ORIGINAL ARTICLE

The effect of alpha-lipoic acid supplementation on vascular function and inflammation in patients newly experienced stroke

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Background: Since inflammation and oxidative stress are risk factors for cardiovascular diseases, so it seems that α-lipoic acid consumption as a potent antioxidant can improve vascular function and reduce the risk of vascular disease. The aim of this study is determine the impact of ALA supplementation on vascular function and inflammatory markers in patients who newly experienced stroke. **Materials and Methods:** In this randomized double-blind, placebo-controlled clinical trial, 80 patients were randomly divided into two groups: α-lipoic acid (600 mg ALA daily for 12 weeks) and placebo groups. Serum concentration of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) were measured by the ELISA method, and carotid intima-media thickness (CIMT) and flow-mediated dilation (FMD) were assessed using the Doppler ultrasound method. All statistical analyses were conducted using SPSS-16 and *P* values <0.05 were considered statistically significant. **Results:** After 12 weeks' supplementation, CIMT, FMD and hs-CRP changed between the ALA and placebo groups, significantly but we observed no significant difference in TNF-α and IL-6 levels either within or between the groups. **Conclusion:** The results showed that 600 mg ALA supplementation for 12 weeks improved CIMT, FMD and hs-CRP significantly so it seems that ALA supplementation may reduce the risk of cardiovascular disease.

Key words: Alpha-lipoic acid, carotid intima-media thickness, flow-mediated dilation, high-sensitivity C-reactive protein, interleukin-6, stroke, tumor necrosis factor-α

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INTRODUCTION

Lipoic acid (LA) or alpha-lipoic acid (ALA) is an eight-carbon compound, necessary for mitochondrial dehydrogenase reaction.[1] There is a general agreement on ALA role as a well-defined antioxidant. It exerts its antioxidant effect by cleansing free radicals and chelating metal ions such as iron. ALA can extend the activity of other antioxidants such as Vitamin C and Vitamin E and regenerate glutathione.[2] Overproduction or inadequate neutralization of free radicals can damage proteins, lipids, and other cellular structures that may have different effects on the health of different organs of the body such as the brain, heart, and blood vessels.[3] In addition to the antioxidant properties, ALA can improve vascular function by enhancing nitric oxide synthesis. Alteration of vascular structure or function is associated with coronary artery disease, stroke, hypertension, and/or peripheral artery disease.[4] Studies showed that intakes of 300–1800 mg/d ALA to improve symptoms and health outcomes are safe both in healthy individuals and patients. However, side effects such as allergic reactions in the skin and gastrointestinal symptoms can

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occur in long-term and high-dose use of ALA supplement in humans and signs in behavior (sedation, hunched posture, and eye closure) in animals.[5] Some case report studies reported that LA supplement may cause insulin autoimmune syndrome in some cases.[6]

Stroke is a medical condition in which brain cell death occurred because of poor blood flow to the brain. It is the second cause of death and one of the major causes of long-term disability worldwide.[7] Stroke is a serious disease with an annual mortality rate of about 5.5 million and economic and social consequences. Projections suggest a 20.5% increase in the prevalence of stroke from 2012 to 2030. Diabetes, hyperlipidemia, and hypertension, which promote cerebral atherogenesis, were found to be significant stroke risk factors.[8] There are several diagnostic methods used to diagnose vascular function in stroke patients or those at risk of stroke, such as carotid intima-media thickness (CIMT) measurement and flow-mediated dilation (FMD) of the brachial artery.[9] CIMT is an important marker of subclinical atherosclerosis. Increased CMIT is associated with increased cardiovascular risk and indicates the process of vascular events such as ischemic heart disease, acute coronary syndromes, and stroke.[10] The reduction of endothelium-derived nitric oxide is an early event in atherogenesis, which showed impaired function of the vascular system. FMD is an increased blood flow process facilitating the relaxation of an artery in response to shear stress.[11]

Since oxidative stress and inflammation are the risk factors for cardiovascular disease (CVD), so it seems that ALA as a potent antioxidant can improve vascular function and reduce the risk of vascular disease.[2,4,12] Therefore, we designed this study to determine the impact of ALA supplementation on vascular function and inflammatory markers in patients who newly experienced stroke.

SUBJECTS AND METHODS

Study design and population

This randomized double-blind, placebo-controlled, parallel-designed clinical trial was conducted to determine the effect of ALA supplementation on some cardiovascular functions and some inflammatory markers in newly diagnosed stroke patients. The protocol of this study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IUMS) (code: IR.MUI.REC.1395.3.068) and registered in the Iranian Registry of Clinical Trial (IRCT2016051811763N23). Participants of this study were patients who were newly diagnosed with stroke and referred to Al Zahra Hospital (a referral and governmental hospital affiliated with IUMS). Eighty patients were recruited and enrolled in this trial (from May 2016 to December 2016). Our inclusion criteria were filling informed consent, newly experienced thrombotic and embolic stroke (7 days or less), age 30–70 years, body mass index (BMI) = 18.5–35, lack of malignancies, and specific diseases such as kidney disease, liver disease, and cancer based on self-reports, no antioxidant, Vitamin, and omega-3 supplementation. Besides, subjects with no collaboration, failure to follow the program of the trial (compliance <80%), death, and recurrent stroke were excluded.

Participants were randomly divided into two groups: ALA and placebo groups (using a simple randomization method, from the randomized number in an 80-person list in a double-blind manner). In order to blind the study, supplements and placebo were divided between the two groups of participants by a third person who did not know the contents of the supplements. Individuals in the ALA group were taking a 600 mg ALA capsule and the placebo group a similar capsule (containing wheat flour) daily for 12 weeks. ALA powder was prepared by Caren Company and both ALA and placebo were encapsulated by the School of Pharmacy, IUMS. All participants completed our written informed consent form at the beginning of the study. They were instructed to take capsules 1 h before meals or 2 h after meals. Each week, participants were contacted to be sure of using supplements. Moreover, they were asked to deliver taken and not taken supplements at the end of each week to calculate compliance. During 12 weeks of intervention, 13 people were excluded from the study for different reasons. Finally, 33 and 34 patients completed a study in the intervention and placebo groups, respectively [Figure 1].

Measurements

Trained personnel collected all data. The demographic characteristics of participants were collected through face-to-face interview. Bodyweight was measured by a Seca scale (with an accuracy of 100 g, in the fasting state with minimal clothing) and height by a Seca stadiometer (with an accuracy of 0.5 cm) without shoes. Knee height was determined and the following formula was used for calculating the height of patients who were not able to stand up:

Height in centimeters (for men) = 64.19 – (0.04 × age) + (2.02 × knee height in centimeters)

Height in centimeters (for women) = 84.8 – (0.24 × age) + (1.83 × knee height in centimeters)

We calculated BMI for each patient (BMI = weight in kg/ht^2 in meters).

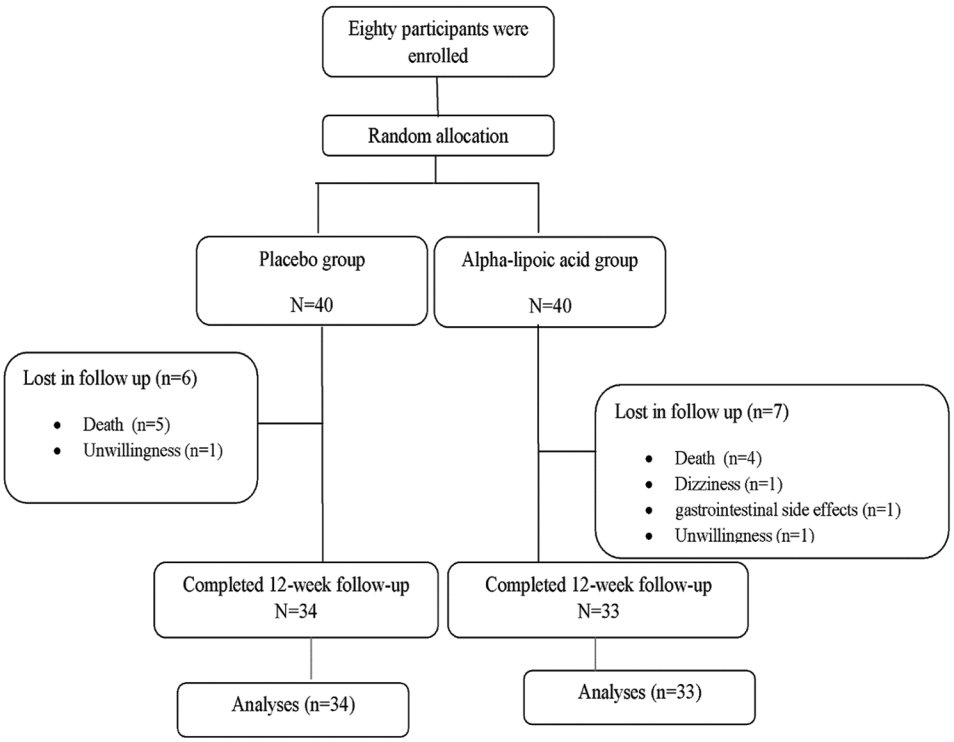

Figure 1: Flowchart of participants throughout the intervention

An Ergonomic Circumference Measuring Tape was used to measure waist circumference at the level of the iliac crest. We measured blood pressure by a mercury sphygmomanometer after 5 min of sitting rest.

Collection and analysis of dietary intake data were done using 24-h food recall questionnaires (by a nutritionist) and nutritionist IV software (Version 4.1, First Databank Division, The Hearst Corporation, San Bruno, CA, USA), respectively.

At the beginning and the end of the study, we collected venous blood samples (after 12-h overnight fasting) to measure laboratory factors. The serum samples were frozen and stored at −70°C, after centrifugation. The serum concentration of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) was measured by the ELISA method (The Binding Site Group Ltd., UK). A CIMT test is used to measure the thickness of carotid arteries' inner and middle layers and brachial artery diameter was measured in response to an increase in blood flow during reactive hyperemia (induced by cuff inflation and then deflation). A neurologist using the high-resolution external vascular Doppler ultrasound (MEDISON model, South Korea) measured carotid intima thickness (CIMT) and FMD.

Statistical analysis

All statistical analyses were conducted using SPSS (version 16; SPSS Inc., Chicago, IL, USA). Data were assessed for normality by the Kolmogorov–Smirnov test. In the case of a normal distribution, an independent *t*-test was used to compare baseline variables and paired *t*-test to compare the pre- and postintervention data within the groups. Comparison of the variables after the intervention was performed by analysis of covariance (ANCOVA) (adjusted for baseline values and energy intake). Quantitative data are presented as mean ± standard deviation. All tests were two-sided and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics were similar in both the ALA and placebo groups. No significant differences were found for age, sex, smoking, weight, height, BMI, waist circumference, blood pressure, fasting blood sugar, serum lipid levels, energy, and macronutrient intake between the two groups before the intervention ($P > 0.05$) [Table 1].

Based on ANCOVA results, statistically significant differences were observed in CIMT and FMD between the ALA and placebo groups (CIMT after intervention in the ALA group = 0.68 ± 0.10, the placebo group = 1.01 ± 0.15, $P < 0.001$; FMD (%) after intervention in the ALA group = 18.92 ± 13.17, the placebo group = 10 ± 8.21, $P < 0.001$) [Table 2]. Our results indicated a significant decrease in CIMT and an increase in FMD in the ALA group at the end of the study (CIMT before intervention in the ALA

Table 1: Baseline characteristics of subjects of the study who received α-lipoic acid (600 mg) or placebo before the intervention

Characteristics	ALA group	Placebo group	*P**
Age (years)*	62.33±6.19	64.23±8.01	0.28
Sex, *n* (%)**			
Male	17 (51.51)	19 (55.88)	0.45
Female	16 (48.48)	15 (44.11)	
Smoking (yes or no), *n* (%)**			
Yes	7 (21.21)	11 (32.35)	0.22
No	26 (78.78)	23 (67.64)	
Weight (kg)*	73.09±13.93	68.49±9.04	0.11
Height (cm)*	162.03±8.72	161.88±5.06	0.93
BMI (kg/m^2)*	165.68±8.95	165.23±9.29	0.85
Waist circumference (cm)*	27.68±3.92	26.14±3.32	0.08
Systolic blood pressure (mmHg)*	133.18±9.90	132.94±11.62	0.92
Diastolic blood pressure (mmHg)*	84.24±6.13	86.02±7.66	0.29
Energy intake (kcal/day)*	2182.3±367.37	2061.5±333.61	0.16
Carbohydrate intake (g/day)*	335.2±56.66	316.21±58.46	0.18
Protein intake (g/day)*	55.87±13.15	52.33±8.82	0.19
Fat intake (g/day)*	68.74±12.52	65.57±10.34	0.26
FBS (mg/dL)*	109.39±20.17	105.68±20.81	0.46
Triglyceride (mg/dL)*	140±50.72	151.44±55.90	0.38
Cholesterol (mg/dL)*	166.21±40.80	173.97±34.97	0.4
LDL-C (mg/dL)*	98.27±30.24	106.41±30.47	0.27
HDL-C (mg/dL)*	46.87±11.36	42.17±8.65	0.06

*Independent *t*-test; **Chi-square test. Values are expressed as mean±SD. SD=Standard deviation; FBS=Fasting blood sugar; LDL-C=Low-density lipoprotein-cholesterol; HDL-C=High-density lipoprotein-cholesterol; BMI=Body mass index; ALA=Alpha-lipoic acid

Table 2: Mean and standard deviation of carotid intima thickness and flow-mediated dilation of subjects of the trial before and after intervention in both groups

Groups / Variables	ALA group			Placebo group			Groups** (*P*)
	Before	After	*P**	Before	After	*P**	
CIMT (mm)	0.94±0.14	0.68±0.10	<0.001	0.93±0.12	1.01±0.15	<0.001	<0.001
FMD (%)	6.84±7.80	18.92±13.17	<0.001	9.88±10.45	10±8.21	0.91	<0.001

*Paired *t*-test; **ANCOVA adjusted for the baseline value of the variable and energy intake. Values are expressed as mean±SD. SD=Standard deviation; CIMT=Carotid intima thickness; FMD=Flow-mediated dilation; ANCOVA=Analysis of covariance; ALA=Alpha-lipoic acid

group = 0.94 ± 0.14, after intervention = 0.68 ± 0.10, $P < 0.001$; FMD (%) before intervention in the ALA group = 6.84 ± 7.80, after intervention = 18.92 ± 13.17, $P < 0.001$) [Table 2].

There was no significant difference in TNF-α and IL-6 levels either within the groups or between the groups. However, we observed a trend of decrease in the serum level of IL-6 in the ALA group ($P = 0.026$). Our result indicated a significant decrease in the hs-CRP level in the ALA group and a significant difference between the groups (hs-CRP after intervention in the ALA group = 7.24 ± 7.71, the placebo group = 17.61 ± 13.16, $P < 0.001$) [Table 3].

DISCUSSION

Results of our study showed that 12 weeks' supplementation with 600 mg ALA in patients who newly experienced stroke can improve vascular function (CIMT and FMD) but the effect on inflammatory markers was limited to a significant decrease in hs-CRP and no effect was found in TNF-α and IL-6 levels. According to our knowledge, the present trial is the first study, which investigated the effect of ALA consumption on CIMT, FMD, and inflammatory markers in patients who experienced a stroke.

Our findings indicate a significant reduction in CIMT in the ALA group compared with the placebo. We did not find any study, which investigated the effect of ALA on CIMT to compare with our findings. Nevertheless, in a study, the effects of flaxseed, olive, and sunflower oil (30 ml for 90 days) on CIMT in obese and overweight nondiabetic elderly people were investigated. This study reports a significant decrease in CIMT in all the three groups and suggests a possible association between improved lipid profile and CIMT.[13]

In another study, the relationship between oxidative stress indices and antioxidant levels with CIMT was investigated

Table 3: Mean and standard deviation of interleukin-6, high-sensitivity C-reactive protein, and tumor necrosis factor-α levels of subjects of the trial before and after intervention in both groups

Groups / Variables	ALA group			Placebo group			Groups** (*P*)
	Before	After	*P**	Before	After	*P**	
hs-CRP (mg/L)	14.99±0.69	7.24±7.71	<0.001	17.34±16.57	17.61±13.16	0.65	<0.001
IL-6 (pg/mL)	14.38±39.99	4.72±5.25	0.26	10.21±18.35	10.21±14.29	0.99	0.08
TNF-α (pg/mL)	7.70±5.11	6.20±3.22	0.13	6.02±3.39	7.26±4.20	0.05	0.05

*Paired *t*-test; **ANCOVA adjusted for the baseline value of the variable and energy intake. Values are expressed as mean±SD. SD=Standard deviation; TNF-α=Tumor necrosis factor-α; IL-6=Interleukin-6; hs-CRP=High-sensitivity C-reactive protein; ANCOVA=Analysis of covariance; ALA=Alpha-lipoic acid

in hemodialysis patients. The results of this study indicate the potential effect of antioxidant intake on CIMT as a predictor of cardiovascular events.[14] In line with these findings, Kajbaf *et al*. showed that supplementation with omega-3 (6 g, for 6 months) resulted in a significant CIMT reduction in dialysis patients.[15] These findings suggested an inverse association between antioxidants status and CIMT and the relationship between inflammatory markers and CIMT as a risk factor for CVD.[14] It seems that boosting the immunity system with supplements that have strong antioxidant properties such as ALA can reduce CIMT.[16] In addition, results of a prospective observational cohort study in patients with diabetic polyneuropathy showed that the risks of early neurological deterioration and hemorrhagic transformation were significantly lower in patients who were treated with ALA.[17] One of the reasons for the effects of ALA on CIMT reduction is due to its decreasing effect on lipid profile in different patients. In addition, a systematic review and meta-analysis of controlled clinical trials in 2019 showed that supplementation with ALA significantly decreased the serum concentrations of TG, total cholesterol, and low-density lipoprotein in adults.[18] CIMT is an important marker of subclinical atherosclerosis; therefore, an improvement in lipid profile may reduce CIMT.[10] In an animal study that investigated the effect of alpha-LA (ALA) supplementation on oxidative stress, plasma lipid, and vascular changes in diabetic rats, results showed that ALA can have a role in preventing the alteration of vascular morphology in diabetic rats because of its antioxidant properties.[19]

We found that 12 weeks of ALA supplementation in patients newly experienced stroke significantly increased FMD. Consistent with our findings in a study by Rahman *et al*. that investigated the effect of 600 mg ALA supplementation on endothelial function in 40 diabetic patients with primary hypertension treated with quinapril in 8 weeks, FMD increased significantly in the ALA group.[20] In another double-blind crossover study, the effects of 400 mg ALA and 1000 mg acetyl-L-carnitine on vascular function in patients with coronary artery disease were assessed and reported significant changes in baseline FMD by 2% but no changes in posthypoxia.[21] Another study in patients with Type II diabetes and hypertension indicated that supplementation with ALA (600 mg/day during the first 4 weeks and 1200 mg/day during the second 4 weeks) significantly increased FMD in both the groups of patients.[22] Consistent with our findings, intervention with 150 mg of irbesartan or 300 mg of ALA or both or placebo for 4 weeks increased FMD significantly.[23]

Dilatation caused by an increase in blood flow following temporary ischemia causes tensile stress to release nitric oxide (NO), called flow-mediated dilatation.[11] NO is produced by endothelial NO synthase. Alterations in endothelial-derived NO production have been associated with various vascular system dysfunction. ALA acts as an antioxidant and has anti-inflammatory properties, so the consumption of antioxidant compounds such as ALA and its contact with aortic endothelial cells can improve vascular function by increased NO production.[2,4,12]

Although we observed a significant reduction in hs-CRP, our findings indicate no change in TNF-α and IL-6 levels after 12 weeks ALA supplementation. In a study by Ramos *et al*., no significant change in inflammatory markers was observed in patients with chronic kidney disease after 8 weeks' supplementation with 666-unit tocopherol plus 600 mg ALA.[24] In another study, supplementation with ALA (800 mg) and pyridoxine (80 mg) daily for 12 weeks did not alter hs-CRP and IL-6 levels in diabetic nephropathy patients.[25] Mohammadi *et al*. also found no significant change in inflammatory markers after 12-week supplementation with 600 mg ALA in patients with chronic spinal cord injury.[26] In addition, Mendoza-Núñez *et al*. investigated the effect of 600 mg ALA supplementation on oxidative stress and inflammation in older adults with type 2 diabetes mellitus and they observed no statistically significant reduction in CRP, TNF-α, IL-6, IL-8, and IL-10 compared with placebo.[27] Besides mentioned studies, some others observed a significant reduction in inflammatory markers levels after ALA supplementation. In a study by Sola *et al*., intervention with 150 mg of Irbesartan or 300 mg of ALA or both or placebo for 4 weeks decreased IL-6 in intervention groups.[23] In another study, 600 mg ALA supplementation for 8 weeks in hemodialysis patients significantly decreased hs-CRP level.[28] In addition, results of a review article showed that supplementation of ALA can reduce ischemia-reperfusion injuries in multiple organs (nervous system, heart, kidney, liver, intestine, gonad gland, retina, and limb).[5]

Several studies have demonstrated the antioxidant and anti-inflammatory properties of ALA[1] and shown that ALA decreases the expression of vascular adhesion molecule-1, endothelial adhesion of human monocytes, and inhibits NF-κB.[29] NF-κB is a cytokine-mediating expression of several genes involved in inflammation and the migration of endothelial cells. Changes in the redox state and the protein structure of cell signaling may alter the activity of this factor. ALA inhibits activation and release of NF-κB by involvement in phosphorylation of factor inhibitor protein κB.[1,2] However, according to the contradictory results of studies, it seems that more studies with higher doses and longer period of intervention are needed to determine the effect of ALA on inflammatory markers.

CONCLUSION

This study showed that supplementation with 600 mg ALA for 12 weeks significantly improved CIMT and FMD, so it can improve vascular function. It was also able to significantly decrease the level of hs-CRP but did not change TNF-α and IL-6 significantly. Regarding these results, it seems that ALA supplementation could change the risk of CVD.

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Conflicts of interest

There are no conflicts of interest.

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