Alpha-Lipoic Acid

Alpha-lipoic acid (ALA), also known as thioctic acid, has been studied in the treatment of various medical conditions, including type-2 diabetes, burning mouth syndrome, fibromyalgia, chronic fatigue syndrome, neuropathy, cancer, and atherosclerosis.

Type-2 Diabetes

Type-2 diabetes is associated with high levels of oxidative stress.[1] Specifically, diabetes impairs endothelial nitric oxide synthase activity and increases the production of reactive oxygen species, thus resulting in diminished nitric oxide bioavailability and increased oxidative stress.[2] Alpha-lipoic acid, a disulfide compound that is produced in small quantities in cells and serves as an antioxidant at pharmacological doses, has been shown to improve insulin sensitivity in type-2 diabetic patients. In addition to its antioxidant properties, it is also beneficial in cases of diabetes because of its anti-inflammatory[3] and hypoglycemic[4] properties.

In one recent open-label study in which lean and obese individuals with type-2 diabetes were administered 600 mg ALA by mouth, twice per day for four weeks, treatment with ALA was associated with increased glucose effectiveness in both lean and obese diabetics relative to non-diabetic lean and obese controls.[4] Lean diabetic patients were also found to have a higher degree of insulin sensitivity and lower fasting glucose. Furthermore, after ALA treatment, lactate and pyruvate before and after glucose loading were approximately 45% lower in both obese and lean diabetics, leading researchers to conclude that treatment with ALA prevents hyperglycemia-induced increments of serum lactate and pyruvate levels and increases glucose sensitivity.

As the result of another study, researchers concluded that oral treatment with 800 mg/day for 4 months may improve cardiac autonomic dysfunction in type-2 diabetics.[5]

Intravenous administration of ALA has also been shown to be beneficial in type-2 diabetes. In a small, randomized, controlled trial, 13 patients received either 1000 mg ALA or normal saline.[6] Both groups were comparable in age, BMI, and duration of diabetes. They also had similar degrees of insulin resistance at baseline. After administration of ALA, patients experienced a significant increase of insulin-stimulated glucose disposal. Metabolic clearance rate for glucose rose by about 50% in the treatment group, while the control group did not experience any significant change. Similar results, specifically a 30% increase in insulin-

stimulated glucose disposal, were demonstrated in an uncontrolled, pilot trial that administered 500 mg ALA intravenously per day over a 10-day period.[7]

In another study, while both oral and intravenous administration of ALA led to improvements in insulin sensitivity, the improvements associated with oral administration were minimal (about 20%) compared to the improvements seen with intravenous administration. The intravenous route of administration remained superior, despite higher doses of oral ALA (up to 1800 mg) and longer treatment time (30 days oral vs. 10 days IV).[8-9]

Burning Mouth Syndrome

As the name implies, burning mouth syndrome (BMS) is a chronic condition characterized by burning in the oral cavity. The syndrome is frequently associated with hyposalivation, xerostomia, and taste disturbances. While the exact etiology is unknown, BMS has been associated with psychological factors such as anxiety, depression, and cancer phobia, as well as systemic conditions such as menopause, nutrient deficiencies (B vitamins including folate, iron), hypothyroidism, diabetes mellitus (type-2 more than type-1), and pharmacological use of anti-hypertensive agents.[10]

Recent studies have also suggested that the cause of BMS may be neurological in nature and that BMS may actually be a neuropathy.[11] Because of ALA's role in the treatment of diabetes and diabetic neuropathy, researchers have explored its use in the management of BMS.[10]

One double-blind, randomized, placebo-controlled trial administered 400 mg ALA or 400 mg ALA plus vitamins to two treatment groups and placebo to a control group over the course of 8 weeks.[12] At the end of the study, all three groups had significant reductions in visual analogue scale (VAS) and in the mixed affective/evaluative subscale of the McGill Pain Questionnaire (MPQ). No significant differences were observed between the three groups, leading researchers to conclude that there may be no therapeutic role for ALA in the management of BMS. Another randomized, controlled trial showed no significant differences between the ALA group (800 mg per day for 8 weeks) and placebo group.[13]

In contrast to these studies, several other studies have assessed the efficacy of ALA in the treatment of BMS and results have been promising. In one study, 64% of ALA patients reported

clinical benefit at a dosage of 600 mg per day, while 27.6% of the placebo group demonstrated reduction in BMS symptoms.[10] Of the ALA patients who reported benefit, 68.75% maintained their improvement one month after treatment. Another study revealed significant improvement in BMS symptomatology at a dosage of 600 mg per day orally for 20 days followed by 200 mg per day for 10 days.[14] Up to 66% of ALA patients reported benefit, while 15% of the placebo group reported benefit and 66% of those who tried the placebo then switched to ALA also reported benefit. In a retrospective review of medical records, 35% of patients reported benefit from taking ALA.[15]

Researchers found that duration of the syndrome, intensity of symptoms,[10] and previous treatment with psychotropic medication[16] are factors that influence the likelihood of benefit with ALA in the management of BMS.

Fibromyalgia

Fibromyalgia is a functionally disabling disorder characterized by widespread pain, and frequently accompanied by sleep disturbance, fatigue, depression, and cognitive dysfunction. The commonly prescribed analgesics provide incomplete relief, possibly due to incomplete efficacy and dose-limiting adverse events. Specifically, the side effects of the drugs aggravate some symptoms of the disease they are prescribed to treat, namely fatigue and cognitive dysfunction. These complications have led researchers to search for new treatment options.

While the exact etiology of fibromyalgia is unknown, recent studies have provided evidence that oxidative stress[17] and inflammation[18] play a role in the pathophysiology of fibromyalgia. Alpha-lipoic acid, which at pharmacologic doses acts as a potent antioxidant, has also been demonstrated to have anti-inflammatory[3] effects on the body.

When administered orally, ALA is rarely present in tissues above micromolar levels and is therefore unlikely to function as a primary cellular antioxidant.[19] Instead, its potent antioxidant properties appear to be attributable to the fact that ALA increases cellular glutathione levels by regulating glutathione synthesis and ameliorating oxidative stress.[20]

ALA may exert its anti-inflammatory effects by scavenging free radicals and down-regulating pro-inflammatory redox-sensitive signal transduction processes including nuclear

factor kappa B translocation, leading to decreased release of other free radicals and cytotoxic cytokines.[21-22]

While no randomized controlled trials evaluating the efficacy of ALA in the treatment of fibromyalgia have been completed, one is currently underway[23] and the research that we do have available suggests that its results will be favorable.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis, is an illness characterized by debilitating and relapsing fatigue and often accompanied by neuropsychiatric concerns, such as depression, irritability, sleep disorders, autonomic symptoms and neurocognitive defects, as well as physiosomatic concerns, such as malaise, hyperalgesia, irritable bowel, and muscle pain and tension.

Oxidative stress[24-25] and inflammation[25] play important roles in the pathogenesis of CFS. In fact, some have suggested that CFS should be renamed in order to better reflect the oxidative and inflammatory nature of the condition.[26] Some have also suggested that mitochondrial dysfunction may play a role in the condition.[27]

Researchers have studied ALA in the treatment of CFS because of its antioxidant and anti-inflammatory properties, as well as its role in mitochondrial function.

When administered orally, ALA is rarely present in tissues above micromolar levels and is therefore unlikely to function as a primary cellular antioxidant.[19] Instead, its potent antioxidant properties appear to be attributable to the fact that ALA increases cellular glutathione levels by regulating glutathione synthesis and ameliorating oxidative stress.[20]

ALA may exert its anti-inflammatory effects by scavenging free radicals and down-regulating pro-inflammatory redox-sensitive signal transduction processes including nuclear factor kappa B translocation, leading to decreased release of other free radicals and cytotoxic cytokines.[21-22]

Evidence implicates mitochondrial dysfunction, impaired oxidative phosphorylation and abnormally high lactate levels in the pathophysiology of CFS.[25] ALA acts as a critical cofactor in mitochondrial alpha-ketoacid dehydrogenases, including pyruvate dehydrogenase. As a result, it

is important in mitochondrial, oxidative-decarboxylation reactions and plays a critical role in mitochondrial activity and energy metabolism.[28] Furthermore, supplementation with ALA has been demonstrated to lead to a decrease in abnormally elevated lactate levels,[4] likely as a result of its role in stabilizing and regulating pyruvate dehydrogenase and other mitochondrial 2-ketoacid dehydrogenase complexes.[29]

Although there are no randomized controlled trials using ALA in the treatment of chronic fatigue syndrome, when we consider its widespread use as a safe nutrient with the ability to reduce oxidative stress, decrease inflammation, and support mitochondrial function, its use in addressing chronic fatigue syndrome appears to be justified.

Neuropathy

Diabetic neuropathy, which is diagnosed in diabetic patients with peripheral nerve dysfunction when other causes of neuropathy have been excluded, is believed to be due to increased flux through the polyol pathway, leading to accumulation of sorbitol, a reduction in myoinositol, and an associated reduced Na+-K+-ATPase activity, as well as nitric oxide inactivation by increased oxygen free radical activity leading to endoneurial microvascular damage and hypoxia.[30] As a potent antioxidant, ALA appears to retard or reverse the progression of peripheral diabetic neuropathy.

In a study designed to assess the efficacy of ALA in the improvement of sural nerve conduction velocity and amplitude in patients with diabetic neuropathy, participants were administered 600 mg ALA per day.[31] At the conclusion of the study, ALA failed to improve sural nerve conduction velocity and amplitude; however, researchers noted that their study results should be interpreted with caution due to the study's uncontrolled nature, researchers' failure to assess patient compliance, small sample size, and short study duration.

Several studies demonstrate beneficial effects of ALA in the management of peripheral neuropathy. In one study that compared results of patients who were administered 600 mg, 1200 mg, and 1800 mg ALA by mouth, patients reported significant improvements in stabbing and burning pain (subset of total symptom score, or TSS), the Neuropathy Symptoms and Change (NSC) score, and the patients' global assessment of efficacy.[32] Benefits were not remarkably

different between the three groups, suggesting that an oral dosage of 600 mg provides the most favorable cost-benefit ratio.

In another study that administered ALA orally at a dosage of 600 mg per day for 40 days, ALA administration was found to be associated with reductions in neuropathic symptoms [as demonstrated by reduced Neuropathy Symptom Score (NSS), Subjective Peripheral Neuropathy Screen Questionnaire (SPNSQ), and douleur neuropathique (DN4) questionnaire scores at day 40 versus baseline] and in triglycerides.[33]

One systematic review of the literature concluded that, when administered intravenously at a dosage of 600 mg per day over a period of 3 weeks, ALA leads to a significant and clinically relevant reduction in neuropathic pain (grade of recommendation A). These researchers also studied orally administered ALA and stated that it was unclear whether or not the improvements seen after 3-5 weeks at an oral dosage of 600 mg were clinically relevant.[34]

Other systematic reviews maintained that oral and intravenous administration may provide similar benefits. For example, one stated that an oral or intravenous ALA dose of at least 600 mg per day resulted in a 50% reduction in the TSS[35] and a more recent (2018) systematic review on ALA in the management of diabetic peripheral neuropathy concluded that current data provides evidence for the benefits of ALA in diabetic peripheral neuropathy treatment at a dose of 600 mg per day, either intravenously or orally, for a duration of at least 3 weeks with minimal side effects.[36]

Cancer

Most cancer cells utilize aerobic glycolysis, which is the preferential conversion of glucose to lactate for ATP generation, even when oxygen is present. This phenomenon, referred to as the Warburg effect, can be seen in cancer cells of different origin. Because aerobic glycolysis is grossly inefficient, producing only two molecules of ATP per molecule of glucose, cancer cells metabolize large amounts of glucose to keep up with their energy demands. Researchers hypothesized that by shifting cancer cell metabolism toward complete oxidation of glucose and away from aerobic glycolysis, they could effectively reduce proliferation of cancer cells.[37]

Because ALA is a cofactor of pyruvate dehydrogenase, it was a key consideration in nutrients that can steer energy production away from aerobic glycolysis and toward complete oxidation of glucose, resulting in a decrease in lactate production and an inhibition of glycolysis. Pre-clinical studies designed to investigate ALA's role in this capacity demonstrated that ALA can reduce cancer cell viability and proliferation, as well as lactate production.[37] ALA was also found to induce apoptosis in the following cell lines: neuroblastoma cell lines Kelly, SK-N-SH, Neuro-2a and the breast cancer cell line SkBr3.

ALA also inhibits cancer cell proliferation and induces apoptosis by other mechanisms. The nutrient was found to inhibit cell proliferation and induce apoptosis in MDA-MB-231 breast cancer cell lines[38] and to inhibit the colony-forming ability of the highly invasive MDA-MB-231 and 4T1 breast cancer cells. ALA inhibited the migration and invasion of metastatic breast cancer cells at least in part through inhibiting ERK1/2 and AKT signaling.[39]

Additionally, ALA has been shown to effectively induce apoptosis in human colon cancer cells (HT-29) by a pro-oxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria,[40] and ALA dramatically decreased non-small cell lung cancer (NSCLC) cell proliferation by down-regulating growth factor receptor-bound protein 2 (Grb2).[41]

Studies evaluating the efficacy of ALA in the inhibition/treatment of cancer are limited to experimental data; however, the research appears to be very promising.

Atherosclerosis

Oxidative stress is considered to be the primary cause in many cardiovascular diseases, including atherosclerosis.[42] As we age, oxidative stress increases through an increase in the production of reactive oxygen species and/or a decrease in the body's antioxidant defenses. This increase in oxidative stress is paralleled by an increase in cardiovascular conditions like atherosclerosis. Research demonstrates that antioxidants help to decrease the incidence of atherosclerosis. ALA exerts potent antioxidant effects on the body and has been studied in experimental models for its ability to prevent and reverse atherosclerosis.

In one study, Watanabe heritable hyperlipidemic rabbits were fed with high cholesterol chow for 6 weeks and then randomized to receive either high cholesterol diet alone or high

cholesterol diet combined with 20 mg/kg/day of ALA for 12 weeks.[43] At the end of the 12 weeks, researchers found that ALA decreased body weight by 15 ± 5% without alterations in lipid parameters and reduced atherosclerotic plaque in the abdominal aorta with morphological analysis revealing reduced lipid and inflammatory cell content. Furthermore, ALA improved vascular reactivity (as revealed by decreased constriction to angiotensin II and increased relaxation to acetylcholine and insulin), inhibited NF-κB activation, and decreased oxidative stress and expression of key adhesion molecules in the vasculature.

An unrelated study demonstrated the cardioprotective effects of ALA. Eighteen adult male New Zealand White rabbits were randomly assigned to three groups for 10 weeks. One group was fed with normal chow (control group), one was fed with a 1% high cholesterol diet to induce hypercholesterolemia, and the third group was fed a 1% high cholesterol diet plus 4.2 mg/body weight of ALA. At the end of the study, blood total cholesterol (TCHOL) and low-density lipoprotein (LDL) levels were found to be significantly lower in the ALA group compared to that of the group that consumed a high cholesterol diet alone. The ALA group also had less atherosclerotic plaque in their aortas than the group that consumed a high cholesterol diet alone, leading researchers to conclude that, apart from its antioxidant activity, ALA may also exert a lipid-lowering effect on TCHOL and LDL levels and may reduce atherosclerosis formation in rabbits fed a high cholesterol diet.

A similarly designed study conducted on streptozotocin-induced diabetic mice models revealed that ALA completely prevented the increase in TCHOL, atherosclerotic lesions, and the general decline in health typically observed with diabetes, suggesting that ALA is a promising protective agent for reducing cardiovascular complications of diabetes.[44]

Studies evaluating the efficacy of ALA in the prevention/treatment of atherosclerosis are limited to experimental data; however, the safety of the supplement and the potential benefits make it a promising intervention in primary care and cardiology settings.

Adverse Effects

While intravenous ALA prevents damage to the membranous structures of cells (including the mitochondria) at typical doses, animal studies suggest that excessively high doses may result in mitochondrial damage. LD50 studies performed on six rhesus monkeys

demonstrated that doses of approximately 90 mg/kg to 100 mg/kg of intravenous ALA were lethal to three of the six monkeys.[45] Researchers extrapolated this data, stating that this dose would likely be lethal to all primates.

Researchers believe this toxicity may be due to the formation of superoxide anions when ALA comes into contact with diatomic oxygen in the mitochondria.[46] These damaging free radicals may then react with the unsaturated double bonds in the lipids of the mitochondrial membrane.

Adverse effects associated with therapeutic doses of ALA include adverse gastrointestinal effects[13] such as nausea and vomiting, vertigo,[32] and chest distress (however, researchers noted that this may have been due to the velocity of the IV drip, as it improved the same day after the velocity was adjusted).[47]

There was no laboratory evidence of deficiencies in iron, vitamins, or thyroid function and no hyperglycemia associated with ALA supplementation.[11]

Reference List

1. Paolisso G, D'Amore A, Volpe C, Balbi V, Saccomanno F, Galzerano D, Giugliano D, Varricchio M, D'Onofrio F. Evidence for a relationship between oxidative stress and insulin action in non-insulin-dependent (type II) diabetic patients. *Metabolism*. 1994;43:1426–9.
2. Rochette L, Ghibu S, Muresan A, Vergely C. Alpha-lipoic acid: molecular mechanisms and therapeutic potential in diabetes. *Can J Physiol Pharmacol*. 2015;93(12):1021-7.
3. Akbari M., Ostadmohammadi V., Tabrizi R., et al. The effects of alpha-lipoic acid supplementation on inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. *Nutrition and Metabolism*. 2018;15(1).
4. Konrad T, Vicini P, Kusterer K, Hoflich A, Assadkhani A, Bohles HJ, Sewell A, Tritschler HJ, Cobelli C, Usadel KH. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. *Diabetes Care*. 1999;22: 280–7.
5. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes*. 1997;46 Suppl 2:S62-6.
6. Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, Jung WI, Augustin HJ, Dietze GJ. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. *Arzneimittel-Forschung*. 1995;45:872–874.
7. Jacob S, Henriksen EJ, Tritschler HJ, Augustin HJ, Dietze GJ. Improvement of insulin-stimulated glucose-disposal in type 2 diabetes after repeated parenteral administration of thioctic acid. *Exp Clin Endocrinol Diabetes*. 1996;104:284–288.
8. Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, Rett K. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. *Free Rad Biol Med*. 1999;27:309–14.
9. Evans JL, Goldfine ID. Alpha-lipoic acid: a multifunctional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. *Diabetes Technol Ther*. 2000;2(3):401-13.

10. Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, Llamas-Martínez S, Esparza-Gómez G. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. *Med Oral Patol Oral Cir Bucal*. 2015;20(4):e435–e440.
11. Femiano F, Scully C. Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med*. 2002;31(5):267-9.
12. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. *Eur J Pain*. 2009;13(5):492-6.
13. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. *J Oral Rehabil*. 2009;36(1):52-7.
14. Femiano F, Gombos F, Scully C, Busciolano M, De Luca P. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis.* 2000;6(5):274-7.
15. Steele JC, Bruce AJ, Drage LA, Rogers RS 3rd. Alpha-lipoic acid treatment of 31 patients with sore, burning mouth. *Oral Dis*. 2008;14(6):529-32.
16. Femiano F, Gombos F, Scully C. Burning mouth syndrome: the efficacy of lipoic acid on subgroups. *J Eur Acad Dermatol Venereol*. 2004;18(6):676-8.
17. Fatima G, Das SK, Mahdi AA. Some oxidative and antioxidative parameters and their relationship with clinical symptoms in women with fibromyalgia syndrome. *Int J Rheum Dis*. 2017 Jan;20(1):39-45.
18. Coskun Benlidayi I. Role of inflammation in the pathogenesis and treatment of fibromyalgia. *Rheumatol Int.* 2019;39(5):781-91.
19. Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. *Biochim Biophys Acta*. 2009;1790(10):1149–1160.
20. Yoshida K, Hirokawa J, Tagami S, Kawakami Y, Urata Y, Kondo T. Weakened cellular scavenging activity against oxidative stress in diabetes mellitus: regulation of glutathione synthesis and efflux. *Diabetologia*. 1995;38(2):201–210.
21. Wong A, Dukic-Stefanovic S, Gasic-Milenkovic J, Schinzel R, Wiesinger H, Riederer P, et al. Anti-inflammatory antioxidants attenuate the expression of inducible nitric oxide

synthase mediated by advanced glycation endproducts in murine microglia. *Eur J Neurosci*. 2001;14:1961–1967.

22. Bierhaus A, Chevion S, Chevion M, Hofmann M, Quehenberger P, Illmer T, et al. Advanced glycation end product-induced activation of NF-kappaB is suppressed by alpha-lipoic acid in cultured endothelial cells. *Diabetes*. 1997;46:1481–1490.
23. Gilron I, Tu D, Holden R, et al. Innovations in the Management of Musculoskeletal Pain With Alpha-Lipoic Acid (IMPALA Trial): Study protocol for a Double-Blind, Randomized, Placebo-Controlled Crossover Trial of Alpha-Lipoic Acid for the Treatment of Fibromyalgia Pain. *JMIR Res Protoc*. 2017;6(3):e41.
24. Lee JS, Kim HG, Lee DS, Son CG. Oxidative Stress is a Convincing Contributor to Idiopathic Chronic Fatigue. *Sci Rep*. 2018;8(1):12890.
25. Morris G, Maes M. Oxidative and Nitrosative Stress and Immune-Inflammatory Pathways in Patients with Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). *Curr Neuropharmacol*. 2014;12(2):168–85.
26. Maes M. A new case definition of Neuro-Inflammatory and Oxidative Fatigue (NIOF), a neuroprogressive disorder, formerly known as chronic fatigue syndrome or Myalgic Encephalomyelitis: results of multivariate pattern recognition methods and external validation by neuro-immune biomarkers. *Neuro Endocrinol Lett*. 2015;36(4):320-9.
27. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med*. 2009;2(1):1–16.
28. Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. *Biochim Biophys Acta*. 2009;1790(10):1149–1160.
29. Solmonson A, DeBerardinis RJ. Lipoic acid metabolism and mitochondrial redox regulation. *J Biol Chem*. 2018;293(20):7522–30.
30. Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic Acid and diabetic neuropathy. *Rev Diabet Stud*. 2009;6(4):230–236.
31. Papazafeiropoulou A, Xourgia E, Papantoniou S, Trikkalinou A, Melidonis A. Effect of 3-month α-lipoic acid treatment on sural nerve conduction velocity and amplitude in patients with diabetic neuropathy: a pilot study. *Arch Med Sci Atheroscler Dis*. 2019;4:e141–e143.

32. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care*. 2006;29(11):2365-70.
33. Agathos E, Tentolouris A, Eleftheriadou I, et al. Effect of α-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. *J Int Med Res*. 2018;46(5):1779–1790.
34. Mijnhout GS, Kollen BJ, Alkhalaf A, Kleefstra N, Bilo HJ. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol*. 2012;2012:456279.
35. Mijnhout GS, Alkhalaf A, Kleefstra N, Bilo HJ. Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes? *Neth J Med.* 2010;68(4):158-62.
36. Nguyen N, Takemoto JK. A Case for Alpha-Lipoic Acid as an Alternative Treatment for Diabetic Polyneuropathy. *J Pharm Pharm Sci*. 2018;21(1s):177s-191s.
37. Feuerecker B, Pirsig S, Seidl C, et al. Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo. *Cancer Biol Ther*. 2012;13(14):1425–35.
38. Na MH, Seo EY, Kim WK. Effects of alpha-lipoic acid on cell proliferation and apoptosis in MDA-MB-231 human breast cells. *Nutr Res Pract.* 2009;3(4):265–271.
39. Tripathy J, Tripathy A, Thangaraju M, Suar M, Elangovan S. α-Lipoic acid inhibits the migration and invasion of breast cancer cells through inhibition of TGFβ signaling. *Life Sci*. 2018;207:15-22.
40. Wenzel U, Nickel A, Daniel H. alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O2-*-generation. *Apoptosis*. 2005 Mar;10(2):359-68.
41. Yang L, Wen Y, Lv G, Lin Y, Tang J, Lu J, Zhang M, Liu W, Sun X. α-Lipoic acid inhibits human lung cancer cell proliferation through Grb2-mediated EGFR downregulation. *Biochem Biophys Res Commun*. 2017;494(1-2):325-31.
42. Skibska B, Goraca A. The Protective Effect of Lipoic Acid on Selected Cardiovascular Diseases Caused by Age-Related Oxidative Stress. *Oxid Med Cell Longev*. 2015;2015:313021.

43. Ying Z, Kherada N, Farrar B, et al. Lipoic acid effects on established atherosclerosis. *Life Sci*. 2010;86(3-4):95–102.
44. Yi X, Maeda N. alpha-Lipoic acid prevents the increase in atherosclerosis induced by diabetes in apolipoprotein E-deficient mice fed high-fat/low-cholesterol diet. *Diabetes*. 2006;55(8):2238-44.
45. Couch RC, Vigil M., Thomas MA, Sibert G. A dose escalation toxicity study of DL-6-8 thioctic acid (lipoic acid) in Rhesus monkeys. Annual Meeting of Toxicology; Cincinnati, Ohio; March12, 1997.
46. Vigil M, Berkson BM, Garcia AP. Adverse effects of high doses of intravenous alpha lipoic Acid on liver mitochondria. *Glob Adv Health Med*. 2014;3(1):25–27. doi:10.7453/gahmj.2013.011
47. Liu F, Zhang Y, Yang M, Liu B, Shen YD, Jia WP, Xiang KS. [Curative effect of alpha-lipoic acid on peripheral neuropathy in type 2 diabetes: a clinical study]. *Zhonghua Yi Xue Za Zhi*. 2007;87(38):2706-9.