α-Lipoic Acid and Cardiovascular Disease[1]

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ABSTRACT α-Lipoic acid (ALA) has been identified as a powerful antioxidant found naturally in our diets, but appears to have increased functional capacity when given as a supplement in the form of a natural or synthetic isolate. ALA and its active reduced counterpart, dihydrolipoic acid (DHLA), have been shown to combat oxidative stress by quenching a variety of reactive oxygen species (ROS). Because this molecule is soluble in both aqueous and lipid portions of the cell, its biological functions are not limited solely to one environment. In addition to ROS scavenging, ALA has been shown to be involved in the recycling of other antioxidants in the body including vitamins C and E and glutathione. Not only have the antioxidant qualities of this molecule been studied, but there are also several reports pertaining to its blood lipid modulating characteristics, protection against LDL oxidation and modulation of hypertension. Therefore, ALA represents a possible protective agent against risk factors of cardiovascular disease (CVD). The objective of this review is to examine the literature pertaining to ALA in relation to CVD and describe the most powerful actions and potential uses of this naturally occurring antioxidant. Despite the numerous studies on ALA, many questions remain relating to the use of ALA as a supplement. There is no consensus on dosage, dose frequency, form of administration, and/or preferred form of ALA. However, collectively the literature increases our understanding of the potential uses for supplementation with ALA and identifies key areas for future research. J. Nutr. 133: 3327–3330, 2003.

KEY WORDS: • α-lipoic acid • antioxidant • cardiovascular disease

α-Lipoic acid (ALA)[3] is a natural compound chemically named 1,2-dithiolane-3-pentanoic acid ($C_8H_{14}O_2S_2$). It is also referred to as thioctic acid (1). In humans, ALA is synthesized by the liver and other tissues, and functions as a cofactor within pyruvate dehydrogenase and α keto-glutarate dehydrogenase (2). Recently ALA has been shown to be required for the oxidative decarboxylation of pyruvate to acetyl-CoA, the critical step bridging the gap between glycolysis and the citric acid cycle (3). α-Lipoic acid is both water and fat soluble, and therefore, is widely distributed in plants and animals in both cellular membranes and cytosol (4). In addition, ALA and its reduced dithiol form, dihydrolipoic acid (DHLA), are powerful antioxidants **(Fig. 1)**, their functions described by Biewenga et al. (5) include: *1*) quenching of reactive oxygen species, *2*) regeneration of exogenous and endogenous antioxidants such as vitamins C and E, and glutathione, *3*) chelation of metal ions, and *4*) reparation of oxidized proteins. In most cells containing mitochondria, ALA is reduced by an NADH-dependent reaction with lipoamide dehydrogenase to form DHLA. In cells that lack mitochondria ALA can be reduced to DHLA via NADPH with glutathione and thioredoxin reductases (6).

Recent studies suggest that oxidative stress plays an important role in the etiology of cardiovascular disease (CVD). Related research investigated approaches that reduce oxidative stress through supplementation with antioxidant compounds. The main objective of this review is to examine animal and human research to critically define the plausible health benefits of ALA supplementation, and to assess the possible mechanisms by which they manifest themselves with regard to CVD risk factors.

Properties of ALA. Environmental oxygen, which fuels biological systems, coordinates biochemical reactions essential for the production of energy and enables the synthesis of biologically essential compounds. However, these powerful molecules, referred to as reactive oxygen species (ROS), also have the capacity to exert toxic effects on aerobic organisms. ROS have the capacity to oxidize lipids, sugars, proteins and DNA. Such events can lead to food deterioration, membrane dysfunction, protein modification, enzyme inactivation, breaking of DNA strands and modification of DNA base sequences (7). The current understanding of the actions of ROS suggests a causative role in chronic diseases including heart disease, cancer, diabetes and more generally aging. Consequently, the role of antioxidants and their ability to protect biological systems from oxidative damage has received increased attention. Hence, ALA is of interest because it is known to scavenge hydroxyl radicals, singlet oxygen, hydrogen peroxide, hypochlorous acid, peroxynitrite and nitric oxide. DHLA also quenches peroxyl and superoxide radicals making the ALA/DHLA redox couple one of the most powerful biological antioxidant systems (8). Furthermore, these two molecules exert additional antioxidant actions through the chelation of copper, iron and other transitional metals (9).

ALA occurs naturally in the human diet and is found in abundance in animal tissues with high metabolic activity such as heart, liver and kidney, and to a lesser extent in fruits and vegetables (10). The concentrations from highest to lowest in nonanimal sources are: spinach, broccoli, tomato, garden pea, brussel sprouts and rice bran. All ALA supplied by the diet is transported in the bloodstream to tissues and incorporated into cells. Once part of the cell, ALA must be translocated into the mitochondria where ALA-requiring enzyme complexes exist (11). ALA of animal origin is absorbed as lipoyl-lysine, due largely to the fact that digestive proteolytic enzymes do not effectively cleave the peptide bond between the two. ALA can be obtained through de novo synthesis via lipoic acid synthase originating from the fatty acid octanoic acid and cysteine

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[3] Abbreviations used: AAPH, 2,2′-azobisamidinopropane hydrochloride; ALA, α-lipoic acid; AT, α-tocopherol; CVD, cardiovascular disease; DHLA, dihydrolipoic acid; LD_{50}, lethal dose; GSH, reduced glutathione; GSSG, oxidized glutathione; IP, interperitoneal; IV, intravenous; ROS, reactive oxygen species; SHR, spontaneously hypertensive rats.

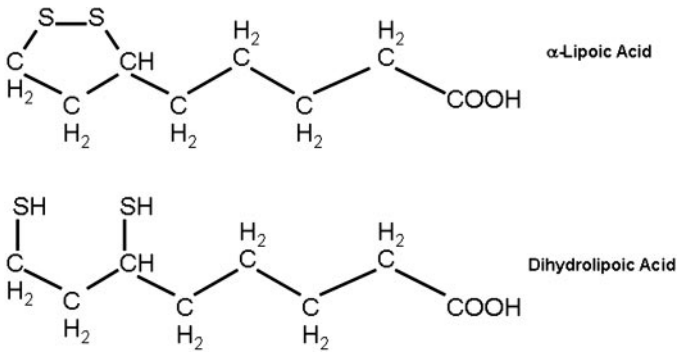

FIGURE 1 Simplified diagram of alpha-lipoic acid and its reduced form dihydrolipoic acid.

within the mitochondria (11–13). Morikawa et al. (11) commented that in mammals, ALA is not sufficiently supplied by the diet and therefore de novo synthesis takes place in the heart, liver and testis to form ALA needed for purposes such as incorporation into enzyme complexes. Hence, these sources of ALA are thought to provide very little free ALA into circulation. It is only through supplementation that ALA reaches potentially therapeutic levels.

Researchers have reported therapeutic doses in humans ranging from 200 to 1800 mg ALA/d (14–19). Hermann et al. (18) found that the half-life of racemic ALA in plasma is 30 min. The authors presumed that the liver was responsible for the elimination of ALA, and that the bioavailability can range from 20 to 38% depending on the isomer *R* or *S* and the formulation tested. ALA exists as two different enantiomers; the biologically active (R)-isomer and the (S)-isomer, the latter being part of the synthetic racemic mixture but found minimally in biological tissues (20). The ALA range in bioavailability leads to differences in detrimental effects after oral dosing when compared with interperitoneal (IP), subcutaneous and intravenous (IV) administration. The oral lethal dose (LD_{50}) for rats and mice is 1130 and 502 mg/kg, respectively, as compared with an IP LD_{50} of 200 and 160 mg/kg for rats and mice, respectively (5). Extrapolation of these data would lead to the assumption that human beings can tolerate several grams of ALA given orally (5).

After absorption into the cells of various tissues, ALA is reduced to DHLA, which can then be easily transported out of the interior of the cell and function effectively in the extracellular space (21). It is in this form that it is believed to possess its greatest antioxidant potential. Kagan et al. (21) reported that DHLA/ALA has a redox potential of −0.32 V compared with the reduced glutathione/oxidized glutathione (GSH/GSSG) couple at −0.24 V. This difference establishes that DHLA has greater reducing potential within the cell and therefore could offer more protection from oxidative damage than glutathione, a well-established cellular protector.

Schupke et al. (22) have identified a series of ALA metabolites that may offer some level of protection within cellular systems. These metabolites are produced via β-oxidation of the ALA pentanoic side chain. Some of the principal metabolites are 3-methoxylipoic acid, 3-ketolipoic acid and bisnorlipoic acid (22). The complete β-oxidation of ALA has been shown experimentally by Harrison and McCormick (23). Knowing that CO_2 is a product of substrate metabolism produced by the degradation of acetyl-CoA via the TCA cycle, these researchers administered ^{14}C-lipoic acid to rats. Their results indicated that 25% of the administered dose was exhaled as $^{14}CO_2$ within 2 h after administration, reaching a total amount of 30% after 24 h. The authors then concluded that ~60% of the ALA dose had been metabolized via β-oxidation. Biewenga et al. (5) also confirmed β-oxidation in humans by measuring the appearance of the metabolite bisnorlipoic acid in plasma. Peak concentrations appeared ~189 min after oral administration of 1 g of (*R*)-lipoic acid. The exact functions of these metabolites are not clearly understood, however, it is believed that these components may contribute to the benefits of therapeutic use of ALA (5).

ALA and CVD Risk Factors. LDL oxidation. The risk factors of atherosclerosis are well established as mainly hyperlipidemia, smoking, diabetes mellitus, hyperhomocyste(i)nemia and hypertension (24). The mechanisms that each of these factors contributes to the disease process and any interactions that take place between them are not fully understood. One event that is common to these risk factors is the generation of oxidative stress (24). The hypothesis that oxidative stress constitutes a major causative factor in atherosclerosis is gaining greater acceptance (25,26). Oxidative modifications to LDL cholesterol increase atherogenicity by altering cell receptor uptake of these particles, particularly cells in the intima of blood vessels (26). Furthermore, oxidized LDL is taken up by scavenger receptors on monocytes, smooth muscle cells and macrophages in an uncontrolled process leading to the accumulation of lipid and formation of foam cells, an early feature of atherosclerotic plaques. Within this early atherosclerotic lesion, increased oxidative stress evokes inflammatory events that further generate peroxides, superperoxides and hydroxyl radicals within the endothelium. The inflammatory events in turn continue the cycle of damage to the vasculature. In light of these mechanisms, current research focusing on the effect of antioxidants exhibiting a protective effect on the oxidation of LDL cholesterol may lead to the mitigation of the atherosclerotic process (27). Therefore, it is reasonable to believe that the administration of low to moderate amounts of antioxidants would make a substantial contribution towards decreasing the risk of heart disease, stroke and hypertension, which are associated with the atherosclerotic process (26,28).

Knowing that ALA has the capacity to recycle endogenous antioxidants **(Fig. 2)**, any attributed cardiovascular benefits established for these recycled entities could possibly be enhanced synergistically through supplementation with ALA. Although not conclusively proven, it has been suggested through epidemiological and clinical evidence (29) that high concentrations of vitamin E may protect against free radical LDL cholesterol oxidation and decrease the risk of CVD (30,31). Kagen et al. (21) maintained high concentrations of vitamin E in humans and found that ALA is effective in recycling vitamin E by interacting synergistically with vitamin C. The authors concluded that the recycling of vitamin E and

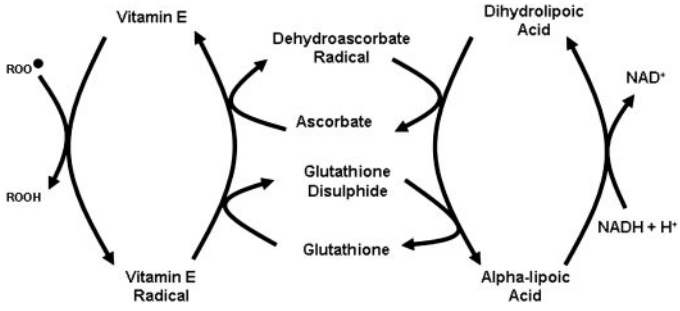

FIGURE 2 The role of α-lipoic acid in the recycling of other antioxidant systems. Adapted from (9).

other antioxidants by plasma reductants such as ALA may be an important mechanism for enhanced antioxidant protection of LDL.

Further evidence was provided by Marangon et al. (16), who compared the effects of ALA and α-tocopherol (AT) supplementation on measures of oxidative stress. Thirty-one healthy adults participated in the randomized parallel study testing ALA at 600 mg/d or AT at 400 IU/d for 2 mo followed by a combination of both supplements for an additional 2 mo. The results indicated no change in BMI or lipid profile regardless of the supplement taken. When measures of oxidative stress were analyzed, ALA decreased plasma carbonyls whereas AT had no effect. In addition, both AT and ALA alone decreased urinary F_2-isoprostane levels. In combination, the two supplements further decreased F_2-isoprostane levels. However, there appeared to be a sequence of addition rule in play, whereby adding AT to ALA induced an effect, but not vice versa. The reasons for such a sequential additive effect have not been defined within the literature. Furthermore, ALA was shown to increase LDL oxidizability lag time to lipid peroxide formation after both copper and 2,2′-azobisamidinopropane hydrochloride (AAPH) catalyzed oxidation. However, oral supplementation with ALA did not affect conjugated diene formation. Marangon et al. (16) concluded that ALA prevents premature atherosclerosis via its antioxidant effect.

The capacity for the protection of human LDL peroxidation and thiol chelation of Cu^{2+} by DHLA has been investigated (32). DHLA increased lag time in a concentration-dependent manner with treatment concentrations ranging from 0 to 10 μmol/L. Similarly, DHLA reduced Cu^{2+} chelation in a dose-dependant manner, but when the concentration of DHLA exceeded 5 μmol/L this effect was inhibited (32). ALA was reported as having no effect on Cu^{2+}-induced peroxidation of LDL at any concentration. The reasoning behind this finding is based on the evidence that the beneficial effects of DHLA chelation are mediated via the carboxylic and free sulfydral groups of the DHLA molecule, otherwise the same type of effect would have been elicited through the use of ALA in its oxidative form (32).

ALA effects on blood lipid profile and plaque formation. As early as 1958, researchers investigated the lipid-lowering capacity of ALA in rabbits (33,34). The results of these two studies were contradictory with Angelucci and Mascitelli-Coriandoli (33) reporting that ALA decreased plasma cholesterol levels by 50%, yet Kritchevsky (34) showed increased aorta atherosclerosis in rabbits and no cholesterol-lowering activities with ALA supplementation. In an effort to resolve this discrepancy, Ivanov (35) found that dietary ALA of 1 mg/kg of diet not only reduced the levels of total cholesterol and lipoproteins in the serum and aortic tissue of rabbits, but also intensified tissue respiration in the heart, liver and blood vessels. Later, Shih (36) studied the effects of ALA on atherosclerosis in Japanese quail. The birds were fed diets containing 0.25% cholesterol for 12 wk, while receiving 2.5 mg/wk of ALA from a slow release capsule implanted subcutaneously on the dorsal surface of the neck. The results indicated a decrease in total cholesterol and β-lipoproteins of 40 and 42%, respectively. The author concluded that ALA exhibits a protective effect in the prevention of elevated blood lipids and atherosclerosis. This study by Shih (36) remains as one of the only recent in vivo trials testing the primary outcome of ALA on atherosclerotic formation. Although Shih's model of atherosclerosis in the aorta of the quail is thought to be characteristic of human disease, caution in extrapolating these results must be applied until they are supported by other animal studies.

More recently, Ford et al. (37) studied the effects of an evening primrose oil supplement and an ALA supplement on a variety of lipid and hemostatic parameters in control and diabetic rats for 2 wk. Supplementation with ALA at 300 mg/(kg body weight·d) caused a decrease in plasma triglyceride concentrations in diabetic rats. However, cholesterol and HDL-cholesterol levels did not differ. This decrease in plasma triglycerides could possibly facilitate improved endothelial function, which could prove beneficial in CVD and, hence, warrant further study (37). These results are consistent with those of a previous study (38), in which ALA supplementation given via IP injection of 7.5 mg/(100 g body weight·d) for 9 d elicited a 45% decrease in triglyceride concentrations.

Hypertension. Vasdev et al. (39) determined whether dietary supplementation of ALA could lower blood pressure in spontaneously hypertensive rats (SHR). Nonhypertensive, SHR control and SHR-supplemented rats were fed ALA at 500 mg/kg feed for 9 wk. The results showed no effect of ALA on body weight during supplementation, however, supplementation did attenuate hypertension measured by tail cuff methodology. The authors speculated that ALA increased the free sulfydral groups of calcium channels leading to a decrease in cystolic free calcium, vascular tone and hypertension (39). Similarly, Midaoui and Champlain (40) reported that hypertension was induced by the addition of a 10% D-glucose drink to either the control diet or the ALA-supplemented diet (500 mg/kg feed). Feeding with the glucose solution alone increased systolic blood pressure on average of 166 mm Hg after 3 wk (40). However, supplementation with ALA attenuated this rise enabling ALA animals to maintain blood pressure values the same as those not receiving the induced glucose hypertension. The authors postulated that the antihypertensive effects of ALA are associated with an attenuation of oxidative stress in the aortic vessel and the preservation of glutathione peroxidase activity in the plasma of glucose-treated rats.

ALA: The Remaining Questions. The literature on ALA describes a powerful natural compound that elicits a variety of health benefits in animals and humans. However, there is an absence of consistent findings within the existing literature and several questions remain. First, there exists the issue of the form of ALA to be used as a supplement; *R, S* or a racemic mixture of the two. No conclusive evidence supports the use of one formulation over another. Second, discrepancy remains concerning the therapeutic dose. The studies reviewed here cover a possible dose ranging from 200 to 1800 mg/d in humans with no consensus as to optimum dose. From this review it is difficult to pinpoint a dose that will reach the functional threshold necessary to produce beneficial effects most of the time. Lastly, the methods of supplementation should not go unnoticed. Reviewed studies have shown ALA supplementation using tablets, powder or liquid solutions given orally, as IV infusions, as IP injections and as subcutaneous implants. Therefore, to provide the optimal beneficial effects for the treatment of oxidative stress and/or chronic disease it becomes important to consider the type of ALA used as a supplement, the dose provided and supplementation method used to obtain the desired effects.

Conclusion. One of the first nontraditional ideas about the relationship between food and health was the hypothesis that antioxidant nutrients might protect against chronic diseases. The literature has clearly established the antioxidant properties of ALA and demonstrated important areas of medicine in which it can be employed. By understanding the health benefits of a natural compound, science can inevitably determine

the means of putting a compound to good use within a population. The data presented here elucidate the ways by which ALA may impact the CVD risk profile through the beneficial actions on LDL oxidation, blood lipid profiles, plaque formation and hypertension. All of the aforementioned benefits must be weighed carefully against the lack of consensus regarding the most appropriate form, dose and supplementation method for ALA.

What remains now is for the implementation of reasonable and appropriate guidelines for the public to follow regarding supplementation with ALA. For instance, there is the need to determine what dose is beneficial as an adjunct to healthy living and what dose is too much. Such guidelines are required in that ALA is currently available within neutraceutical and natural health product marketplaces, warranting health professionals' attention in order to protect the health and well being of society.

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