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Review

Is Alpha-Lipoic Acid Effective in the Treatment of Obesity?

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ABSTRACT

Alpha-lipoic acid (ALA, also thioctic acid) is an organosulfur component and has antioxidant properties. It functions as a crucial cofactor for the respiratory enzymes in the mitochondria. Additionally, ALA can be used as a supplement to help with weight loss and is known to have anti-obesity properties. Since obesity is an inflammatory health problem that can induce an excessive fat build-up in adipose tissue and chronic diseases, insulin resistance, macrophages, tumor necrosis factor-alpha, interleukin-6, interleukin-2, leptin, and adiponectin all play a role in its pathogenesis. Alpha-lipoic acid enhances energy expenditure by upregulating uncoupling protein-1 expression in brown adipose tissue via hypothalamic 5'-AMP-activated protein kinase. Furthermore, ALA has the ability to directly or indirectly regulate the expression of genes involved in energy balance, food consumption, hepatic cholesterol clearance, and fat synthesis and oxidation. The weight control can have an impact by lowering the body mass index or weight. Although the reviewed literature contains studies on the amount of dose and duration of administration, investigations that provide a comprehensive conclusion about the effect of ingesting ALA in liquid and solid form on obesity are insufficient. This review combined papers on the use of ALA as a supplement in the treatment of obesity and demonstrated the need for additional research on the topic.

Keywords: ALA, alpha-lipoic acid, energy homeostasis, insulin resistance, leptin, obesity

Alpha-lipoic acid (ALA; also thioctic acid; chemically named 1,2-dithiolane-3-pentanoic acid) is an organosulfur compound found in plants, animals, and humans. It has a high antioxidant capacity. It is a cofactor for mitochondrial pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase complexes. The therapeutic effectiveness of ALA is relatively poor. Because of hepatic breakdown, low solubility, and stomach instability, ALA has a short half-life and low bioavailability (about 30%). However, the adoption of novel formulations has significantly boosted ALA bioavailability. Because of its higher bioavailability, the R enantiomer of ALA has a superior pharmacokinetic effect than the S enantiomer. In fact, the use of amphiphilic matrices boosts ALA bioavailability and allows for improved intestinal absorption. Furthermore, liquid formulations of ALA had higher plasma concentrations and bioavailability than solidified dosage forms. As a result of the enhanced formulation, ALA absorption and bioavailability can be increased, resulting in therapeutic efficacy. Surprisingly, ALA bioavailability is age dependent, whereas gender has no effect.[1]

Alpha-lipoic acid is a popular antioxidant supplement that has gained popularity in recent years.[2] It is also known as thioctic acid and is a naturally occurring short-chain fatty acid with two reduced lipids and oxidized thiol groups.[3] The human body (heart, liver, muscles, and kidney) produces limited amounts of ALA through lipoic acid synthesis,[4] and the average daily ingestion of ALA with food is insufficient to achieve a therapeutic effect.[5] Alpha-lipoic acid is found naturally in mitochondrial respiratory enzymes such as α-ketoglutarate dehydrogenase, branched-chain alpha-keto acids, and PDH.[6] It is an effective antioxidant since it scavenges free radicals, chelates metal ions, and stimulates the endogenous antioxidant defense system[7,8] by rebuilding the oxidized forms of vitamins E, C, and glutathione.[9]

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Several recent studies have found that ALA has significant anti-obesity effects in both human and animal models.[10-14] Alpha-lipoic acid supplementation has been shown in animal models to promote fat mass reduction, possibly by suppressing hypothalamic AMP kinase activity, which may reduce food intake and promote weight loss by increasing energy expenditure.[11,15] However, human research with ALA supplementation is limited and yields contradictory results. According to some studies, ALA has no effect on weight.[16,17] In contrast, some studies have found that ALA supplementation may help obese or overweight people lose weight and improve treatment response.[11,15] According to a meta-analysis, ALA has anti-obesity effects.[18-20] Twelve studies considered up until September 2016 demonstrated that ALA supplementation had a positive effect on body mass index (BMI) and body weight (BW), although the effect of ALA dosage intake on dose response and supplementation duration could not be examined. This meta-analysis is noteworthy since it indicates the influence of ALA supplement consumption on obesity. The current comprehensive review and dose-response meta-analysis show that ALA therapy reduces BMI and BW considerably. Depending on the timing of administration, ALA supplementation was observed to reduce waist circumference (WC) in a dose-response manner. With these findings, practical uses of ALA supplementation for the treatment of obesity are possible.[21]

Obesity is defined by the World Health Organization as an abnormal or excessive build-up of fat in adipose tissue that harms health.[22] Obesity in adults is clinically defined as a BMI greater than 30 and, in particular, improper fat distribution.[23] This definition, however, is unsatisfactory since it does not account for the spatial distribution of fat inside the body (abdominal/visceral vs. subcutaneous). Obesity and comorbidities are also risk factors for abnormal fat distribution.[24]

Obesity causes severe systemic alterations in the body. Obesity in the abdomen (or viscera) is related to an increase in the production of free fatty acids (FFA) from visceral fat storage, as well as metabolic instability, including insulin resistance.[25] Hyperlipolysis occurs in hypertrophic intra-abdominal adipocytes, resulting in increased FFA inflow to numerous organs, including the liver. Increased FFA flow affects liver function by increasing hepatic glucose synthesis and insulin resistance. Insulin resistance in the liver is related to reduced apolipoprotein B breakdown and increased triglyceride-rich lipoproteins. In obese individuals, macrophage infiltration into adipose tissue leads to a low, continuous level of inflammation. Proinflammatory substances such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) may also contribute to the altered metabolic profile of obese people. A rise in inflammatory markers such as plasma C-reactive protein appears to confirm the inflammatory condition of visceral obesity. Other molecules affected by obesity include leptin, adiponectin, and endothelial adhesion molecules. In other words, extra intra-abdominal fat indicates an inability of subcutaneous adipose tissue to store surplus energy. The inability of the subcutaneous tissue to store excess fat, known as ectopic fat accumulation, causes excess fat to be deposited in undesirable locations such as the liver, skeletal muscle, and heart, as well as pancreatic β cells.[26]

Obesity is regarded as the most serious public health issue in both developing and developed countries, causing a wide range of disorders such as type 2 diabetes mellitus (T2DM), cancer, hypertension, cardiovascular disease, and other health problems that can contribute to mortality and morbidity. It is caused by an excessive accumulation of body fat and a long-term positive energy imbalance.[27-31] By 2030, the global obesity rate will have increased by more than 57.8%. Several traditional techniques for controlling obesity, such as lifestyle adjustment, increased physical activity, and calorie-restricted diets, are unsatisfactory in the long run. As a result, complementary therapies such as anti-obesity supplements can help obese people adapt to and comply with lifestyle adjustments. can carry out the task.[32-36] In this situation, antioxidant therapy appears to be extremely important.

Alpha-lipoic acid is an organosulfur molecule found in nature and generated by plants, animals, and humans that works as a cofactor for specific enzyme complexes involved in the Krebs cycle's energy generation for the cell. It is vital in many chemical processes and has medicinal potential by creating covalent connections with proteins. It has a single chiral center and asymmetric carbon, which results in two optical isomers: R- and S-lipoic acid.[1] The S and R enantiomers of ALA are considered mirror reflections of one another. Although ALA contains both the S and R enantiomers in equal amounts, the R isomeric form naturally occurs and the S isomeric form is produced by chemical reactions. Foods are a natural supply of the R enantiomer of ALA, which is formed by covalent interactions with proteins within living organisms. While the R enantiomer of

ALA occurs in nature, a racemic mixture of the R and S forms is accessible as a synthetic supplement.[1,37] The quantity of ALA synthesized and generated by the human body is insufficient to supply the energy requirements of the cell. It is mostly derived from meat, vegetables, and fruits.[38]

Many therapeutically useful qualities are found in ALA. It functions as an enzymatic cofactor, as well as being involved in glucose and lipid metabolism and regulating gene transcription. Alpha-lipoic acid also functions as an antioxidant, enhancing and repairing innate antioxidant systems and promoting their synthesis or cell accessibility.[38-42] It also efficiently eliminates heavy metals that cause oxidative stress in the bloodstream.[43-45] It is distinguished from other antioxidants by its ability to operate as both a lipid and a water-soluble molecule.[38] There is no question that it is a potent antioxidant, but its medicinal usage is restricted for a variety of reasons; yet, it is used as a supplement in certain states and therapeutically in others.[38,44] The reason for this limitation is related to some inherent attributes of the material itself, such as variability caused by dithiolane ring exposure and the formation of disulfide bonds between molecules. The reduction in ALA solubility in the gastrointestinal system, which increases the hepatic metabolic rate, restricts its oral usage. In addition to its well-known antioxidant properties, ALA functions as a cofactor for several enzymes involved in metabolism. It is found in the energy-producing mitochondria and serves a variety of additional roles.[38]

Alpha-lipoic acid is essential for glucose reduction during metabolism. For example, ALA has been used as a racemic medication to treat pain and paresthesia associated with diabetic polyneuropathy.[46] In the transfer of energy through mitochondria, ALA also has a significant role.[47] In each ALA molecule, there are two reduced or oxidized thiol groups. Dihydrolipoic acid is the reduced form, whereas ALA, or simply lipoic acid, is the oxidized form. Free radicals are neutralized by ALA, which also reacts with the reduced form of reactive oxygen species.[40,48,49] A cofactor for both the PDH and α-ketoglutarate dehydrogenase complexes, ALA is naturally present in mitochondria where it interacts with the E2 subunit.[48] Since ALA is generated in the body in extremely small levels from cysteine and fatty acids, it must be obtained from outside sources.[49]

Alpha-lipoic acid improves glycemic control, reduces heavy metal toxicity, and alleviates problems of diabetes mellitus (DM) and peripheral neuropathy symptoms.[50-52]

The pancreatic cells that generate the hormone insulin are destroyed by the immune system, leading to type 1 diabetes mellitus (T1DM) or juvenile diabetes.[53] Insulin should be administered to the patient on a regular basis. In T2DM, insulin is either not created in sufficient quantities or the cells do not respond normally. Insulin transports glucose to cells in the heart, skeletal muscle, and adipose tissue mostly via the glucose transporter (GLUT)-4, but modest quantities of GLUT1 are also found in these tissues.[54,55] Insulin promotes GLUT4-containing vesicle transfer from intracellular reserves to the plasma membrane. This immediately increases glucose transport by 10-20 times.[54] Additionally, in T2DM, deficiency may be the result of defects in the molecules in GLUT4 that are responsible for sorting, retention, movement, insertion, binding, and the assembly's transport mechanism.[55] In T2DM, the insulin-dependent increase in surface GLUT4 is incomplete. Although GLUT1-3 transporters are not needed for insulin to absorb glucose; GLUT4 transporters are necessary for lowering the acute postprandial rise in plasma glucose levels by being sensitive to insulin levels. Furthermore, since skeletal muscles and adipose tissue are the main storage sites for glucose and include the GLUT4 transporter, the role of insulin in managing blood sugar levels after a meal should be emphasized.[54] Insulin deficiencies cause extremely high plasma glucose levels, which can harm multiple organs. Obesity may or may not be connected with T2DM. Diet and exercise for weight control, medicines that block the conversion of other metabolites to glucose, and, if necessary, insulin therapy, primarily to reduce blood glucose levels, are all utilized in treatment.

In the absence of suitable adipose tissue precursors, fatty acid storage decreases and excessive adiposity occurs as a result of positive caloric balance and increased circulating FFA concentration (lipotoxicity); this causes the release of inflammatory molecules (from central visceral fat stores), which leads to insulin resistance and increased circulating FFA concentration. This cycle continues indefinitely, with increasing levels of FFA being deposited in the muscles and liver.[56]

Insulin resistance alone does not explain the pathophysiology of obesity. Adipose tissue is an energy-storing organ that plays an active role in the hormonal control of homeostatic processes. Brown and white adipose tissue are the two basic kinds of adipose tissue.[57] While white adipose tissue makes up the vast majority of adipose tissue in the body and

is the site of energy storage, brown adipose tissue is a source of thermogenesis during non-vibrating times. Macrophages account for around 10% of white adipose tissue. The quantity of fat and the size of the adipocytes correlate favorably with the presence of macrophages.

Additional modulator compounds can be found in adipose tissue. The satiety hormone leptin is a 16-kDa protein generated mostly by adipocytes. Obese people may become sensitive to leptin and, hence, may not feel full after eating even if their leptin levels are high. Leptin controls inflammation in the body by stimulating and activating T cells and protecting them from apoptosis. T cells are affected by IL-6, which causes them to secrete cytokines such as IL-2 (a Th1 response that stimulates the innate immune system) and TNF-α.[57] In T2DM and obesity[58], TNF-α is a key molecule, and it may promote insulin resistance directly by increasing serine phosphorylation of the insulin receptor. Adiponectin is well recognized for its function in insulin sensitivity, and it is mostly produced by adipocytes. In response to increased adiposity, leptin levels increase, while adiponectin levels decrease. Leptin increases the expression of endothelial adhesion molecules as well as other adipocyte-produced molecules. The number of macrophages detected in white adipocyte tissue rises as a result of enhanced bone marrow-derived monocyte transportation and increased expression of adhesion molecules. Some of these macrophages combine to generate massive multinucleated cells. When compared to lean people, these macrophages release more TNF-α, IL-6, and chemokines.[57]

The results of dose-response studies investigating the effects of ALA supplementation on obesity measurements indicate the positive benefits of ALA on weight reduction. The systematic review and meta-analysis assessed the effects of ALA supplementation on anthropometric indices, such as BMI, weight, and WC, in adults, as well as in children, adolescents, and pregnant women, whose ages fell within the range of 18 years. In the current meta-analysis, papers on gestational DM were excluded. The primary outcomes of the study were that ALA supplementation lowered BMI and BW substantially more than a placebo. Although the effects of ALA application on WC were not significant in the two-class meta-analysis, the duration of ALA supplementation was dose-dependently correlated with WC.[59-62] Other studies have suggested that weight gain may be dependent on ALA dose and time.[15,63] The analyses revealed a significant relationship between a decrease in BW and BMI and a difference in the intervention time and ALA dosage. Different intervention lengths (two to 48 weeks) and ALA dosages (300 to 1800 mg/day) were studied in these studies. In the study by Koh et al.[15], they evaluated the effects of 1200 and 1800 mg/day ALA supplementation on BW and BMI and found that 1800 mg/day ALA resulted in substantial BW and BMI reductions when compared to the placebo group. Despite the two-class meta-analysis revealing that ALA supplementation had no effect on WC, the reduction in WC was substantial in female patients subgrouped by gender. Over a period of two to 20 weeks, the area decreased non-significantly by roughly -2.57 cm. Interestingly, in the dose-response meta-analysis, the duration of ALA supplementation was an effective parameter for lowering WC. This dose-response relationship between ALA and WC might explain the contradictory results of ALA's effects on WC. Amirkhizi et al.[62] investigated the effect of ALA on the state of oxidative stress in individuals with non-alcoholic fatty liver disease. They discovered that there was no significant difference in WC between the ALA and control groups. Several studies, on the other hand, have found that ALA can have an effect on WC.[60,64,65]

The anorexigenic impact of ALA in both humans and animals accounts for its anti-obesity benefits. Several studies have found that ALA supplementation can help regulate food consumption and human-centered metrics by decreasing appetite and boosting energy expenditure.[10,15,66,67] Several studies have shown that ALA either directly or indirectly regulates the expression of genes involved in energy balance, food consumption, hepatic cholesterol clearance, and fat synthesis and oxidation. The 5'-AMP-activated protein kinase (AMPK) in the hypothalamus is one of the important switches. An increase in the AMP/ATP ratio promotes AMPK, which deactivates anabolic pathways while activating catabolic pathways.[68,69] Alpha-lipoic acid supplementation has been proven to enhance fat mass and weight loss by increasing energy expenditure, decreasing hypothalamic AMPK activity and lowering food intake.[70,71] The AMPK appears to have an important role in regulating energy expenditure and food intake.[72] Furthermore, ALA enhances energy expenditure in brown adipose tissue by increasing the expression of uncoupling protein-1, which dissipates the proton electrochemical gradient in the mitochondrial inner membrane, allowing energy to be released as heat.[13] Furthermore, ALA is a cofactor for several essential respiratory enzymes in the mitochondria and works

as an antioxidant.[73] It has been shown in earlier research to inhibit fat accumulation in adipose tissue, the liver, and skeletal muscle.[74-76]

Although ALA appears to inhibit hypothalamic AMPK, it has been demonstrated to promote AMPK activity in peripheral tissues such as skeletal muscle and liver, which has been proven to directly limit fatty acid synthesis while increasing β-oxidation of fatty acids.[77,78] The expression of acetyl-CoA carboxylase and fatty acid synthase is downregulated when ALA is supplemented, according to a number of studies.[77,79] The duration of ALA usage, dosage, place of residence, health status, and gender all diminish variability in the subgroup analysis. Body mass index and WC show a significant degree of heterogeneity as a result of these measures.

In conclusion, studies on the usage of ALA as a supplement in the treatment of obesity have been included in this review. Although research on dosage and duration of administration are present in the literature review, there are not enough studies to draw a firm conclusion regarding how ingesting ALA in liquid or solid form affects obesity.

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