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## Alpha-lipoic acid supplementation and diabetes

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### Abstract

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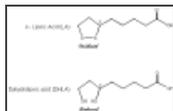
Diabetes is a common metabolic disorder that is usually accompanied by increased production of reactive oxygen species or by impaired antioxidant defenses. Importantly, oxidative stress is particularly relevant to the risk of cardiovascular disease. Alpha-lipoic acid (LA), a naturally occurring dithiol compound, has long been known as an essential cofactor for mitochondrial bioenergetic enzymes. LA is a very important micronutrient with diverse pharmacologic and antioxidant properties. Pharmacologically, LA improves glycemic control and polyneuropathies associated with diabetes mellitus; it also effectively mitigates toxicities associated with heavy metal poisoning. As an antioxidant, LA directly terminates free radicals, chelates transition metal ions, increases cytosolic glutathione and vitamin C levels, and prevents toxicities associated with their loss. These diverse actions suggest that LA acts by multiple mechanisms both physiologically and pharmacologically. Its biosynthesis decreases as people age and is reduced in people with compromised health, thus suggesting a possible therapeutic role for LA in such cases. Reviewed here is the known efficacy of LA with particular reference to types 1 and 2 diabetes. Particular attention is paid to the potential benefits of LA with respect to glycemic control, improved insulin sensitivity, oxidative stress, and neuropathy in diabetic patients. It appears that the major benefit of LA supplementation is in patients with diabetic neuropathy.

**Keywords:** diabetes, diabetic neuropathy, dosage, lipoic acid, oxidative stress

### INTRODUCTION

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Alpha-lipoic acid (LA) also known as thioctic acid, was first isolated from bovine liver in 1950.<sup>1</sup> Lipoic acid contains two thiol groups, which may be oxidized or reduced. As with the thiol antioxidant glutathione, LA is part of a redox pair, being the oxidized partner of the reduced form dihydrolipoic acid (DHLA). Unlike glutathione, for which only the reduced form is an antioxidant, both the oxidized and reduced forms of lipoic acid are antioxidants. LA is 6,8-dithio-octanoic acid, an eight-carbon disulphide containing a single chiral center ([Figure 1](#)). LA also contains an asymmetric carbon, thus resulting in two possible optical isomers (R-LA and S-LA). Only the R-isomer is endogenously synthesized and bound to protein. Lipoic acid supplements may contain either R-LA or a 50/50 (racemic) mixture of R-LA and S-LA. LA is reduced in vivo to its dithiol form, DHLA, which also possesses biological activity.<sup>2</sup> Lipoic acid is a naturally occurring compound that is synthesized in small amounts by plants and animals, including humans.<sup>3</sup> Endogenously synthesized LA is covalently bound to specific proteins, which function as cofactors for mitochondrial dehydrogenase enzyme complexes. In addition to the physiological functions of protein-bound LA, there is an increasing scientific and medical interest in potential therapeutic uses of pharmacological doses of free LA.<sup>4</sup> Considering its role in biochemical processes, lipoic acid was initially included in the vitamin B complex. However, at present, LA is not considered to be a vitamin.



[Figure 1](#)

Structure of lipoic acid (oxidized and reduced form).

### METABOLISM AND BIOAVAILABILITY

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LA is synthesized de novo from an 8-carbon fatty acid (octanoic acid) and cysteine (as a sulfur source) in liver. Its catabolism also takes place in liver. Due to an asymmetric carbon having four different attached groups, LA exists as two enantiomers: the R-enantiomer and the S-enantiomer. Naturally

occurring lipoic acid is the R-form, but synthetic lipoic acid is a racemic mixture of R-form and S-form. Both forms seem to have different potencies; it was previously shown that the R-form is more potent than the S-form in its ability to stimulate glucose uptake in L6 myotubes,<sup>2</sup> as well as to increase insulin-stimulated glucose uptake in obese Zucker rats.<sup>6</sup> On the other hand, the S-form exerts a slightly increased affinity for glutathione reductase.<sup>7</sup> Thus, the two forms of LA differ in the potency in which they exert the various biological activities of this compound.

## LIPOIC ACID AS A PRIMARY ANTIOXIDANT

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As stated by Packer et al.,<sup>8</sup> “an ideal therapeutic antioxidant should fulfill several criteria. These include absorption from the diet, conversion in cells and tissues into usable form, a variety of antioxidant actions (including interactions with other antioxidants) in both membrane and aqueous phases, and low toxicity.” LA is unique among natural antioxidants in its ability to fulfill all of these requirements, making it a potentially highly effective therapeutic agent for a number of conditions in which oxidative damage has been implicated. LA’s antioxidant properties consist of the following: 1) its capacity to directly scavenge reactive oxygen species (ROS); 2) its ability to regenerate endogenous antioxidants, such as glutathione and, vitamins E and C; and 3) its metal chelating activity, resulting in reduced ROS production.

### Scavenging reactive oxygen and nitrogen species

ROS and reactive nitrogen species (RNS) are highly reactive compounds with the potential to damage DNA, proteins, and lipids in cell membranes. Common antioxidants are either water-soluble or lipid membrane-soluble agents. In contrast, LA has both hydrophilic and hydrophobic properties. This amphiphilic characteristic of LA is unique among antioxidants. LA can therefore elicit its antioxidant action in the cytosol as well as in the plasma membrane (aqueous and lipid media of the cell), and in serum and lipoproteins (aqueous and lipid media of blood) in contrast to vitamin C (which is hydrophilic) and vitamin E (which is hydrophobic). The highest tissue concentrations of free LA likely achieved by oral supplementation are at least 10 times lower than those of other intracellular antioxidants, such as vitamin C and glutathione because of its rapid clearance rate. Earlier, our group<sup>9</sup> reported that LA supplementation (600 mg/day for 2 months) in healthy volunteers significantly increased the lag time of LDL lipid peroxide formation for both copper-catalyzed and 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced LDL oxidation, decreased urinary F2-isoprostane levels, and plasma carbonyl levels after AAPH oxidation.

### Regeneration of other antioxidants

When an antioxidant scavenges a free radical, it becomes oxidized itself and is not able to scavenge additional ROS or RNS until it has been reduced. DHLA is a potent reducing agent with the capacity to reduce the oxidized forms of several important antioxidants, including vitamin C and glutathione.<sup>10</sup> In general, DHLA has superior antioxidant activity to LA. DHLA can regenerate vitamin C and vitamin E from their oxidized forms.<sup>11</sup> Although reduced glutathione has twice the chemical reactivity in its thiol group, DHLA is superior to glutathione in regenerating vitamin C.<sup>12</sup> DHLA may also reduce the oxidized form of alpha-tocopherol (the alpha-tocopheryl radical) directly or indirectly, by reducing the oxidized form of vitamin C (dehydroascorbate), which is able to reduce the alpha-tocopheryl radical. Coenzyme Q<sub>10</sub> is an important component of the mitochondrial electron transport chain that has antioxidant activity as well. DHLA can also reduce oxidized forms of coenzyme Q<sub>10</sub>,<sup>13</sup> which may additionally reduce the alpha-tocopheryl radical. Thus, LA also plays an important role in the synergism of antioxidants described as the body’s “antioxidant network” by Packer et al.<sup>8</sup> It directly recycles and extends the metabolic lifespans of vitamin C, glutathione, and coenzyme Q<sub>10</sub>, and it indirectly renews vitamin E. However, in the study reported by our group,<sup>9</sup> LA supplementation did not produce any change in the levels of plasma or LDL alpha-tocopherol, though the baseline levels of AT were not deficient in the study population. Therefore, it was concluded that LA does not appear to act through regeneration of AT levels. Furthermore, LA has been reported to increase glutathione synthesis in aged animals by increasing the expression of gamma-glutamylcysteine ligase, the rate-limiting enzyme in glutathione synthesis, and by increasing cellular uptake of cysteine, an amino acid required for glutathione synthesis.<sup>14</sup> Overall, based on all the above-stated evidence, it is unclear if LA really plays a part in the control of cellular redox status.

### Metal chelation

Redox-active metal ions, such as free iron and copper, can induce oxidative damage by catalyzing reactions that generate highly reactive free radicals.<sup>15</sup> Compounds that chelate (bind) free metal ions in a way that prevents them from generating free radicals offer promise in the treatment of chronic diseases in which metal-induced oxidative damage may play a role.<sup>16</sup> Both LA and DHLA have been found to inhibit copper- and iron-mediated oxidative damage in the test tube<sup>17</sup> and to inhibit excess iron and copper accumulation in animal models.<sup>18</sup>

## LIPOIC ACID AVAILABILITY AND SUPPLEMENTS

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In humans, LA is synthesized in liver and other tissues and is also obtained from both animal and plant sources in the diet. LA is readily absorbed from the diet and is rapidly converted to DHLA by reduced nicotinamide adenine dinucleotide or reduced nicotinamide adenine dinucleotide phosphate in most tissues.

### Food sources

R-LA occurs naturally in foods covalently bound to lysine in proteins (lipoyllysine). High concentrations of LA are found in animal tissues with extensive metabolic activity such as heart, liver, and kidney. The plant sources of LA, listed from highest to lowest, are spinach, broccoli, tomatoes, garden peas, brussel sprouts, and rice bran.

### Supplements

Unlike LA in foods, LA in supplements is free; thus, it is not bound to protein. Moreover, the amounts of LA available in dietary supplements (200–600 mg) are likely to be as much as 1000 times greater than the amounts that could be obtained from the diet. In Germany, LA is approved for the treatment of diabetic neuropathies and is available by prescription.<sup>19</sup> In the United States, LA is available over the counter as a dietary supplement.<sup>19</sup> Food intake is

reported to reduce the bioavailability of LA.<sup>20</sup> Therefore, LA is generally recommended to be taken up on an empty stomach (1 h before or 2 h after eating).

### Racemic versus R-LA supplements

R-LA is the isomer that is synthesized by plants and animals and functions as a cofactor for mitochondrial enzymes in its protein-bound form. Direct comparisons of the bioavailability of oral racemic LA and R-LA supplements have not been published. After oral dosing with racemic LA, peak plasma concentrations of R-LA were found to be 40–50% higher than S-LA, suggesting R-LA is better absorbed than S-LA, but both isomers are rapidly metabolized and eliminated.<sup>21</sup> However, virtually all of the published studies of LA supplementation in humans have used racemic LA. At present, it is not clear whether R-LA supplements are more effective than racemic LA supplements in humans.

### LIPOIC ACID CIRCULATING VALUES AND DEFICIENCY IN TISSUES

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Endogenous levels of plasma LA are reported to be 1–25 ng/mL and of DHLA as 33–145 ng/mL in healthy human volunteers.<sup>22</sup> Overall, humans are able to synthesize enough LA to meet their needs for enzyme cofactors. However, its synthesis declines with age and in people with compromised health<sup>23</sup> including diabetes and associated abnormalities, such as diabetic neuropathy. Thus, in these cases, LA may need to be obtained from outside sources by consuming certain foods and from supplements.

### LIPOIC ACID AND ITS ROLE IN DIABETES

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LA has been reported to have beneficial effects in many disease states such as diabetes, multiple sclerosis, cognitive decline, and dementia. Described here are various lines of evidence for a positive outcome with regards to LA therapy in type 1 (T1) and type 2 (T2) diabetes mellitus (DM) and their associated abnormalities. Importantly, LA has potential for application in treating many aspects of diabetes pathology. In T1DM (IDDM), destruction of beta cells causes loss of insulin secretion, whereas in T2DM (NIDDM), insulin resistance of peripheral tissues is the major problem.

Diabetes mellitus is strongly associated with increased oxidative stress, which could be a consequence of either increased production of free radicals or reduced antioxidant defenses. There is considerable evidence to indicate that oxidative stress plays an important role in the etiology of diabetic complications. Many of the biochemical pathways (e.g., protein glycation, polyol pathway, protein kinase C activation, glucose autoxidation) associated with hyperglycemia can result in increased ROS. Oxidative stress is not only associated with complications of diabetes, it has also been linked to insulin resistance. LA has potential preventive and ameliorating effects in both T1 and T2 diabetes. Briefly, in animal models of T1 diabetes, intraperitoneal administration of LA (10 mg/kg body weight) for 10 days resulted in a 50% decrease in the number of mice developing diabetes, which was induced by cyclophosphamide, an effect that could be due to suppression of NO release by macrophages.<sup>24,25</sup> Furthermore, LA increases glucose utilization<sup>26,27</sup> in isolated rat diaphragm, heart, and cultured myotubes.

### Oxidative stress

Many of the complications induced by diabetes, including polyneuropathy and cataract formation, appear to be mediated by ROS generation. Diabetic patients have elevated serum levels of TBARS, F2 isoprostanes, and 8-OH-guanosine compared to non-diabetics.<sup>28</sup> In addition, oxidative stress is proposed to be an early event in the pathology of diabetes and may influence the onset and progression of late complications. Borcea et al.<sup>29</sup> demonstrated in a cross-sectional study of 107 diabetic (T1 and T2) patients that those taking LA (600 mg/day for >3 months) had decreased oxidative stress compared with those without LA treatment, irrespective of their poor glycemic control and albuminuria. These authors assessed oxidative stress by measuring plasma lipid hydroperoxide (ROOHs), and on the balance between oxidative stress and antioxidant defense, as measured by the ratio ROOH/(alpha-tocopherol/cholesterol). Additionally, the redox-sensitive transcription factor nuclear factor-kappa B (NF-kappa B) is known to contribute to late diabetic complications. In this context, Hofmann et al.<sup>30</sup> reported that LA-dependent downregulation of NF-kappa B is evident in the monocytes of diabetic patients receiving LA therapy.

Additionally, oxidative stress leads to endothelial cell (EC) damage and vascular dysfunction.<sup>31</sup> In this regard, Morcos et al.<sup>32</sup> conducted a prospective, open, and non-randomized study in 84 diabetic patients. In this study, 49 patients (34 with T1DM and 15 with T2DM) had no antioxidant treatment and served as controls. The 35 remaining patients (20 with T1DM and 15 with T2DM) underwent LA therapy (600 mg/day for 18 months). The progression of EC damage in terms of the measurement of plasma thrombomodulin was significantly increased in the control group and decreased in the LA therapy group after 18 months of follow-up. However, the course of diabetic nephropathy, as assessed by urinary albumin concentration, was significantly increased in controls, but was unchanged in the treated group. These authors suggested the need for a placebo-controlled study.

Furthermore, lipid peroxidation of nerve membranes has been suggested as a mechanism by which peripheral nerve ischemia and hypoxia could cause neuropathy. In this regard, Androne et al.<sup>33</sup> investigated the magnitude of oxidative stress in terms of the measurement of serum ceruloplasmin and lipid peroxide levels in 10 patients with diabetic neuropathy before and after 70 days of LA treatment (600 mg/day). LA was administered intravenously (i.v.) once daily for the first 10 days and orally for the next 50 days. Serum ceruloplasmin levels were significantly higher in diabetic patients as compared to healthy subjects, probably related to antioxidant defense. Furthermore, serum lipid peroxide levels were significantly higher in diabetics compared with healthy subjects and were significantly decreased in diabetics after LA treatment with no change in serum ceruloplasmin levels. Overall, LA treatment appears to prevent oxidative stress-induced changes in diabetic patients.

### Insulin signaling and glucose utilization

The binding of insulin to the insulin receptor triggers the auto phosphorylation of several tyrosine residues on the insulin receptor. Activation of the insulin receptor in this manner stimulates a cascade of protein phosphorylations, resulting in the translocation of glucose transporters (GLUT4) to the cell membrane and increased cellular glucose uptake.<sup>3,34</sup> LA has been found to increase GLUT4 translocation to cell membranes and to increase glucose uptake in cultured adipose (fat) and muscle cells.<sup>5,35</sup> Thus, LA appears to engage the insulin-signaling pathway, thereby increasing glucose uptake into

muscle and fat cells. On this basis, LA is referred to as an insulin mimetic agent. Notably, insulin receptor is the hallmark feature of T2DM. As skeletal muscle tissue is the major sink in the body for glucose following a meal, agents that enhance glucose uptake by skeletal muscle are potentially useful in the long-term treatment of T2DM.

Several clinical studies point to a beneficial effect of LA on whole-body glucose metabolism in patients with T2DM. In these studies, glucose metabolism and insulin sensitivity were assessed using the euglycemic-hyperinsulinemic clamp. Jacobs et al.<sup>36</sup> tested for the first time in a clinical setting if LA supplementation augments insulin-mediated glucose disposal in NIDDM. Thirteen patients comparable in age, body-mass index, duration of diabetes, and with a similar degree of insulin resistance at baseline received either LA (1000 mg/500 mL NaCl,  $n = 7$ ) or vehicle only (500 mL NaCl,  $n = 6$ ) during a glucose-clamp study. After acute parenteral administration of LA, the glucose infusion rate increased 47% ( $P < 0.05$ ), metabolic clearance rate increased 55% ( $P < 0.05$ ), and insulin sensitivity increased 57% ( $P < 0.05$ ), whereas the control group did not show any significant change. Thus, this was the first clinical study to show that LA increases insulin-stimulated glucose disposal in NIDDM. Subsequently, the same group of authors<sup>37</sup> reported in an uncontrolled pilot study of 20 patients with T2DM that i.v. infusion of 500 mg/day of racemic LA for 10 days improved insulin sensitivity measured 24 h after the last infusion. To place these results in context, if the reported increases in metabolic clearance rate and insulin sensitivity were to persist with continued LA therapy, then its effect can be compared favorably with metformin, a widely prescribed medication that increases insulin sensitivity and glucose utilization. Importantly, in patients with T2DM, a daily dose of 2 g metformin (monotherapy) for 3 months produced an approximate 25% increase ( $P < 0.03$ ) in peripheral glucose disposal, as measured by the euglycemic-hyperinsulinemic clamp.

Furthermore, Jacob et al.<sup>38</sup> have evaluated the efficacy of oral administration of LA using enteric-coated tablets (600–1800 mg/day) on insulin-stimulated glucose disposal in a placebo-controlled study of 72 patients with T2DM. These authors reported that oral administration of racemic LA at doses of 600, 1200, or 1800 mg/day improved insulin sensitivity by 25% after 4 weeks of treatment. There were no significant differences among the three doses of LA, suggesting that 600 mg/day may be the maximum effective dose. Also, Evans et al.<sup>39</sup> investigated the effect of LA supplementation on long-term glycemic control in a preliminary, open-label study using a novel oral formulation of a controlled-release LA. This formulation was designed to maintain the plasma concentration of LA over time by using controlled-release drug delivery technology (polymeric cellulose resins). Fifteen patients with T2DM were administered controlled-release LA (900 mg/day for 6 weeks and 1200 mg/day for another 6 weeks) in addition to their current medications. At the end of the 12-week period, plasma fructosamine concentrations had decreased significantly (~10%, from 313 to 283  $\mu\text{mol/L}$ ), but glycosylated hemoglobin (HbA1c) levels did not change ( $8.2 \pm 1.5\%$  at baseline and  $8.2 \pm 0.5\%$  at 12 weeks). Importantly, plasma fructosamine levels reflect blood glucose control over the past 2–3 weeks, while HbA1c values reflect blood glucose control over the past 2–4 months. Also, there was no change in fasting plasma glucose ( $157 \pm 34$  mg/dL at baseline and  $150 \pm 47$  mg/dL at 12 weeks) or C-peptide levels ( $5.0 \pm 3.8$  ng/mL at baseline and  $5.0 \pm 3.2$  ng/mL at 12 weeks). The limited outcome from this study was attributable to the abbreviated duration of treatment at the effective 1200 mg dose (6 weeks total exposure) or to a statistical power too limited to detect a significant change, especially in light of the degree of variability of HbA1c at baseline. These authors suggested a need exists for a larger, double-blind, placebo-controlled study of longer duration to address this question.

Another recent open-label study evaluated orally administered LA on insulin sensitivity along with serum lactate and pyruvate levels in patients with T2DM. In this study, LA (1200 mg per day) was administered to ten lean and ten obese patients for 4 weeks.<sup>40</sup> Following treatment with LA, lactate and pyruvate were reduced by approximately 45% after oral glucose loading ( $P < 0.05$ ). In lean and obese patients with diabetes, LA increased insulin sensitivity by approximately 18–20%, although this effect was statistically significant only in the lean patients with diabetes ( $P < 0.05$ ).

Furthermore, very recently, Kamenova<sup>41</sup> reported the effect of oral administration of LA (600 mg twice daily for 4 weeks) on insulin sensitivity in 12 patients with T2DM in good control, defined by HbA1c values of  $5.8 \pm 0.8\%$ . The subjects with normal glucose tolerance served as a control group. Insulin sensitivity was measured by a 2 h manual hyper-insulinemic (insulin infusion rate:  $40 \text{ mU/m}^2$  body surface area/min) euglycemic (blood glucose kept at 5 mmol/L) clamp technique and was expressed as a glucose disposal rate and insulin sensitivity index. At the end of the treatment period, the insulin sensitivity of diabetic patients was significantly increased. Importantly, the difference was not statistically significant between the insulin sensitivity of diabetic patients after LA therapy and control subjects, suggesting that short-term oral LA treatment increases peripheral insulin sensitivity in patients with T2DM. However, there was no change in fasting plasma glucose before ( $6.5 \pm 1.1$  mmol/L) and after ( $5.9 \pm 0.8$  mmol/L) treatment.

Overall, it is evident that in contrast to i.v. LA administration, the improvement in insulin sensitivity following oral administration of LA is only minimal (<20%). This is evident despite the higher doses used (up to 1800 mg) and the longer treatment time (30 days oral versus 10 days i.v.).

### Vascular disease

Endothelial function is often impaired in diabetic patients, who are at high risk for vascular disease.<sup>42</sup> Neuropathy may arise when metabolic changes in diabetic patients cause structural and functional deficits in the vascular system, particularly endothelial dysfunction. Importantly, endothelial function can be assessed non-invasively by using ultrasound to measure flow-mediated vasodilation, which is endothelium-dependent.<sup>43</sup> Heitzer et al.<sup>44</sup> reported that the intra-arterial infusion of racemic LA improved endothelium-dependent vasodilation in diabetic patients ( $n = 39$ ) but not in healthy controls ( $n = 11$ ). Another randomized controlled trial assessed the effect of oral LA supplementation on flow-mediated vasodilatation in 58 patients diagnosed with the metabolic syndrome.<sup>45</sup> Importantly, metabolic syndrome subjects are at increased risk of developing diabetes. Oral supplementation with 300 mg/day of LA for 4 weeks improved flow-mediated vasodilation by 44% compared to placebo. Furthermore, in an uncontrolled study, oral supplementation with 1200 mg/day of racemic LA for 6 weeks improved a measure of capillary perfusion in the fingers of eight diabetic patients with peripheral neuropathy.<sup>46</sup> However, Jin et al.<sup>47</sup> reported no significant changes in skin blood flow measured in 19 patients with diabetic neuropathy compared to 13 control subjects using the Laser Doppler blood flow technique. Overall, the studies reported are equivocal; thus, long-term randomized controlled trials are needed to determine whether LA supplementation can reduce the risk of vascular complications in individuals with diabetes.

### Diabetic polyneuropathies

Pathophysiological nerve dysfunction is associated with both T1DM and T2DM due to alterations in endoneurial blood flow and distal nerve conduction.<sup>48</sup> In an experimental animal model of diabetes, LA treatment improved neural blood flow and nerve conduction.<sup>49</sup> These positive results

prompted numerous clinical trials examining the extent and efficacy of LA to ameliorate diabetes-induced polyneuropathies. LA was first used therapeutically in Germany to treat diabetes-induced neuropathy, despite the scarcity of information regarding the cause of this condition at that time. It was believed that LA increased glucose utilization in peripheral nerves. There have been various controlled clinical trials (see [Table 1](#)) evaluating the efficacy of LA for the treatment of diabetes-induced neuropathy, as discussed below.

Study	Study Design	Population	Intervention	Outcomes
ALADIN I	Randomized, double-blind, placebo-controlled	T2DM with peripheral neuropathy	LA 100, 600, 1200 mg/day vs placebo	Significant improvements in pain, numbness, and paresthesia at higher doses
ALADIN II	Randomized, double-blind, placebo-controlled	T1DM and T2DM	LA 600 or 1200 mg/day vs placebo	Significant improvements in peripheral nerve conduction
ALADIN III	Randomized, double-blind, placebo-controlled	T2DM	LA 600 or 1200 mg/day vs placebo	Significant improvements in peripheral nerve conduction
ORPIL	Randomized, double-blind, placebo-controlled	T2DM	LA 1800 mg/day vs placebo	Significant improvements in endoneurial function
NATHAN I	Randomized, double-blind, placebo-controlled	T2DM	LA 600 mg/day vs placebo	Significant improvements in sensory symptoms and nerve function

**Table 1**

Summary of completed clinical trials with lipoic acid for diabetic polyneuropathy

The so-called ALADIN (Alpha Lipoic Acid in Diabetic Neuropathy; ALADIN, ALADIN II, and ALADIN III) trials and the ORPIL (Oral Pilot) study are the most instructive as these are randomized, double-blind, placebo-controlled studies, as reviewed by Zeigler et al.<sup>50</sup> The ALADIN trial was a 3-week multicenter, randomized, double-blind, placebo-controlled trial. The patients with T2DM exhibiting peripheral neuropathies were given LA at three different doses (100, 600, and 1200 mg/day) or placebo via i.v. infusion. The results revealed significant improvements in pain, numbness, and paresthesia at the higher doses (600 and 1200 mg/day).<sup>51</sup> Following this short-term trial of LA for improving neuropathic symptoms in diabetic patients, the long-term response was investigated in the ALADIN II trial.<sup>52</sup> This trial was carried out for 2 years in T1DM and T2DM patients. At the beginning, 1200 or 600 mg of LA or a placebo was administered intravenously once daily for 5 consecutive days before the patients were enrolled in the oral treatment phase of 600 or 1200 mg/day LA or a placebo for 2 years. The results showed significant improvements in peripheral nerve conduction. Because of these positive results, the ALADIN III study<sup>50</sup> was designed to determine whether short-term i.v. LA treatment followed by longer term oral LA supplementation could effectively ameliorate diabetes-associated polyneuropathies. In this study, T2DM patients were given either 600 or 1200 mg LA/day for 3 weeks followed by 1800 mg/day LA for 6 months. The results showed a trend toward improved neurological pain, but this improvement did not reach statistical significance. However, the ORPIL study, although with a decidedly smaller population (12 in the LA group and 12 in the placebo group) showed that T2DM patients given 1800 mg/day LA (600 mg of LA t.i.d) had significant improvements in endoneurial function after 3 weeks of treatment.<sup>53</sup> One additional study that is ongoing and yet to be published is NATHAN I, which was reviewed recently.<sup>54</sup> NATHAN I is a 4-year international, randomized, double-masked, placebo-controlled study investigating the efficacy of oral LA on peripheral diabetic neuropathy. Outcomes to be measured include a reliable, clinical, and neurophysiologic assessment including neuropathic deficits to determine effects on progression.

Furthermore, Ametov et al.<sup>55</sup> report that the sensory symptoms of diabetic polyneuropathy are improved by LA treatment in terms of the total symptom score (TSS), a measure of positive neuropathic sensory symptoms carried out in the Symptomatic Diabetic Neuropathy (SYDNEY) trial. In this trial, metabolically stable diabetic patients with symptomatic (stage 2) diabetic sensor motor polyneuropathy (DSP) were randomized to a parallel, double-blind study of LA (600 mg) ( $n = 60$ ) or placebo ( $n = 60$ ) and infused daily intravenously for 5 days per week for a total of 14 treatments. The primary endpoint was a change in the sum score of daily assessments of severity and duration of TSS. The results of this trial depict that, at randomization, the groups were not significantly different in metabolic control or neuropathic endpoints. After 14 treatments, the TSS of the LA group had improved from baseline by an average of 5.7 points and the placebo group by an average of 1.8 points ( $P < 0.001$ ). The researchers concluded that intravenously administered racemic LA rapidly, and to a significant and meaningful degree, improved such positive neuropathic sensory symptoms as pain and several other neuropathic endpoints. This improvement of symptoms was attributed to improved nerve pathophysiology and decreased nerve fiber degeneration. Because of its safety profile and its effect on positive neuropathic sensory symptoms and other neuropathic endpoints, these authors postulated that LA appears to be a useful ancillary treatment for the symptoms of diabetic polyneuropathy.

Additionally, Ziegler et al.<sup>56</sup> reported the efficacy of oral LA treatment on improvement of symptomatic diabetic polyneuropathy in the SYDNEY 2 trial. The study was a multicenter, randomized, double-blind, placebo-controlled trial carried out in 181 patients with T1DM or T2DM of at least 1 year's duration and with a HbA1c level of  $<10\%$ , symptomatic DSP attributable to diabetes, TSS  $>7.5$  points, neuropathy impairment score (NIS) subscore for lower limbs of  $\geq 2$  points, neuropathic pain, and reduced or absent sensation on pinprick test. The patients (age range: 18–74 years) received either LA as once-daily oral doses of 600 mg (LA600;  $n = 45$ ), 1200 mg (LA1200;  $n = 47$ ), and 1800 mg (LA1800;  $n = 46$ ) or placebo ( $n = 43$ ) for 5 weeks after a 1-week placebo run-in period. The primary outcome measure was the change in TSS from baseline, including stabbing pain, burning pain, paresthesia, and numbness of the feet while asleep. Mean TSS did not differ significantly at baseline among the treatment groups and, on average, it decreased by 51% in LA600, 48% in LA1200, and 52% in LA1800 compared with 32% in the placebo group (all  $P < 0.05$  compared to placebo). Significant improvements favoring all three LA groups were also noted for stabbing and burning pain. Safety analysis showed a dose-dependent increase in nausea, vomiting, and vertigo. It was concluded that oral treatment with LA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. The researchers concluded that an oral dose of 600 mg once daily appears to provide the optimum risk-to-benefit ratio.

Another neuropathic complication of diabetes is cardiovascular autonomic neuropathy, which occurs in as many as 25% of diabetic patients.<sup>57</sup> Cardiovascular autonomic neuropathy is characterized by reduced heart rate variability and is associated with increased risk of mortality in diabetic patients. In this regard, Zeigler et al.<sup>58</sup> carried out the Deutsche Kardiale Autonome Neuropathie (DEKAN) study in T2DM patients. The efficacy of LA (800 mg/day of LA for 4 months) was tested on patients with cardiovascular autonomic neuropathy assessed by heart rate variability. At the end of the study, there was a significant improvement in two of four measures of heart rate variability compared to placebo. The authors suggested that treatment with LA using a well-tolerated oral dose of 800 mg/day for 4 months slightly improves cardiovascular autonomic neuropathy.

Thus, though the benefit of long-term oral LA supplementation is less clear, there is evidence to suggest that oral LA may be beneficial in the treatment of diabetic peripheral neuropathy (600–1800 mg/day)<sup>36,38</sup> and cardiovascular autonomic neuropathy (800 mg/day).<sup>58</sup>

In 2004, Zeigler et al.<sup>59</sup> published a meta-analysis of controlled clinical trials of LA by searching the database of VIATRIS GmbH, Frankfurt, Germany. For inclusion of a study in this meta-analysis, it had to meet the following prerequisites: randomized, double-masked, placebo-controlled, parallel-group trial using LA infusions of 600 mg i.v. per day for 3 weeks, except for weekends, in diabetic patients with positive sensory symptoms of polyneuropathy, which were scored by TSS in the feet on a daily basis. Four trials (ALADIN, ALADIN III, SYDNEY, and NATHAN II) comprising 1258 patients (LA,  $n$

= 716; placebo,  $n = 542$ ) met these eligibility criteria and were included in a meta-analysis based on the intention-to-treat principle. Primary analysis involved a comparison of the differences in TSS from baseline to the end of i.v. treatment between the groups treated with LA or placebo. Secondary analyses included daily changes in TSS, responder rates ( $\geq 50\%$  improvement in TSS), individual TSS components, NI, NIS of the lower limbs (NIS-LL), individual NIS-LL components, and the rates of adverse events. The authors reported that after 3 weeks, the relative difference in favor of LA compared to placebo was 24.1% for TSS and 16.0% for NIS-LL. The responder rates were 52.7% in patients treated with LA and 36.9% in those receiving the placebo ( $P < 0.05$ ). On a daily basis, there was a continuous increase in the magnitude of TSS improvement in favor of LA compared to placebo, which was noted first after 8 days of treatment. Among the individual components of TSS, pain, burning, and numbness decreased in favor of LA compared to placebo, while among the NIS-LL components, pinprick and touch-pressure sensation as well as ankle reflexes were improved in favor of LA after 3 weeks. The rates of adverse events did not differ between the groups. The results of this meta-analysis provide evidence that treatment with LA (600 mg/day i.v.) over 3 weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.

However, the validity of this meta-analysis was questioned by Tang et al.,<sup>60</sup> who identified some weaknesses in the meta-analysis and published their own report as a critically appraised topic based on a clinical scenario, structured question, search strategy, appraisal, results, summary of evidence, commentary, and bottom-line conclusions. These authors searched the Ovid MEDLINE database for the time period 1966 to January 2007. Further limits were applied utilizing search filters or strategies for systematic reviews, meta-analyses, and therapy-emphasizing relevance to locate randomized clinical trials; this led to a yield of ten articles. From that set of ten articles, a single recent relevant randomized controlled trial<sup>56</sup> (RCT) of oral LA and one relevant systematic review of i.v. LA were located.<sup>50</sup> The RCT-SYDNEY 2 study<sup>56</sup> was selected as the best available evidence to answer the clinical question of whether oral LA is effective in improving neuropathic symptoms compared with placebo. It was concluded that oral LA (600 mg) may improve neuropathic symptoms in diabetic DSP. These authors further reported that adverse events including nausea, vomiting, and vertigo were identified but occurred most frequently with LA doses of 1200 mg and 1800 mg; treatment-emergent adverse events for LA 600 mg were not significantly different than those for placebo. Overall, these authors concluded that the evidence supporting the efficacy of oral LA for diabetic neuropathy is based on a single RCT. Thus, LA's role and place in an algorithm among other commonly prescribed oral treatments for symptomatic relief of neuropathic pain in diabetic DSP remain unclear.

Very recently, Tankova et al.<sup>61</sup> evaluated the effect of LA in autonomic diabetic neuropathy in a controlled, randomized, open-label study. Forty-six patients with T1DM and different forms of autonomic neuropathy were treated with LA for 10 days (600 mg i.v. LA daily followed by one film tablet of 600 mg daily for 50 days). Twenty-nine T1DM patients with autonomic diabetic neuropathy served as a control group. Following treatment, a significant improvement was found in the score for severity of cardiovascular autonomic neuropathy, while in the control group it worsened. Also, there was a beneficial effect of treatment on the change of systolic blood pressure at the lying-to-standing test. These authors further reported a post-treatment improvement in diabetic enteropathy in six patients; in the complaints of dizziness/instability upon standing in six patients; in neuropathic edema of the lower extremities in four patients; and in erectile dysfunction in four patients. In the control group, no change was reported in the symptoms and signs of autonomic neuropathy by the end of the follow-up period. Furthermore, oxidative stress, measured as the total serum antioxidant capacity, serum and erythrocyte SOD activity, was reported to be significantly improved, leading to the conclusion that LA appears to be effective in the treatment of the various forms of autonomic diabetic neuropathy.

Overall, in all these trials, there was no evidence that LA treatment actually affected glycemic control.<sup>50-52</sup> However, case studies have indeed shown improved glucose handling in human diabetic patients.<sup>36-38,40,41</sup> Thus, despite some discrepancies, there is generally strong clinical evidence that LA, especially at relatively high doses, significantly improves neuropathies associated with diabetes.

## CLINICAL USAGE OF LIPOIC ACID

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For the treatment of diabetes, the recommended dosage of LA is 300–600 mg daily. For general antioxidant support, the dosage is 20–50 mg daily.<sup>23</sup> Intravenous and oral LA are approved for the treatment of diabetic neuropathy in Germany.<sup>50-54</sup> Based on the evidence presented above, LA speeds the removal of glucose from the bloodstream,<sup>36,37</sup> at least partly by enhancing insulin function,<sup>38,41</sup> and it reduces insulin resistance, which is an underpinning of many cases of coronary heart disease and obesity.

## SAFETY OF LIPOIC ACID

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There are no indications that low doses of LA, such as 5 mg, have side effects. Higher doses could cause nausea or stomach upset, along with overstimulation, fatigue, and insomnia. High doses may also potentially lower blood sugar. This is often beneficial to patients with diabetes, but it requires close monitoring of blood sugar levels. In general, LA supplementation has been found to have few serious side effects. At higher doses, gastrointestinal symptoms including abdominal pain, nausea, and vomiting, as well as diarrhea and anaphylactic reactions, including laryngospasm, were reported.<sup>56</sup> Also, allergic reactions affecting the skin, including rashes, hives, and itching have been reported. Malodorous urine has also been noted by people taking 1200 mg/day of LA orally.<sup>62</sup> Overall, 600 mg/day is the safe and recommended dose for diabetes.

## LIMITED EFFICACY OF CURRENT ORAL FORM OF LIPOIC ACID DUE TO PHARMACOKINETIC PROFILE

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One possible explanation for the marginal efficacy of oral LA therapy on insulin sensitivity might be the abbreviated time that therapeutic plasma levels of LA are maintained when taken orally. It is possible that this might also account for the lack of efficacy of oral LA therapy with regard to glycemic control. This plasma profile is a function of the short half-life of LA, along with its extensive presystemic elimination. Human pharmacokinetic studies have found that LA possesses an extremely short plasma half-life of about 30 min after both oral and i.v. administration.<sup>21,22</sup> Oral LA is absorbed rapidly and the maximum plasma concentration is reached within 30 min to 1 h for doses of up to 600 mg.<sup>21</sup> The absolute bioavailability after a single oral dose of 200 mg is approximately 30%. Even after repeated oral administration of LA, it appears that accumulation in plasma is not achieved. Presumably, this reflects the short plasma half-life and extensive presystemic elimination, which is thought to be primarily hepatic. Thus, following oral LA administration, a maximum plasma level is quickly reached, but it falls just as quickly to a level insufficient to impact insulin sensitivity or glucose control. It is interesting

to speculate that the superior ability of i.v. LA to improve insulin sensitivity might be due to the fact that i.v. administration achieves a higher plasma level of LA, and maintains it for a longer duration. In this context, the question is raised as to whether maintaining a therapeutically effective level of LA in plasma for an appropriate length of time (i.e., mimicking the i.v. LA situation) using controlled-release drug delivery technology<sup>39</sup> would increase insulin sensitivity and eventually result in a beneficial impact on glucose control in T2 diabetics. In this regard, Bernkop-Schrünron et al.<sup>63</sup> have formulated a sustained release formulation of LA by which increased plasma levels of LA can be achieved for at least 12 h. Owing to the pulsed sustained release of LA, this preparation seems to be very beneficial for stimulating the glucose uptake in T2DM patients. On the other hand, Hermann et al.<sup>64</sup> report that in insulin-dependent diabetics, who usually have delayed gastric emptying, no substantial influence on LA bioavailability is observed in these patients.

## DRUG AND NUTRIENT INTERACTIONS OF LIPOIC ACID

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Because there is some evidence that LA supplementation improves insulin-mediated glucose utilization,<sup>5,35</sup> it is possible that LA supplementation could increase the risk of hypoglycemia in diabetic patients using insulin or oral antidiabetic agents. Consequently, blood glucose levels should be monitored closely when LA supplementation is added to diabetes treatment regimens. Also, the chemical structure of biotin is similar to that of LA, and there is some evidence that high concentrations of LA can compete with biotin for transport across cell membranes,<sup>65</sup> but it is not known whether LA supplementation substantially increases the requirement for biotin in humans.<sup>66</sup>

## CONCLUSION

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Lipoic acid has been shown to have a number of beneficial effects, both in the prevention and treatment of diabetes. LA may act in a number of ways that are especially protective in diabetes: 1) it prevents beta cell destruction, a cause of T1DM; 2) it enhances glucose uptake in T2DM; and 3) its antioxidant effects may be particularly useful in slowing the development of diabetic neuropathy and may especially be significant in alleviating diabetes-induced reduction in intracellular vitamin C levels. Clinical studies show that i.v. administration of LA is able to significantly increase insulin sensitivity in patients with T2DM, while oral administration of LA exerts a marginal effect. This limitation of oral therapy is likely a function of the abbreviated duration for which a therapeutic level of LA is maintained in plasma. If the limitations of oral therapy can be overcome, then LA could emerge as a safe and effective adjunctive antidiabetic agent with insulin-sensitizing activity. Furthermore, very few of the reported effects of LA will manifest as objective improvement over the course of weeks or months. This is demonstrated in trials for the treatment of neuropathy, which lasted up to 12 weeks, in which objective improvement was not observed but clear subjective improvement was present, even in double-blind studies. It is unrealistic to expect dramatic effects in weeks, since diabetic complications develop over years and decades. However, given the array of beneficial effects of LA and the lack of adverse side effects, its usage in Germany, and potential for improvements in neuropathy deficits as well as symptoms, it can be considered as a treatment option for diabetes and its related complications such as peripheral neuropathy and cardiovascular autonomic neuropathy.

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## Footnotes

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