administration at day 40 (*P* < 0.001). Statistically significant reductions were also noted for the DN4 questionnaire scores, in all 10 questions regarding pain characteristics

Table 1. Baseline demographic and clinical characteristics in 72 adult patients with painful diabetic neuropathy scheduled to receive 600 mg/day α-lipoic acid, orally, for 40 days.

Characteristic	Value
Age, years	65.2 ± 8.4
Sex, male	28 (38.9)
Body mass index, kg/m^2	31.3 ± 5.4
Type 1 diabetes mellitus	11 (15.3)
Type 2 diabetes mellitus	61 (84.7)
Duration of diabetes, years	12.7 ± 8.8
Systolic blood pressure, mmHg	134.2 ± 13.9
Diastolic blood pressure, mmHg	75.8 ± 9.6
Heart rate, beats/min	73.8 ± 10.3
Glycosylated haemoglobin HbA$_{1c}$, %	7.8 ± 1.9
Estimated glomerular filtration rate, ml/min/1.73 m^2	75.3 ± 21.2
Location of neuropathic symptoms*	
Foot	67 (93.1)
Calves	17 (23.6)
Thigh	8 (11.1)
Medical history*	
Coronary artery disease	12 (16.7)
Stroke	6 (8.3)
Peripheral vascular disease	33 (45.8)
Diabetic nephropathy	13 (18.1)
Retinopathy	14 (19.4)
Fasting glucose, mg/dl	141.4 ± 53.7
Total cholesterol, mg/dl	190.4 ± 24.7
Triglycerides, mg/dl	146.8 ± 73.4
High density lipoprotein cholesterol, mg/dl	49.7 ± 9.6
Low density lipoprotein cholesterol, mg/dl	110.6 ± 17.4

Data presented as mean $\pm$ SD or *n* (%) patient prevalence.
*More than one answer is possible in these items.

Table 2. Baseline medications of 72 adult patients with painful diabetic neuropathy scheduled to receive 600 mg/day α-lipoic acid, orally, for 40 days.

Treatment type	Prevalence
Diabetes treatment*	
Insulin	56 (77.8)
Biguanide	46 (63.9)
Dipeptidyl peptidase 4-inhibitor	22 (30.6)
Sulfonylurea	11 (15.3)
Glinide	1 (1.4)
Glucagon-like protein-1 receptor agonist	4 (5.6)
Pioglitazone	3 (4.2)
Sodium-glucose co-transporter 2 inhibitors	1 (1.4)
Other treatment*	
Statin	50 (69.4)
Fibrate	8 (11.1)
Antihypertensive	60 (83.3)
Antiplatelet therapy	45 (62.5)
Medication for painful neuropathy*	
Pregabalin	18 (25.0)
Gabapentin	8 (11.1)
Paracetamol	3 (4.2)
Duloxetine	2 (2.8)

Data presented as *n* (%) patient prevalence.
*Patients may receive more than one medication.

(Table 4). In addition, patients' mean DN4 questionnaire score was also significantly reduced from baseline (mean score, 5.7 [range, 1–9]) compared with day 40 (mean score, 2.8 [range, 0–8]; $P < 0.001$).

Regarding patients' QoL, BPI scores revealed a significant reduction in pain severity (mean score, 4.3 [range, 0–9] at baseline versus 2.3 [range, 0–9] at day 40; $P < 0.001$) and pain interference (mean score, 5.2 [range, 0–10] at baseline versus 3.2 [range, 0–9.7] at day 40; $P < 0.001$). Similarly, a significant reduction in NPSI score was noted in terms of NPSI Total Intensity Score (mean score, 40.1 [range, 8–88] at baseline versus 20.3 [range: 0–86] at day 40; $P < 0.001$), burning (superficial) spontaneous pain (mean score, 5.6 [range, 0–10] at baseline versus 2.9 [range, 0–10] at day 40; $P < 0.001$), pressing (deep) spontaneous pain (mean score, 3.5 [range, 0–10] at baseline versus 1.8 [range, 0–9.5] at day 40; $P < 0.001$), paroxysmal pain (mean score, 4.3 [range, 0–9.5] at baseline versus 2.0 [range, 0–9.5] at day 40; $P < 0.001$), evoked pain (mean score, 2.3 [range, 0–8.7] at baseline versus 1.5 [range, 0–6.3] at

Table 3. Baseline and end-of-treatment Subjective Peripheral Neuropathy Screen Questionnaire responses of 72 adult patients with painful diabetic neuropathy treated with 600 mg/day α-lipoic acid, orally, for 40 days.

Neuropathic symptom	Positive response rate		Statistical significance[a]
	Baseline	End of treatment	
Do you ever have legs and/or feet that feel numb?	63 (87.5)	30 (41.7)	$P < 0.001$
Do you ever have any burning pain in your legs and/or feet?	60 (83.3)	28 (38.9)	$P < 0.001$
Are your feet too sensitive to touch?	26 (36.1)	16 (22.2)	$P = 0.013$
Do you get muscle cramps in your legs and/or feet?	53 (73.6)	20 (27.8)	$P < 0.001$
Do you ever have any prickling or tingling feelings in your legs or feet?	56 (77.8)	20 (27.8)	$P < 0.001$
Does it hurt at night or when the covers touch your skin?	26 (36.1)	10 (13.9)	$P < 0.001$
When you get into the tub or shower, are you unable to tell the hot water from the cold water with your feet?	22 (30.6)	17 (23.6)	NS
Do you ever have any sharp, stabbing, shooting pain in your feet or legs?	47 (65.3)	17 (23.6)	$P < 0.001$
Have you experienced an asleep feeling or loss of sensation in your legs or feet?	18 (25.0)	5 (6.9)	$P < 0.001$
Do you feel weak when you walk?	51 (70.8)	34 (47.2)	$P < 0.001$
Are your symptoms worse at night?	48 (66.7)	27 (37.5)	$P < 0.001$
Do your legs and/or feet hurt when you walk?	46 (63.9)	26 (36.1)	$P < 0.001$
Are you unable to sense your feet when you walk?	39 (54.2)	24 (33.3)	$P < 0.001$
Is the skin on your feet so dry that it cracks open?	37 (51.4)	27 (37.5)	$P = 0.002$
Have you ever had electric shock-like pain in your feet or legs?	44 (61.1)	17 (23.6)	$P < 0.001$

Data presented as *n* (%) positive response.
[a]Statistically significant differences at $P < 0.05$ (McNemar's test).
NS, no statistically significant between group difference ($P > 0.05$; McNemar's test).

day 40; $P < 0.001$), and paraesthesia/dysesthesia (mean score, 5.9 [range, 0–10] at baseline versus 3.0 [range, 0–10] at day 40; $P < 0.001$). Statistically significant reductions were also evident in the SDS score between the baseline and day 40 visit, in terms of work disability score, social life disability score, and family life disability score ($P < 0.001$; Figure 1).

Lastly, PGI-I at the day 40 visit revealed that 36 patients (50%) rated their health condition as 'very much better' or 'much better'. No change was reported by 14 patients (19.4%), and none of the patients reported worsening of symptoms.

In terms of laboratory parameters, mean fasting triglyceride levels were significantly reduced during the α-lipoid acid

Table 4. Baseline and end-of-treatment douleur neuropathique (DN)4 questionnaire responses of 72 adult patients with painful diabetic neuropathy treated with 600 mg/day α-lipoic acid, orally, for 40 days.

Pain characteristic	Positive response rate [see		
	Baseline	End of treatment	Statistical significance[a]
Burning	57 (79.2)	24 (33.3)	P <0.001
Painful cold	22 (30.6)	13 (18.1)	P = 0.012
Electric shock	43 (59.7)	17 (23.6)	P <0.001
Tingling	61 (84.7)	33 (45.8)	P <0.001
Pins and needles	62 (86.1)	26 (36.1)	P <0.001
Numbness	62 (86.1)	31 (43.1)	P <0.001
Itching	22 (30.6)	12 (16.7)	P = 0.006
Hypoesthesia to touch	31 (43.1)	19 (26.4)	P = 0.002
Hypoesthesia to prick	29 (40.3)	15 (20.8)	P <0.001
The pain is caused or increased by brushing	22 (30.6)	10 (13.9)	P <0.001

Data presented as *n* (%) positive response.
[a]Statistically significant differences (*P* < 0.05; McNemar's test).
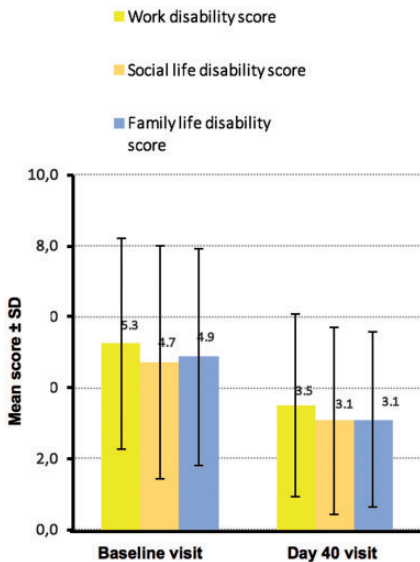
Figure 1. Sheehan Disability Scale scores of 72 adult patients with painful diabetic neuropathy treated with 600 mg/day α-lipoic acid, orally, for 40 days; Data presented as mean ± SD; *P* < 0.001 between baseline and day 40 visit for all comparisons (Student's *t*-test).

administration (146.8 mg/dl [range, 49–390 mg/dl] at baseline versus 135.5 mg/dl [range, 56–337 mg/dl] at day 40; *P* = 0.004). No statistically significant difference was found in terms of fasting glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, HbA$_{1c}$, BMI, arterial blood pressure or heart rate between the baseline and day 40 visits (data not shown).

A-lipoic acid was well tolerated, no patient discontinued treatment, and no adverse events were noted during the 40-day treatment period.

Discussion

The aim of the current study was to prospectively investigate the effects of α-lipoic acid on neuropathic symptoms, laboratory parameters and overall quality of life in patients with diabetic neuropathy. Treatment with 600 mg/day α-lipoic acid, orally for 40 days was found to be

associated with a clinically significant and prompt reduction in neuropathy symptoms and an overall improvement in patients' quality of life. Indeed, treated patients noted significant improvements in neuropathic symptoms, indicated by reduced NSS, SPNSQ, and DN4 questionnaire scores following 40 days of treatment with α-lipoic acid compared with baseline scores. Importantly, the patients noted an overall improvement in quality of life, which was reflected by the reduction in pain severity and pain interference in terms of BPI scores; total score, burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paraesthesia/dysesthesia in NPSI scores; and work disability score, social life disability score, and family life disability score in the SDS. In addition, fasting triglyceride levels were significantly reduced during the 40-day period. The overall treatment demonstrated an excellent safety profile. It remains to be determined if the improvement of neuropathy symptoms could be further enhanced by treatment prolongation beyond 40 days and more importantly if this will have an impact on the long-term course of diabetic neuropathy *per se.*

A-lipoic acid, an essential co-enzyme for energy production in mitochondria, demonstrates substantial antioxidant properties and an effect on whole-body physiology.[23] A-lipoic acid is found in very low quantities in almost all foods, and is used as a dietary supplement and a pharmaceutical agent.[24] A-lipoic acid is well absorbed, diffuses efficiently in both extra-cellular and intra-cellular spaces, and penetrates the blood-brain barrier.[25] It has been used in several oxidative-stress models such as diabetes, ischemia-reperfusion injury, cataract, and neurodegenerative disorders, as well as in mushroom and heavy metal poisoning. Adverse events of α-lipoic acid may include nausea, vomiting and mild skin reactions.[25]

A meta-analysis of four clinical trials comprising 1 258 patients with diabetic neuropathy (α-lipoic acid-treated group, 716 patients; placebo group, 542 patients) showed a favourable effect for 600 mg/day α-lipoic acid, administered i.v., for three weeks.[26] In particular, the relative difference between baseline and the end of the three-week treatment was 24.1% for Total Symptom Score (a composite score of all neuropathic symptoms), and 16.0% for Neuropathy Impairment Score.[26] In addition, the responder rates were 52.7% ($\geq 50\%$ improvement in Total Symptom Score) in the α-lipoic acid-treated group compared with 36.9% in the placebo group ($P < 0.05$).[26] This meta-analysis showed a clear reduction in pain, burning, paraesthesia, and numbness in the α-lipoic acid-treated group,[26] and no difference in terms of adverse events and overall safety was noted between the two groups. Moreover, another meta-analysis of 15 randomized controlled trials involving patients with diabetic peripheral neuropathy showed that treatment with 300–600 mg/day α-lipoic acid, i.v. for 2–4 weeks was statistically superior to the control group for increasing median and peroneal motor nerve conduction velocity and median and peroneal sensory nerve conduction velocity.[13]

The pathogenesis of diabetic neuropathy remains largely unknown. Metabolic and vascular defects, under increased oxidative stress, are both implicated in nerve injury in patients with diabetes.[7,13] The rationale for improvement in neuropathic symptoms in patients with diabetes, following treatment with α-lipoic acid, most probably relies on its antioxidant action. A-lipoic acid, and its reduced form, dihydrolipoic acid, act as antioxidants through neutralization of a variety of reactive oxygen species, inhibition of reactive-oxygen generators, and repair of damage caused by other oxidants.[23,24] The antioxidant action of α-lipoic acid may also contribute to the clinically-significant subsidence of neuropathic symptoms through improvement in nerve blood flow.[27]

Moreover, α-lipoic acid may interact with other antioxidants or contribute additively to the antioxidant effect through different parameters.[25] A recent study compared the effects of 300 mg/day α-lipoic acid for 90 days with two other antioxidants, namely omega 3 fatty acids and vitamin E, in patients with type 2 diabetes mellitus.[28] In this study, significant improvements were found in all treatment groups in parameters of oxidative stress, insulin resistance, BMI, waist circumference, and total cholesterol levels.[28]

Evidence-based clinical indications for administration of α-lipoic acid include migraine and chronic pain. In patients suffering from migraines, 600 mg/day α-lipoic acid, administered orally for three months, showed a statistically significant reduction in the number, duration and severity of migraine crises per month, and an overall response rate of 30%, while these outcomes remained unchanged in the placebo group.[29] In patients with peripheral neuropathic sciatic pain caused by herniated disc, 600 mg/day α-lipoic acid for 60 days significantly improved signs and symptoms and electromyography findings compared with 1180 mg/day acetyl-L-carnitine. In addition, more patients receiving α-lipoic acid than acetyl-L-carnitine reported a reduced need for analgesics (71% versus 45.5%; $P = 0.05$).[30] Similar results have been noted with 600 mg/day α-lipoic acid in patients with lower back pain and chronic cervical pain, and with 300 mg/day α-lipoic acid in patients with carpal tunnel syndrome.[31–33]

Clear advantages of the current study include its prospective design and the very high precision with the specific sample size. Moreover, the study was a conducted in a single centre, thus limiting the possibility of between-centre variability, as noted by others.[26] This was an open-label study, however, without a placebo treatment arm, and as such has inherent limitations, since both the study participants and the health-care providers were aware of the treatment provided. Thus, imagined or random effects of the agent cannot be ruled out. Furthermore, it is unclear if and at what extent the recorded benefits in the present study group would subside after α-lipoic discontinuation.

In conclusion, the current study suggests that 600 mg/day α-lipoic acid, administered orally for 40 days, to patients with painful diabetic neuropathy, has a clinically significant impact on controlling neuropathy symptoms, fasting triglycerides, and quality of life. Moreover, half of the treated patients rated their health status as 'much better' or 'very much better' following 40 days of treatment. The current findings suggest that α-lipoic acid is beneficial and thus should be considered for routine administration in patients with diabetes and peripheral neuropathy. Whether the recorded improvements could be augmented further by prolongation of α-lipoic acid administration beyond 40 days, or if α-lipoic acid could decelerate the course of neuropathy in the long-term, remains to be determined.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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