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The Use of Alpha-Lipoic Acid Supplementation in Diabetes: The Available Evidence

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Abstract

Dietary health supplements have been increasingly used in the treatment and prevention of chronic disorders. During the previous years, lipoic acid has been reported to have a beneficial effect on diabetes and some of its complications. The aim of this paper is to review the evidence provided by lipoic acid research findings relevant to its use in diabetes. Since, the1950s, there has been an accumulating experimental evidence showing that that lipoic acid, a naturally occurring substance, has a protective effects against the development of diabetes and its complications especially neuropathy. The beneficial use of oral lipoic acid in diabetic neuropathy has been reported mostly from Germany as early as the 1960s.

Keywords: lipoic acid, diabetes, research findings, expert opinion

During the 1950s, experimental studies showed that lipoic acid; a naturally occurring substance can prevent the development of alloxan diabetes in rats (Cutolo E & Reduzzi F., 1955).

The use of oral lipoic acid in diabetic neuropathy has been reported as early as the 1960s (Sladki E, Maldyk H & Prusinski A., 1963).

Klein (1975) reported the treatment of 100 patients who had diabetic neuropathy with oral alpha-lipoic acid. Treatment was considered successful in 23 patients of 29 patients who received 50 mg twice daily, and in 51 of 60 patients who received 100 mg twice daily (Klein W., 1975).

Faust et al (1994) from Germany reported an experimental study on non-obese diabetic mice with type I diabetes which showed that lipoic acid had a protective effect against the development of cyclophosphamide-induced diabetes. The anti-diabetic effect of lipoic acid was associated with partial inhibition of islet inflammation. The anti-inflammatory effect of lipoic acid was attributed to scavenging oxygen radicals and to inhibiting nitric oxide generation (Faust A, Burkart V, Ulrich H & Weischer CH, Kolb H., 1994).

Strödter et al (1995) from Germany reported an experimental study on streptozotocin induced type 1 diabetes and cardiomyopathy in rats which showed that lipoic acid has beneficial anti-diabetic effects on cardiac metabolism and has the potential of correcting metabolic and hemodynamic abnormalities of diabetes in the `heart. The suggested mechanisms of action include (Strödter D, Lehmann E, Lehmann U, Tritschler HJ, Bretzel RG & Federlin K., 1995):

1) Increasing glucose uptake.

2) Improving utilization of endogenous glycogen in the diabetic heart through increasing glycogen breakdown.

3) Increasing glucose oxidation.

Jacob et al (1995) from Germany reported a study which included thirteen patients with type II diabetes. Seven patients received lipoic acid 1g in 500 ml NaCl, and six patients received 500 ml NaCl without lipoic acid.

Parenteral lipoic acid was associated with a considerable elevation of insulin-stimulated disposal of glucose (Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, Jung WI, Augustin HJ & Dietze GJ., 1995).

Nagamatsu et al (1995) from the USA reported an experimental study on streptozotocin induced diabetes which showed that the nerve blood flow in the diabetic animals was reduced by 50%, and it returned to normal after one month of treatment with lipoic acid 100 mg per kilogram. This beneficial effect was associate with evidence of reduction of oxidative stress (Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritschler H & Low PA., 1995).

Ziegler et al (1995) from Germany reported a 3-week double-blind placebo-controlled study which included 328 diabetic patients (Non-insulin-dependent) from several centers who had symptomatic peripheral neuropathy. The patients were treated with intravenous infusion of alpha-lipoic acid using or placebo. The study showed that intravenous alpha-lipoic acid in a dose of 600 mg daily for three weeks was associated with significant reduction of the symptoms of diabetic peripheral neuropathy and was not associated with important adverse reactions (Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schütte K & Gries FA., 1995).

Khamaisi et al (1997) reported an experimental study on rats with streptozotocin induced diabetes which showed that daily treatment with lipoic acid can decrease blood glucose level in diabetic rats by augmenting gastrocnemius muscle crude membrane protein content and by improving muscle glucose utilization (Khamaisi M, Potashnik R, Tirosh A, Demshchak E, Rudich A, Tritschler H, Wessel K & Bashan N., 1997).

Ziegler et al (1999) reviewed the evidence available from clinical trials in Germany using alpha-lipoic acid in the treatment of diabetic polyneuropathy. The found that Treatment with lipoic acid 600 mg intravenously for three weeks improves the main symptoms of diabetic polyneuropathy. Oral lipoic acid for 4-7 months can improve neuropathic deficits and cardiac autonomic neuropathy. Two years treatment can lead to long-term improvements in motor and sensory nerve conduction in the lower limbs. Ziegler et al emphasized that treatment with lipoic acid is very safe (Ziegler D, Reljanovic M, Mehnert H & Gries FA., 1999).

Khamaisi (1999) emphasized that lipoic acid is an anti-oxidant that has a beneficial effect in diabetes that is attributed to enhancing utilization of peripheral glucose. They reported an experimental study which included non-diabetic and diabetic rats having streptozotocin-induced diabetes. The study showed that short-term intake of lipoic acid at high dosage to non-diabetic rats can inhibit of gluconeogenesis through interfering with fatty acid oxidation in the liver (Khamaisi M, Rudich A, Potashnik R, Tritschler HJ, Gutman A & Bashan N., 1999). This finding suggests that lipoic acid can possibly help in preventing diabetes in susceptible individuals.

Jacob et al (1999) from Germany reported a study which included 74 diabetic patients (Type-2). Nineteen patients received 600 mg lipoic acid once daily, eighteen patients received 600 mg lipoic acid twice daily, eighteen patients received 600 mg lipoic acid three times daily, and nineteen patients received placebo. All patients who received lipoic acid experienced considerably different changes in insulin-stimulated glucose disposal and improvement insulin sensitivity after one month of treatment (Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ & Dietze GJ, Rett K., 1999).

Gleiter et al (1999) from Germany reported a study which included 14 male and 10 female healthy volunteers and showed that lipoic acid in a dose of 600 mg has no interaction with glibenclamide and acarbose, a commonly used oral anti-diabetic agents (Gleiter CH, Schreeb KH, Freudenthaler S, Thomas M, Elze M, Fieger-Büschges H, Potthast H, Schneider E, Schug BS, Blume HH & Hermann R., 1999).

Cakatay et al (2000) from Turkey reported an experimental placebo-controlled study on male Wistar rats which showed that the increased lipid hydro-peroxide which occurs in association with streptozotocin diabetes is significantly reduced by alpha-lipoic acid suggesting that alpha-lipoic can reduce oxidative stress (Cakatay U, Telci A, Kayali R, Sivas A & Akçay T., 2000).

Androne et al (2000) emphasized that diabetes is accompanied by oxidative stress and the associated lipid peroxidation of nerve membranes contributes to the development of ischemia and hypoxia of peripheral nerve which led to neuropathy. The reported a study which included 10 diabetic patients with neuropathy and twelve healthy individuals as controls. The study showed that treatment with lipoic acid for 70 days was associated with lowering of lipid peroxide an index of lipid peroxidation (Androne L, Gavan NA, Veresiu IA & Orasan R., 2000).

The experimental work of Obrosova and colleagues on rats with streptozotocin- induced diabetes suggested that excessive 4-hydroxyalkenals is an early indicator of retinal oxidative stress in the diabetes. Lipid peroxidation increases in the diabetic retina despite the availability of reduced glutathione, and alpha-lipoic acid reduce lipid peroxidation (Obrosova IG, Fathallah L & Greene DA., 2000).

Strokov et al (2000) from Moscow emphasized that alpha lipoic acid is a powerful antioxidant that is effective

for the prevention and treatment of diabetic neuropathy. They found that plasma level of nitrites and nitrates in patients with insulin-dependent diabetes and polyneuropathy was about 2-fold less than the normal. However, Alpha-lipoic acid treatment was associated with completely normalization of plasma level of nitrites and nitrates. They also reported that most patients with insulin-dependent diabetes and polyneuropathy had also lower level of stress proteins (HSP72). Alpha-lipoic acid treatment was also associated normalization of stress proteins (HSP72) level. Therefore, Strokov et al suggested that activation of nitric oxide and stress proteins HSP protective systems contributes to the therapeutic effect of alpha-lipoic acid in type 1 diabetes mellitus associated with polyneuropathy (Strokov IA, Manukhina EB, Bakhtina LY, Malyshev IY, Zoloev GK, Kazikhanova SI & Ametov AS., 2000).

The experimental work of Melhem and colleagues (2001) on rats with streptozotocin diabetes suggested that lipoic acid supplementation could possibly help in the prevention early glomerular injury through increasing glutathione in the renal cortex (Melhem MF, Craven PA & Derubertis FR., 2001).

Tankova and colleagues (2004) from Bulgaria reported a controlled study which included 46 diabetic patients (Type 1) who various forms of autonomic neuropathy. They were treated with 600 mg of intravenous alpha-lipoic acid given daily for ten days, followed by oral lipoic, 600 mg/day for fifty days. 29 diabetic patients (Type 1) with autonomic diabetic neuropathy were included in the study as controls.

Treatment was associated with a considerable improvement in cardiovascular autonomic neuropathy with a beneficial effect on the change of systolic blood pressure at the lying-to-standing test. Improvement in diabetic enteropathy was observed in six patients. Six patients reported improvement in dizziness and instability upon standing. Four patients reported improvement in neuropathic edema of the lower limbs. Four patients reported improvement in erectile dysfunction.

Therefore, lipoic acid was considered to be useful in the treatment of various forms of autonomic diabetic neuropathy (Tankova T, Koev D & Dakovska L., 2004).

Hahm and colleagues (2004) from South Korea reported a study which included 61 diabetic patients with polyneuropathy associated with pain, burning sensation, paresthesia, and numbness. The patients were treated with oral lipoic acid 600 mg once daily for two months. 38 patients completed 2 months of the study. The overall efficacy was estimated at about 76%, and treatment was not associated with occurrence of serious side effects (Hahm JR, Kim BJ & Kim KW., 2004).

Liu et al (2007) from China reported the treatment of fifty diabetic patients (Type 2) who had peripheral neuropathy with lipoic acid 600 mg given in 250 normal saline once daily for two weeks. The findings were compared with a placebo group which included 43 diabetic patients (Type 2) who had peripheral neuropathy and received radix salviae infusion. Lipoic acid treatment was associated with an improvement rate of 90% which was considerably higher than the placebo group (Liu F, Zhang Y, Yang M, Liu B, Shen YD, Jia WP & Xiang KS., 2007).

Xiang et al (2008) from China reported a controlled study which included 42 patients with impaired glucose tolerance and 26 healthy controls group. 21 one patents received 300 mg of alpha-lipoic acid before oral glucose tolerance test, while the remaining 21 one patents, and the 26 healthy controls received 0.9% sodium chloride (250 ml) before oral glucose tolerance test.

The patients with impaired glucose tolerance had endothelial dysfunction (Lower flow-mediated endothelium-dependent arterial dilation measured by high-resolution ultrasound) in the fasting state and after a glucose challenge. Treatment with alpha lipoic acid was associated with improvement in endothelial dysfunction which is considered early warning of the development of atherosclerosis (Xiang GD, Sun HL, Zhao LS, Hou J, Yue L & Xu L., 2008).

Han et al (2012) from China conducted a meta-analysis which included randomized controlled trial studying the use of α-lipoic acid in diabetic peripheral neuropathy. The meta-analysis revealed that treatment with intravenous α-lipoic acid 300-600 mg daily for 2-4 weeks was safe and associated improvement in nerve conduction velocity and neuropathic symptoms (Han T, Bai J, Liu W & Hu Y., 2012).

Cassanego et al (2022) conducted a systematic review and meta-analysis of randomized controlled trials which included nine studies studying the use of lipoic acid in diabetic polyneuropathy and recommended that lipoic should be considered in the treatment of diabetic polyneuropathy (Cassanego G, Rodrigues P, De Freitas Bauermann L & Trevisan G., 2022).

Conclusion: There is convincing research evidence suggesting that lipoic acid has a beneficial effects in diabetes, and is particularly useful in the prevention and treatment of diabetic neuropathy. The beneficial effects of lipoic acid in diabetes and diabetic neuropathy are attributed to increasing insulin sensitivity, reduction of hyperglycemia-induced oxidative stress, and lipid peroxidation. Lipoic acid can possibly help in preventing

diabetes in susceptible individuals, and the current expert opinion suggests that lipoic acid can be used in patients with patients with impaired glucose tolerance.

Conflict of Interest

None.

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