

# A novel approach to alpha-lipoic acid therapy in the treatment of diabetic peripheral neuropathy

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## ABSTRACT

Diabetic peripheral neuropathy (DPN) is a heterogenic disorder prevalent amongst patients suffering from diabetes mellitus (DM), with symptoms comprising neuropathic pain, paresthesia, and numbness in distal lower limbs. Alpha-lipoic acid (ALA) is proposed as a pathogenesis-oriented treatment option, targeting underlying causes of neural lesions such as hyperglycemia, metabolic and microvascular dysfunctions, and cellular oxidative stress. We performed a comprehensive review of controlled clinical trials demonstrating the clinical usefulness of ALA in the treatment of DPN, published in the last 5 years to determine the benefits of ALA monotherapy and combined treatments with other known antioxidants. We also investigated the differential efficacy of oral versus intravenous ALA administration. Clinical trials show the efficacy of ALA treatment, attributed to its anti-inflammatory, anti-hyperglycemic, and antioxidant properties, as well as its function in the endothelial activation and lipid metabolism parameters. ALA supplementation is associated with amelioration in nerve conduction velocity scores, clinically significant reduction of reported neuropathic pain, burning and paresthesia, as well as a decrease in serum triglycerides, improved insulin sensitivity, and quality of life.

## Introduction

Diabetic peripheral neuropathy (DPN) is a symmetrical, length-dependent sensorimotor polyneuropathy related to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. Despite the advances in knowledge of the pathogenesis of neuropathy, there are still few causal therapeutic options. Alpha-lipoic acid (ALA) is suggested as a pathogenesis-oriented treatment option, targeting underlying causes of neural lesions. The efficacy of ALA in patients with diabetes mellitus (DM) is attributed to its anti-inflammatory, anti-hyperglycemic, and antioxidant properties, as well as its role in endothelial function, insulin sensitivity, and lipid metabolism parameters.

## Pathophysiology of diabetic peripheral neuropathy

DPN is a neurodegenerative disorder, characterized by morphological changes and lesions mainly to the peripheral nerves. The major pathomechanisms include demyelination and thickening of the axon, contraction, and diminishment of Schwann cell as well as distortion of Ranvier nodes. An overall decrease in unmyelinated fibers which innervate organs of the abdominal cavity is usually present, however negative changes in peripheral nerves are observed more frequently. The pathogenesis of this disease has a complex mechanism. Nevertheless, two potential mechanisms of DPN are proposed: metabolic and ischemic. Hyperglycemia is considered a major factor causing disorders of the nervous system in DM [1].

The current state of knowledge indicates that hyperglycemia causes nerve damage in four mechanisms: activation of the polyol pathway and hexosamine pathway, kinase A activation, and oxidative stress. In the polyol pathway glucose is converted to sorbitol by aldose reductase and then to fructose by sorbitol dehydrogenase. Elevated levels of glucose, sorbitol, and fructose have an impact on the metabolism disorder of neurons. The abnormal activation of the polyol pathway increases the osmotic pressure which can result in nerve cell damage. In addition, activation of the polyol pathway decreases nicotin-

amide adenine dinucleotide phosphate (NADPH) levels, which is essential for the regeneration of glutathione (the main cellular antioxidant). The insufficiency of NADPH leads to disturbance in the redox potential may cause rapid intensification of oxidative stress. Chronic hyperglycemia induces oxidative stress which has a wide impact on nerves such as accelerated apoptosis of ganglionic cells and Schwann cells.

The hexosamine pathway is activated by high glucose concentration. Glucose is a substrate in glycolysis where it is transformed to fructose-6-phosphate, fructose-6-phosphate is then converted to glucosamine-6-phosphate and subsequently to N-acetylglucosamine. The connection of N-acetylglucosamine with serine and threonine leads to pathological gene expression of transforming growth factor-beta, plasminogen activator inhibitor-1. All those changes have a negative effect on blood vessels [2].

In the vascular theory of DPN, pathological changes in the vasa nervorum can be observed. Blood samples from the patients with DM show elevated levels of alfa-2-globulin, fibrinogen, and reduced level of albumin, all of which may lead to a lower concentration of nitric oxide, one of the diastolic factors in the cardiovascular system. All these factors reduce blood supply and lower the microcirculation around the nerve via vasoconstriction, increasing the osmotic pressure [3]. Additional risk factors in the development of DPN include immune system disorders, a disorder in axonal transport, hyperlipidemia and dyslipidemia [4, 5].

## Current treatment options in DPN

Nowadays, the treatment of DPN is considered to be an extensive and demanding issue. The treatment is difficult to execute and often ineffective, especially in the advanced stages of DPN. No treatment has been invented yet, that could either fully cure, or at least entirely prevent neuropathic changes. Complete pain relief or reduction of its intensity by half is achieved only in about 50% of the cases [6]. Therefore, treatment goals are mainly focused on managing conditions that could lead to neuropathy, and secondly, on providing at least partial relief of symptoms.

The preventive treatment of DPN is based on education regarding risk factors and adapting

therapies and habits that alter pathological pathways. As evidenced by large observational and randomized control trials, such as DCCT (Diabetes Control and Complications Trial), strict control of glycemia is essential in the prevention and delay of symptoms onset of distal symmetrical polyneuropathy and cardiovascular autonomic neuropathy in type 1 DM [7]. It has been proven that intensive insulin therapy in the treatment of type 1 diabetes plays a crucial role in slowing down the progress of DPN. In addition, maintaining normalized blood pressure and body weight, supported by a non-sedentary lifestyle is also suggested in DPN prevention [8]. A balanced and healthy diet, smoking cessation, and alcohol restriction have been proven to have a positive impact on reducing the risk of DPN [9,10].

Much evidence points to the role of oxidative stress in the pathogenesis of DPN [11]. Therefore, supplements containing  $\alpha$ -lipoic acid (ALA), a potent antioxidative agent are used in the preventive treatment of DPN, along with other active agents such as angiotensin-converting-enzyme inhibitors (ACE-I), benfotiamine, an S-acyl derivative of thiamine (vitamin B1) and acetyl-L-carnitine [12].

It is important to note that DPN is symptomatic in only 50% of all diagnosed cases. Symptomatic treatment is focused on reducing pain that often accompanies DPN. It is a crucial aspect of the therapeutic approach, as pain management contributes to improving a patient's quality of life. In pharmacotherapy, anticonvulsant agents such as gabapentin or pregabalin, as well as antidepressants: duloxetine, and venlafaxine are recommended as first-choice medication for reducing pain and paresthesia. The standard therapeutic approach includes gradual dose increase until a therapeutic concentration of selected medication is set. In case of ineffectiveness, it is possible to attempt a combined agent therapy with two different types of medication or to change treatment to another medication entirely. A second-choice option in pharmacological treatment are tricyclic antidepressants (TCA), serotonin-noradrenaline reuptake inhibitors (SNRI), and  $\alpha_2$ - $\delta$  calcium channel ligands (the latter in case of autonomic nervous system neuropathy) [13,14]. In difficult cases, with neuropathic pain resistant to standard treatment options, tramadol or other potent opioids can be administered, however, long-term

use of opioids is not recommended due to multiple adverse effects and highly addictive properties. The use of over-the-counter analgesics such as metamizole(dipyrone) and mefenamic acid can be considered as a treatment option, but often proves to be insufficient in pain management amongst DPN patients. Adverse effects of certain drugs, such as anxiety, nausea, cardiovascular complications, or addiction are prevalent [15]. Other medications, while not listed in current treatment guidelines, can play a supplementary role in DPN pain management, preventing sorbitol accumulation and regulating polyol pathway (aldose reductase inhibitors), improving microvascular blood flow and functions of nerve fibers (protein kinase – C inhibitors), or by simply alleviating neuropathic pain (N-methyl-D-aspartate receptor antagonists, NMDAR) [5, 15].

## ALA in current clinical recommendations

Due to the important clinical significance of ALA, it has been repeatedly mentioned as supplementary pathogenesis-oriented pharmacotherapy treatment of DPN over the past few years. This clinical recommendation remains consistent since 2014 and is underlined in 2022 guidelines issued by Diabetes Poland [14]. Currently, ALA is listed by Diabetes Poland as a first choice supplementary medication, alongside other agents such as benfotiamine and angiotensin-converting-enzyme inhibitors. The usefulness of ALA in DPN treatment was indicated in the 2022 guidelines of the International Diabetes Federation, listing ALA (600 mg/d, oral or i.v.) together with vitamin-B1 derivative Benfotiamine as pathogenically oriented treatment of symptomatic diabetic sensorimotor polyneuropathy. Currently, ALA is a drug licensed and approved for the treatment of DPN in several countries worldwide [16].

## Materials and Methods

We conducted detailed research of articles published in the English language, with full-text access available via the PubMed database. The database was searched using the following keywords: "a-lipoic acid" or "thioctic acid" and one

of the subsequent terms: "polyneuropathy", "diabetic neuropathy", "diabetes mellitus" and "hyperglycemia". The following inclusion criteria were applied: (1) studies published between 2017 and 2022, (2) controlled clinical trials conducted on humans and/or other mammals (3) meta-analyses meeting the criteria identified in (1) and (2). Using the aforementioned criteria, a total of 1,830 articles were identified, out of which 57 were found to be fully relevant and included in this review.

## ALA monotherapy in DPN – evidence in clinical studies

Both hyperglycemia-triggered oxidative stress and defects in microvasculature are associated with the progression of nerve damage. By addressing each of these pathologies consecutively, ALA supplementation may bring successful outcomes in DPN treatment. Ziegler et. al. meta-analysis summarized the results of multiple double-blind clinical trials investigating ALA treatment [17]. Trials using alpha-lipoic acid infusions of 600 mg i.v. per day for 3 weeks, except for weekends, in diabetic patients with DPN were included. These were four trials: ALADIN I, ALADIN III, SYDNEY, and NATHAN II. Together 1258 patients (alpha-lipoic acid n=716; placebo n=542) were included in a meta-analysis. After 3 weeks the relative difference in favor of alpha-lipoic acid vs. placebo was 24.1% for Total Symptom Score (TSS) and 16.0% for Neuropathy Impairment Score of the lower limbs (NIS-LL). Among the individual components of the TSS, pain, burning, and numbness decreased in favor of alpha-lipoic acid compared with placebo, while among the NIS-LL components pin-prick and touch-pressure sensation, as well as ankle reflexes, were improved in favor of alpha-lipoic acid.

In detail, the ALADIN trial revealed clinically relevant improvement in Total Symptom Score, Neuropathy Disability Score (NDS), and Hamburg Pain-Adjective (HPA) results in patients who received daily (100/600/1200 mg/day, intravenous) ALA supplementation over the course of 3 weeks [18]. The objective of subsequent studies on ALADIN II and ALADIN III was to find an optimal therapeutic dose and regimen [19]. The ALADIN II study analyzed the response of patients

with DM2 to ALA treatment (600/1200 mg/day oral) over the course of 2 years as measured by sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) before and after treatment. After 2-year treatment with ALA, an amelioration of both clinical parameters was observed. ALADIN III broadened the scope of research, by introducing a combined treatment schedule, consisting of 3 weeks of intravenous, and subsequent 6 months of oral ALA supplementation (600 mg and 1800mg/day). The clinical parameters applied in this study were TSS, NIS-LL, and general NIS. Treatment results showed improvement in TSS, NIS-LL, and NIS, as assessed by pin-prick, touch-pressure sensation, and ankle reflexes [20].

These findings correspond with outcomes of the SYDNEY clinical trial, where 3-week intravenous ALA supplementation (600mg/day) proved effective in the amelioration of TSS, NIS, and Neuropathy Symptoms and Changes (NSC) versus placebo [21]. It should be noted that no adverse effects were observed in either of the clinical trials as presented in the Ziegler et. al. meta-analysis except SYDNEY 2 and Mansoura studies. The former observed an incidence of dose-dependent (1200mg/day and up) adverse effects, while the latter showed nausea as the most common adverse effect, with no correlation to the dose applied [22].

A long-term (4-year duration) Neurological Assessment of Thioctic Acid in Diabetic Neuropathy (NATHAN) reported improvement in pain, paresthesia, and numbness in participants suffering from DM2 and largely asymptomatic diabetic sensorimotor polyneuropathy. NATHAN I supplied evidence for the safety and efficacy of long-term ALA supplementation in the 600 mg/day dose in the treatment of neurological deficits related to DPN [23]. A recent clinical trial study by Agathos et al. researching the benefits of a 600mg/day dose of ALA showed similar findings. In this trial, a significant improvement in the quality of life, as assessed by reduction of pain severity and pain interference, was observed amongst participants with painful DPN who were subjected to 40 days of oral ALA supplementation. Assessment with Neuropathy Symptom Score (NSS), Subjective Peripheral Neuropathy Screen Questionnaire (SPNSQ), and Disability Score showed a decrease in neuropathic signs, symptoms, and pain on day

40 versus baseline. A reduction in fasting triglyceride serum levels was also observed over the course of the trial. Similarly to earlier studies (ALADIN II, ALADIN III, NATHAN I) excellent safety profile of ALA was indicated as a key advantage of this therapeutic approach [24].

ALA has been also studied as one of the active agents directly addressing the underlying pathophysiology of DPN. ALA treatment over the course of 16 weeks in type 2 diabetic patients with symptomatic DPN showed a positive response to the treatment after just 4-weeks of high-dose supplementation [25]. Amelioration of nerve conduction velocity was also reported in a recent single-arm study conducted by S. Mrakic-Sposta et al., although the results of the study may be inaccurate due to the lack of a control group [26]. Importantly, this study indicates the low efficacy of short-term ALA supplementation on long-term patient outcomes, as anti-oxidative cell capacity returns to baseline level 60 days post-treatment termination, suggesting a need for optimal dose and treatment schedule to sustain therapeutic effect.

### Effects of ALA supplementation as compared to other antioxidants. Benefits of ALA monotherapy versus combined agent treatment in patients with DPN

The isolated efficacy of vitamin B12, vitamin B9, vitamin E, vitamin D, and ALA supplementation in the treatment of DPN was investigated in several studies [27-29]. Vitamin B12 deficiency, associated with neurological disorders (peripheral, autonomic, and cardiovascular neuropathy) is a common occurrence in patients with type 2 diabetes (DM2) on metformin treatment, and those older than 60 years [30]. Combined ALA and B12 supplementation were shown to be successful in reducing burning sensation and pain in patients with DPN. A study by Han Y. et al. investigating the differential efficacy of methylcobalamin over ALA revealed that ALA treatment was superior in reducing burning and pain symptoms of DPN, while methylcobalamin reduced paresthesia and numbness to a greater extent [31]. ALA exhibited stronger antioxidant properties, while reduction

of abnormal pressure sensation was caused by B12 supplementation only.

Vitamin D deficiency was found to be present in patients with DM2 and peripheral polyneuropathy, and current data shows that patients with DPN can benefit from high-dose cholecalciferol supplementation, leading to a decrease in neuropathy severity and amelioration of pain scores [28]. Similarly, the administration of folic acid is considered to enhance nerve conduction velocity in patients with DPN. Nano-curcumin supplementation was revealed to improve the total reflex score, and total score of neuropathy and reduce glycated hemoglobin in patients with diabetic sensory-motor polyneuropathy. Numerous research indicates that tocotrienol-rich vitamin E can improve nerve condition velocity in these patients due to its antioxidant, anti-inflammatory, and neuroprotective properties [32-35].

The efficacy of combined antioxidant therapy was confirmed in a randomized, double-blind trial conducted on a population of DM type 2 patients, all of whom experienced generalized neuropathy and underwent metformin treatment for at least four years [36]. The proposed treatment included a single tablet, four element combination of 10 mg superoxide dismutase, 570 mg  $\alpha$ -lipoic acid, 300mg N-acetyl carnitine, and 250 mcg vitamin B12, administered daily for the period of 12 months. The study showed an improvement of the neurophysiological parameters in the study group, assessed by vibration perception threshold, conduction velocity, and amplitude of sural nerve. A notable improvement in the patient's condition was observed, with a pain reduction of 16% in the study group and improved quality of life score. Another study comparing the effectiveness of  $\gamma$ -linolenic acid with  $\alpha$ -lipoic acid in pain management amongst painful diabetic peripheral neuropathy patients found no preference for either treatment [37]. Research conducted by Memeo et. al. showed the superiority of 600 mg/day ALA treatment over 1180 mg/day acetyl-L-carnitine treatment, with improved symptoms, electromyography findings, and reduced need for analgesics in patients receiving ALA supplementation [38].

The benefits of ALA monotherapy over combined treatment with ALA and other antioxidants require further research. A study by Huerta et al. suggests that  $\alpha$ -lipoic acid in connection with



eicosapentaenoic acid helps to regulate adipose tissue metabolism, which may be beneficial in maintaining optimal blood sugar levels in DPN patients with dyslipidemia, preventing protein glycation and endothelial damage leading to neural ischemia and neuronal lesions [39]. The anti-inflammatory properties of ALA function are hypothesized to further enhance this result. The efficacy of commonly used vasodilatory drugs in DPN treatment can be strengthened by combining them with ALA. The effectiveness of combined alprostadil and ALA treatment is suggested by a recent study [40]. This result is attributed to the mechanisms of action of both substances, which simultaneously target microangiopathy and oxidative stress, which are considered major factors in DPN pathogenesis. When combined with alprostadil, ALA enhances the therapeutic effect by increasing the activity of Na<sup>+</sup>/K<sup>+</sup>-ATPase to protect the endothelium function of blood vessels, blocking protein glycation and increasing blood flow of neurotrophic blood vessels.

A meta-analysis of Jiang et al. showed that another vasodilator and anti-platelet drug, fasudil, when combined with either vitamin B12 or ALA, attenuates nerve conduction velocity more significantly than B12 or ALA monotherapy [41]. The superiority of combined epalrestat and ALA treatment compared to ALA monotherapy was recognized in the study of Zhao et al., with a greater reduction of high sensitivity C-reactive protein level and increase in nerve conduction velocity observed in the combined therapy group, later confirmed in a large meta-analysis study [42,43]. However, a need for subsequent high-quality randomized controlled trials is expressed in the literature.

Finally, in patients with distal symmetric painful diabetic neuropathy, a greater reduction of pain intensity and diabetic neuropathy symptom score was obtained with concurrent administration of benfotiamine (B1) and ALA as compared to monotherapy with either agent. When compared with monotherapy, a combined approach of menhaden fish oil, enalapril, and ALA brought promising results in the reversal of corneal sensation and nerve loss in a type 2 rat model of chronic diabetes [44].

A study by Peralice et al. investigating combined ALA ± palmitoyl-ethanolamide (PEA) treatment on patients with neuropathic symptoms

(600 mg/day ALA ± 600 mg/ day PEA orally) reported a clinically significant reduction in neuropathy symptoms. Notably, the time needed for symptoms' relief was much shorter than indicated in studies focusing on isolated ALA supplementation, which was attributed to the anti-inflammatory and analgesic effects of PEA [45]. Further research is needed to investigate interactions between these two agents and their clinical application in DPN treatment.

In all cases, it is hypothesized that the superior therapeutic effect of combined therapies is derived from all agents working synergistically, each targeted at a different metabolic key point. There exists, however, a limited body of research on the combined effects of different antioxidants and ALA and the benefits of combined therapies as compared to monotherapy, underlying the importance of further studies.

## Oral versus intravenous supplementation of ALA

In the ALADIN study, ALA was administered intravenously for three weeks in subjects with symptomatic DN at a dose of 600 or 1200 mg daily. This treatment reduced the symptoms of DPN without significant adverse effects [18]. SYDNEY study demonstrated that, in addition to DPN symptoms, nerve conduction was also improved by ALA, administered intravenously for five days in 14 perfusions [21]. In the SYDNEY 2 study, the oral 600 mg dose of ALA was proven the most effective dose (among 600, 1200, and 1800 mg) in reducing symptoms and with the fewest side effects during a follow-up of 5 weeks [22]. Similarly, in the 'Oral Pilot' (ORPIL) study, ALA, administered orally at a dose of 600 mg for three weeks, decreased DPN symptoms, including pain, burning sensation, paraesthesia, and numbness [46]. However, clinically relevant reductions in Total Symptom Score (i.e. >30%) were only observed with intravenously administered ALA at 600 mg/day for 3 weeks, but not with orally administered ALA at a dose of >600 mg/day for 3-5 weeks in the meta-analysis of Mijnhout et al. [47].

Based on the current research it can be concluded that both ways of administration may bring a clinically significant reduction of neuropathic symptoms such as burning, pain, numb-

ness, or paresthesia and amelioration of nerve conduction velocity, with probable best outcomes present while combining both IV and O. therapeutic approach [48].

### Alfa-lipoic acid- biokinetics, clinically significant properties, and mechanisms of action as supported by the latest studies

ALA is characterized by several unique biochemical properties. ALA penetrates the blood-brain barrier, while its liposoluble and water-soluble character allows it to function both -intra and -extracellularly in the human organism. Evidence-based clinical applications of ALA include a variety of neuropathic pain disorders, such as carpal tunnel syndrome, peripheral neuropathic sciatic pain caused by herniated disc and chronic migraines (30% response rate in reduction of occurrence, duration and pain intensity). According to the neuropathic pain model of migraine pathophysiology, the onset of migraine pain is derived from the neurogenic inflammation affecting cranial vessels, which results in changes of blood perfusion. Therefore, a chemical agent such as ALA, targeting the underlying neurological cause of migraine attack, can prove to be an effective treatment strategy. Other clinical applications of ALA can be found in the treatment of neurodegenerative disorders, ischemia-reperfusion injuries, cataracts and chronic pain [19].

Current research on the biokinetics of drugs containing ALA shows rapid absorption of the active agent, with the highest serum ALA concentration levels after approximately 60 to 90 minutes post oral administration, respectively in tablet and capsule formula. The half-life of a 1200 mg ALA oral dose arrives at  $81.2 \pm 97.1$  minutes in the human organism [49]. Alpha-lipoic acid is generally considered safe when taken as an oral supplement or used as a topical ointment. A maximum daily dose of up to 1800 mg is safe for adult patients. For maximum absorption, the supplements should be administered upon fasting [50].

Adverse effects are rare and may include insomnia, fatigue, diarrhea, skin rash, headache, muscle cramp, or a tingling "pins and needles" sensation, and will usually resolve once treat-

ment is stopped. Current research on the long term safety of ALA indicates possible toxicity of doses 2400 mg /day or greater [51]. Due to potential adverse effects and no available clinical trials performed alpha-lipoic acid should not be used in the treatment of pediatric patients, pregnant women, or nursing mothers. ALA can lower blood sugar levels, thyroid hormone, or vitamin B1 levels. It can be dangerous in patients suffering from alcoholism where malnutrition and vitamin B1 insufficiency is already present.

ALA therapeutic efficacy is relatively low due to its pharmacokinetic profile. Due to fast hepatic degradation, reduced solubility, as well as instability in the digestive system and short half-life, bioavailability of ALA, oscillates around 30%. Liquid forms of ALA are more bioavailable than solid dosage forms. The former enhances the recovery of sensory and motor nerve conduction velocity altered by diabetic neuropathy in animal models [52,53]. New, improved forms of distribution, show better absorption rate and therapeutic outcomes. While the bioavailability of ALA depends on the patient's age, there is no correlation between the patient's gender and the absorption rate of the substance [52].

In its reduced form – dihydrolipoic acid (DHLA), ALA exhibits potent antioxidant properties, successfully eradicating reactive oxygen species (ROS), chelating metals, and regenerating other antioxidants [54]. These features of ALA have found clinical implementation primarily in the treatment of diseases associated with oxidative stress, for instance in diabetes, neurological and cardiovascular disorders. Some findings show improved arterial stiffness parameters and insulin resistance (IR) reduction in patients subjected to ALA treatment, suggesting that the antioxidant properties of ALA can be responsible for the improvement in arterial wall elasticity [55]. Moreover, intravenous infusion of ALA was associated with improved microcirculation in patients with DPN, as shown by accelerated time to peak capillary blood cell velocity (CBV). This effect was attributed to post-ALA-infusion improvement of nitric oxide (NO) mediated endothelium-dependent vasodilatation, as well as a reduction in malondialdehyde and increase in ubiquinol-10 plasma level.

Similarly, in Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study the

authors evaluated the ability of irbesartan, an angiotensin receptor blocker, and lipoic acid to affect endothelial function and inflammation in patients with the metabolic syndrome. Oral ALA supplementation improves endothelial function and reduces proinflammatory markers, improving endothelium-dependent flow-mediated vasodilatation [56]. ALA is also thought to attenuate renal and vascular endothelin I production and restore Ca<sup>++</sup> levels, which allows it to successfully lower blood pressure in hypertensive animal models [57].

The presence of ALA in a human organism has been linked to several health benefits. ALA is known as a potent antioxidant and anti-diabetic substance, present in low quantities in almost all foods. Hyperglycemia is one of the main factors that initiate the production of free oxygen radicals, increasing the likelihood of oxidative stress present in the human body. Therefore, the anti-oxidative function of this featured acid might play a positive role in the treatment of diabetes and subsequent DPN. Due to bipolar properties, ALA may have an anti-oxidative effect on the majority of the body's tissues and cells, whereas other antioxidants can function only selectively.

ALA present in therapeutic doses mediates the effects of oxidative stress caused by Fenton's reaction. The sulfur group present in ALA causes the chelation of heavy metals such as iron ions, which are substrates in the Fenton reaction resulting in the generation of hydroxyl radicals. These compounds immediately react with lipids and cause lipid peroxidation in biological membranes. This process exhibits a negative effect on the cardiovascular system, contributing to the damage to endothelial lining. ALA and iron ions form a complex, resulting in a significant reduction of free oxygen radical production [58].

Recent studies have shown that ALA enhances glutathione synthesis, a crucial intracellular antioxidant [58, 59]. ALA is thought to act as a pro-oxidant, indirectly inducing antioxidant enzymes gene expression via binding nuclear factor E2-related factor 2 (Nrf2) [57]. Furthermore, ALA enhances the efficacy and increases the activity of other important antioxidants such as ubiquinone, L-ascorbic acid, or Vitamin E. Moreover, by interacting with Vitamin C and Vitamin E, ALA protects biological membranes and indirectly maintains cellular antioxidant status. Anti-oxidative

functions of ALA reduce the risk of the blood vessel and nerve fiber degeneration. A recent study by Salehi et al. revealed that ALA improves blood flow in peripheral nerves affected by diabetic neuropathy by 50% [52]. There is also evidence that ALA shows an immunomodulatory effect, suggesting that ALA could be used in the treatment of autoimmune diseases including SLE (systemic lupus erythematosus), RA (rheumatoid arthritis), and primary vasculitis [60]. Furthermore, by activating the prostaglandin receptors (EP2 and EP4) ALA increases the synthesis of cAMP and in this way is responsible for the uprising of the immunomodulatory effect. Exploration of this hypothesis has shown different results respectively for animal and human models, with the latter group displaying increased numbers of Th cells associated with an increase in cAMP levels [61].

Dydoń-Pikor investigated the effects of ALA supplementation on the lipid-peroxidation process induced by a high-fat diet and showed promising outcomes [62]. The study was carried out on animal models, the diet of which was appropriately modified by introducing oxidized and non-oxidized lipoic acid and rapeseed oil in various combinations. Study results showed that animals receiving dietary ALA supplements exhibited reduced levels of high-fat diet-induced lipid peroxidation.

Beyond its powerful antioxidative properties, the biochemical role of ALA in the treatment of type 2 diabetes is furthermore associated with its participation in mitochondrial respiration as a cofactor. Yang et al. showed that ALA can prevent excessive fatty acid accumulation by increasing insulin sensitivity [63]. This results in the activation of the AMP-activated protein kinase (AMPK), an energy-sensing enzyme triggering insulin-sensitizing effect on muscle and adipose tissue. This further increases the glucose uptake in insulin-sensitive cells (primarily liver and skeletal muscles), connected with the translocation of GLUT4 glucose transporter and fatty acid (FA) oxidation. By increasing insulin sensitivity in human tissues and consequently reducing hyperglycemia, ALA directly eliminates the key factor contributing to DPN. Moreover, ALA lowers the number of noxious triglycerides in beta cells found in pancreatic islets. It was also observed that ALA significantly improved glucose metabolism (affecting glycolysis, glu-



coneogenesis, and glycogen pathways) in the livers of HFD-induced NAFLD mice via the modulation of key molecules such as ChREBP and GSK3 $\beta$  [63].

## Conclusions

DPN is a heterogenous disorder prevalent amongst diabetic patients, with pathogenesis closely associated with hyperglycemia, inflammation and metabolic and microvascular disturbances. ALA supplementation addresses many of these underlying causes, therefore its efficacy in the treatment of DPN cannot be overstated. The powerful antioxidant, anti-hyperglycemic and anti-inflammatory properties of ALA, in connection with its role in the regulation of several gene transcription mechanisms, improving microcirculation, and normalizing serum triglyceride levels make ALA a promising agent in developing an effective therapeutic approach to diseases associated with neuropathic lesions and nerve damage, such as chemotherapy-induced neuropathy and trigeminal neuralgia. ALA, administered either intravenously or orally, is characterized by its good bioavailability and amphiphilicity as well as limited adverse effects. When combining these features of ALA with other agents exhibiting antioxidant properties, it is possible to achieve highly effective treatment inhibiting the progression and symptoms of DPN.

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The authors declare no conflict of interest.

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