Review paper
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THE BENEFITS OF NUTRITION AND SUPPLEMENTATION TREATMENT FOR CHRONIC NON-COMMUNICABLE DISEASE WITH ALPHA LIPOIC ACID

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Abstract

Alpha-Lipoic acid (ALA), also known as thioctic acid, is non-essential sulfur-containing food constituent present in foods, generally bound to protein (lipoyllisine) at very low concentrations. The natural compound is the R enantiomer, while in food supplements is used generally the racemic form.

ALA is not only an antioxidant, but the only one that protects water-soluble as well as oil-soluble bio-molecules. Inside the body it is in an equilibrium with its reduced form dihydrolipoic acid and has the ability to regenerate or recycle other antioxidants, such as vitamins C and E. With age glutathione, the master antioxidant, declines but lipoic acid can restore its function, and also that of co-enzyme Q10, to much higher levels. In addition lipoic acid has various key functions in the body. A chronic condition is a human health condition or disease that is persistent or otherwise long lasting in its effects or a disease that come with time. Non-communicable disease is a medical condition that is non-infectious or non-transmittable. Chronic non-communicable diseases account for almost 60% of global mortality. The major causes of non-communicable-attributable mortality are cardiovascular disease, chronic respiratory disease, diabetes, metabolic syndrome etc.

Many studies have shown that Alpha-Lipoic acid has anti-inflamatory properties, enhances immune functions, and neutralizes free radicals in both the fatty and watery regions of cells witch can directly or non-directly help manage chronic non-communicable diseases. The most frequent clinical condition in which alpha-lipoic acid has been studied was in the management of diabetic peripheral neuropathy in patients with type 1 as well type 2.

***Key words**: Alpha-Lipoic acid, Nutrition, Supplementation, Antioxidant, Anti-inflammatory, Chronic non-communicable disease.*

1. Introduction

Alpha-Lipoic acid (ALA) also known as thioctic acid, and 1, 2 dithiolane-3-pentaonic acid, is a naturally occurring substance, which is essential for the function of different enzymes of oxidative metabolism [1]. This acid was discovered in 1937 by Snell [2] and isolated from bovine liver in 1950. The first clinical use of ALA was in Germany in 1959 for the treatment of acute poisoning with *Amanita phalloides* mushroom. Lipoic acid contains two thiol groups, which may be oxidized or reduced. As shown in Figure 1, lipoic acid is a part of a redox pair, being the oxidized partner of the reduced form dihydrolipoic acid (DHLA), (both forms have antioxidant properties). ALA contains an isometric carbon, thus resulting in two optical isomer forms R and S, (Figure 2). Only the R-isomer is endogenously synthesized and bound to protein. Lipoic acid supplements may contain either R -ALA or 50/50 (racemic) mixture of R and S forms. ALA has been reduced *in vivo* to its dithiol form, DHLA, which also possesses biological activity [3]. As a naturally occurring this compound is synthesized in small amounts by plants, animals and humans [4]. Endogenously synthesized ALA is covalently bound to specific proteins, which serves a critical role in mitochondrial energy metabolism. There is an increasing scientific interest in potential dietotherapeutic uses of ALA and growing awareness that is readily absorbed from diet, and orally derived ALA has unique biochemical activates separate from normal

metabolic function. Based largely on *in vitro* and some *in vivo* studies ALA is potent antioxidant. Both ALA and DHLA terminates a number of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and also chelates redox active transition metals, by reducing the oxidized forms of other antioxidant agents such as Vitamin C and E, and glutathione (GSH). It also protects against the development of atherosclerosis and inhibits the progression of established atherosclerosis plaque [5, 6]. Considering this role in physiological antioxidant actions, ALA can be included in treatment of chronic non-communicable diseases like cardiovascular disease (CVD), diabetes, metabolic syndrome etc.

2. Alpha lipoic acid role in human nutrition and health

2.1 Metabolism, absorption and bioavailability

ALA is commonly found in dietary components such as vegetables (spinach, broccoli, tomato, Brussel sprouts, rice bran etc.), meats and in many dietary supplements. ALA is synthesized *de novo* from an 8-carbon fatty acid (octanoic acid) and cysteine as sulfur donor in the liver. This catabolism naturally also takes place in liver. ALA exists in two enantiomeric forms, R and S. 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. R-form is more potent than the S-form in its ability to stimulate glucose uptake [7]. On the other hand, the S-form exerts an increased affinity for glutathione reductase [8]. Thus the two forms exert various biological activities of this compound. The absorption and bioavailability of ALA have been studied mainly from dietary supplements where ALA exists in racemic form and in general, the bioavailability of both optical isomers is not greater than 40%, which decreases with food intake [9]. Therefore, ALA must be taken 30 minutes before meals. After oral intake, ALA is absorbed by the gastrointestinal tract and is transported to different organs such as the brain, because it has the potential of freely crossing the blood-brain barrier [10]. Independently of the original sources (diet or nutritional supplements), ALA is reduced to HLA and metabolized in the liver in different metabolites, and has renal excretion.

2.2 Antioxidant properties of ALA

ALA and its reduced form DHLA, are considered powerful natural antioxidant agents with a scavenging capacity for many reactive oxygen species [11]. ALA/DHLA has some important advantages over other antioxidant agents such as vitamin C and vitamin E, because they have amphiphilic properties that confer their antioxidant actions in the membrane as well as in the cytosol [11]. ALA/DHLA can also regenerate other antioxidant substances such vitamin C, Vitamin E, and the ratio of reduced/oxidized glutathione [12]. Glutathione is a sulfur tripeptide containing glutamate, cysteine and glycine. Their biosynthesis depends on the substrate availability (cysteine), which is enhanced by ALA/DHLA [9]. GSH has many functions over different intracellular process like aging, oxidative balance and detoxification of many pollutants [13].

2.3 ALA as a modulator of anti inflammatory pathways

Oxidative stress-associated inflammation is thought to provoke early vascular events in atherogenesis, including the upregulation of vascular adhesion molecules. These events require the activation of transcription factor NF-kB, that induces the expression of many genes involved in the inflammation and endothelial cell migration. Inflammatory processes have a pro oxidant nature. ALA is an inhibitor of NF-kB activation via a mechanism different from traditional endogenous antioxidants such as ascorbate or reduced GSH [14]. This ALA/DHLA may reduce the pro inflammatory conditions by its interaction with NF-kB.

2.4 ALA and its role in diabetes

Diabetes mellitus (DM) 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

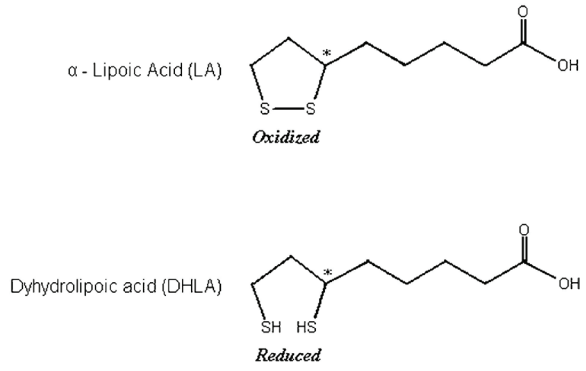

Figure 1. Chemical structure of lipoic acid, oxidized and reduced form

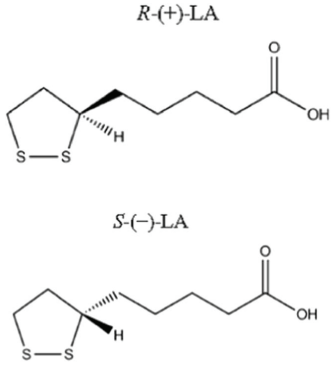

Figure 2. Two optical isomers forms of ALA

evidence to indicate that oxidative stress plays an important role in etiology of diabetic complications. Many of the biochemical pathways 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. ALA has potentially preventive and ameliorating effects in both type 1 and type 2 diabetes. Many of the genes involved in mediating the cellular stress resistance are linked to the insulin signaling pathway. The binding of a ligands such as insulin to its receptor creates its own localized burst of H_2O_2 that causes auto phosphorylation of the tyrosine kinase domain on the insulin receptor (IR), initiating a signaling cascade [15]. ALA interaction with the insulin signaling pathway I is well recognized, ALA is similar to insulin in its ability to activate signaling molecules in the insulin/insulin-like growth factor-1 (IGF-1) pathway, though it may not work as a ligand. ALA/DHLA may modulate the critical cysteine residues in the IR beta-subunit and other critical thiol-containing proteins of the insulin signaling pathway [16].

A lot of ALA investigations used animal models to define its function. There have been several important trials that examine the potential health benefits of ALA. Many of the outcomes for dietotherapeutic use of ALA in humans lend support to its general role as an antioxidant. There is little evidence that lipoic acid produces this effect by its antioxidant scavenging prosperities or by its modulatory action on cell signaling networks that maintain endogenous antioxidant capacity.

ALA has been used in Germany for over 30 years in the treatment of diabetic neuropathies [17]. The ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy) II, and III, and SIDNEY clinical trials of ALA showed that its oral administration improves nerve condition velocity and neuropathic symptoms, such as pain, burning and paresthesia [18]. The therapeutic use of ALA in the treatment of diabetic neuropathies remains the best documented and most significant benefit of ALA to human health. Experimental evidence supports a role for ALA as an oxidative stress in disease mitigate, but also for its means to affect glucose handling [19]. A number of reports now show that ALA improves glucose disposal in patients with type 2 diabetes receiving ALA [20].

2.5 Alpha-lipoic acid availability in food and supplements

In humans ALA is synthesized in liver and other tissues and is also obtained from both animal and plant sources in the diet. ALA is readily absorbed from the diet and is rapidly converted to DHLA in most tissues. R-ALA occurs naturally in food where is covalently bound to lysine in proteins (lipoullysine). Humans are able to synthesize enough ALA to meet their needs for enzyme cofactors with healthy diet. However, its synthesis declines with age and in people with compromised health, including chronic non-communicable disease. Thus in these cases, ALA may need to be obtained from outside sources by consuming certain foods and from supplements. Unlike ALA in foods, ALA in supplements is free it is not bound with proteins. The amounts of ALA available in dietary supplements (200 - 600 mg) are 1000 times greater than the amounts that could be obtained from the diet. ALA supplementation is recommended to be taken on an empty stomach (1h before, or 2h after eating).

3. Conclusions

- Currently, there are compelling evidences linking oxidative damage to the majority of chronic diseases with increasing prevalence worldwide such as: DM, CVD, obesity, respiratory disease, metabolic syndrome and etc.

- Considering the role of ALA is essential for the function of different enzymes that take part in mitochondrial oxidative metabolism, it is believed that ALA/DHLA have many biochemical functions acting as biological antioxidants, as metal chelators, reducers of the oxidized forms of other antioxidant agents such as vitamin C and E and modulator of the signaling transduction of several pathways.

- The most frequent clinical condition in which ALA has been studied was in the management of diabetic peripheral neuropathy in patients with type 1 and type 2 diabetes. Considering the pleiotropic action of ALA upon different pathways associated with mentioned disease, its use as potential therapeutic agent seems promising.

4. References

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