

Alpha-lipoic acid and diabetic cardiac autonomic neuropathy

Abstract

Alpha-lipoic acid (ALA) supplementation may provide benefits in the prevention of diabetes-related vascular and neuronal comorbidities. The mechanism of ALA influence on diabetic neuropathies pathogenesis is not well-known. Thus, further investigations aimed to understand the mechanism of action and for confirmation of the beneficial effect of ALA on biochemical parameters, dynamics of independent cardiovascular tests daily, monitoring of electrocardiography, arterial wall stiffness parameters among patients with type 2 diabetes mellitus, diabetic neuropathies and its associated comorbidities may be needed to validate this clinical findings.

Keywords: alpha-lipoic acid, type 2 diabetes mellitus, cardiac autonomic neuropathy

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Introduction

The number of persons suffering from types 2 diabetes (T2D) is rapidly increasing worldwide. Diabetes mellitus (DM) and insulin resistance are related to nervous and cardiovascular diseases development.¹⁻³ The large number of persons with a long duration of DM (mainly T2D) are diagnosed with cardiac autonomic neuropathy (CAN).⁴⁻⁷ Pathogenetic therapy of CAN includes: modification of lifestyle (physical activity and diet); reducing insulin resistance; appropriate glycaemic control; treatment of hyperlipidaemia, metabolic abnormalities in myocardium; prevention and treatment of thrombosis; antioxidants, first of all α -lipoic acid (ALA); ω -3 polyunsaturated fatty acids; vasodilators; fat-soluble vitamin B₁ (benfotiamine); therapy of concomitant diseases (arrhythmias, hypertension, heart failure) and others.⁸⁻¹² This mini-review was aimed to analyze the latest evidence about the effects of ALA on some metabolic and functional parameters in T2DM patients with diabetic CAN.

Discussion

Development of CAN among patients with DM often causes heart rate control abnormalities and defects in vascular dynamics. Persons with decreased parasympathetic activity have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Subjects with affection of both parasympathetic and sympathetic parts of autonomic nervous system have slower heart rates. By development of severe nerve dysfunction, heart rate is fixed.^{13,14} Chronic hyperglycaemia can affect the autonomic nervous system and accelerate development and progression of autonomic dysfunction. Heart rate variability (HRV) is regulating by autonomic innervation, so cardiac autonomic dysfunction by DM is associated with a decrement of HRV.^{15,16} Chronic hyperglycaemia is accompanied by excessively generation and accumulation of free radicals which have detrimental and neurotoxic effects.¹⁰ In this regard ALA (thioctic acid) appears to be effective in treatment of CAN.¹⁷⁻¹⁹ The relevance of oxidative stress (OS) in the pathogenesis of diabetic micro, and macro vascular diseases, as well as CAN and diabetic peripheral neuropathy (DPN), has been extensively investigated and proved.^{15,20,21} Furthermore, different antioxidants have been shown to avoid the development of CAN and DPN in experimental studies.^{22,23} For example, administration with the antioxidant ALA blocked the

generation of reactive oxygen species (ROS), caspase-3 invigoration, nuclear DNA degeneration and stimulating of the receptor for advanced glycation end-products, which have all been shown to benefit the advancement of CAN.^{7,21,24,25}

Given the role of OS in CAN, diabetic neuropathy (DN) progression, antioxidants such as acetyl-L-carnitine, taurine and ALA have been proven to be effective in preventing or delaying the onset of DN, in particular, CAN.^{1,26-28} ALA is considered as potent antioxidants with the ability to raise glutathione (GSH) intracellularly and regenerate vitamins E and C.^{26,29} The following ways are thought to explain the valuable effects of ALA in reducing the age-associated alterations in GSH:

- I. Impossible delivery of exogenous GSH in heart and brain.
- II. The bioavailability of cysteine delivery agents is low.

However, ALA can regulate the age-related alteration in levels of GSH as it is simply taken up into neural tissues.^{26,30} In addition, in the experimental studies that maintained a ground for the current clinical investigations, Pop-Busui R. et al.,²¹ evidence that ALA, allopurinol and nicotinamide had autonomous properties on OS and neuronal stability, as well as supporting neural safeguard when prescribed in coalescence.^{21,31} In double-blind placebo controlled trial DEKAN persons with T2D and CAN were randomized to take 800mg of ALA daily or placebo during 16wks. Cardiovascular autonomic reflex tests and HRV were performed at the beginning and after the treatment. The prescription of ALA was associated with increase of power spectrum in low-frequency band and root mean square successive difference.¹⁹ Other multicenter randomized, double-blind placebo-controlled study was conducted among patients with T2D and CAN using 600mg/day during 12wks and then 1.200mg/day of ALA for 12wks. A positive trend has been found in some parameters of HRV in the treatment group, namely increase of power spectrum of the low frequency (LF) band in the standing position by 15.77ms², the standard deviations of normal-to-normal RR intervals by 1.87 and high frequency/LF ratio in the upright position by 0.35.¹⁶

In the other study to 46 subjects with DM and different severity of autonomic neuropathy ALA 600mg daily i.v. for 10days, then 600mg orally for 50days was prescribed. The significant improvement of CAN severity score was found ($p < 0.001$). Authors found improvement in the systolic blood pressure at the lying-to-

standing test, deep-breathing test and the Valsalva man oeuvre after treatment ($p < 0.001$). Obtained results demonstrate that ALA appears to be a promising medication of the diabetic autonomic neuropathy treatment.¹⁷ In the ISLAND Study, 300mg of ALA was prescribed to patients with metabolic syndrome as monotherapy and in combination with 150 mg imbesartan daily. After four wks the significant increase in endothelium-dependent flow-mediated vasodilation of the brachial artery (by 44% and 75% respectively) was found. This effect was accompanied by reductions in plasma levels of plasminogen activator-1 and interleukin-6, suggesting that ALA may improve endothelial dysfunction *via* antithrombotic and anti-inflammatory mechanisms.^{32,33} As hyperglycaemia is strongly associated with increased excessive ROS production, resulting in development of neuronal diseases and endothelial dysfunction, the prescription of several antioxidants has been suggested as potential treatment for CAN. Results of small studies with ALA prescription suggested that this agent might have a favorable impact on CAN.^{13,19,34,35} However, other RCT with prescription of triple-antioxidant regime (ALA, allopurinol and nicotinamide) for 2yrs failed to prevent progression of CAN and had no effect on myocardial perfusion, as demonstrated with scintigraphic imaging modalities.^{19,21,35}

Conclusion

ALA exactly removes free radicals, converted other native antioxidants, defends distal nerves from lipid peroxidation and increases the activity of catalase and superoxide dismutase, possibly resulting in the normalisation of impaired endoneural blood flow and nerve conduction velocity.^{17,18} Additionally mechanisms of ALA consist of:

- A. Correcting the antioxidant protection system through gene expression.
- B. Suppressing nuclear factor κ B.
- C. Stimulating adenosine monophosphate-activated protein kinase, with each of these components having numerous consequences.^{21,26,36,37}

The positive influences of ALA on such metabolic and functional parameters are partly confirmed by its neurotropic, cardioprotective, angioprotective and cytoprotective properties; this finding suggests its usefulness in the treatment of T2D patients with diabetic cardiac autonomic neuropathy.

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None.

Conflicts of interest

The authors declare that there is no conflicts of interest.

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