

Effect of Alpha-Lipoic Acid and Vitamin E Supplementation on Oxidative Stress, Inflammation, and Malnutrition in Hemodialysis Patients

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Introduction. Increased oxidative stress, inflammation, and malnutrition are present in hemodialysis patients and these factors exacerbate cardiovascular comorbidities. Vitamin E and α -lipoic acid (ALA) may have a protective role against cardiovascular disease risk factors via anti-oxidative and anti-inflammatory properties. The aim of this study was to evaluate the effect of ALA and vitamin E administration (alone or combined) on hemodialysis-induced stress oxidation, inflammation, and malnutrition.

Materials and Methods. In a randomized placebo-controlled trial, we examined the effects of 2-month supplementation by vitamin E and ALA (alone or combined) on biomarkers of lipid peroxidation (malondialdehyde), inflammation (high-sensitivity C-Reactive protein and interleukin-6), and malnutrition (Subjective Global Assessment and body mass index) in 85 hemodialysis patients receiving ALA (600 mg), vitamin E (400 IU), ALA and vitamin E, and placebo.

Results. After supplementation, no significant changes were observed in malondialdehyde level; however, there was a decrease in the ALA and vitamin E group during the period of the study. Also, a nonsignificant decrease was seen in the high-sensitivity C-Reactive protein concentration of the interventional groups. Supplementation of vitamin E with and without ALA significantly reduced interleukin-6 concentration. A significant improvement was observed in malnutrition status of all groups.

Conclusions. Vitamin E and ALA supplementation, especially their combination, might improve inflammation and malnutrition status, which suggest it as a potential preventive strategy against CVD among end-stage renal disease patients.

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INTRODUCTION

Cardiovascular Disease (CVD) is a common cause of morbidity and mortality among hemodialysis patients,¹⁻⁴ among whom it is on average 5 to 20 times higher than in the general population.⁵

Some of the risk factors such as oxidative stress and chronic inflammation are related to the progress of CVD in hemodialysis patients.⁶ Inflammatory processes promote reactive oxygen species production and cause the consumption of

liposoluble antioxidants and consequently produce lipid peroxidation products and oxidized low-density lipoprotein cholesterol (LDLC).⁷ Conversely, oxidative stress can also induce inflammation by activation of the nuclear factor kappa-light-chain-enhancer of activated B cells signaling and subsequently synthesis of pro-inflammatory cytokines.^{8,9} Oxidative stress can also lead to a syndrome known as malnutrition, inflammation, atherosclerosis.¹⁰

With regards to the linkage between oxidative stress and inflammation, anti-oxidative therapy strategies can be useful to reduce CVD risk factors.¹¹ Both α -lipoic acid (ALA) and vitamin E are known as potent reactive oxygen species scavengers.^{12,13} Since oxidative stress and inflammation are significantly increased in patients with end-stage renal disease, in this trial, we investigated the effect of ALA and vitamin E supplementation on oxidative stress, inflammatory markers, and the subsequent malnutrition status in hemodialysis patients.

MATERIALS AND METHODS

Patients

This 2-month randomized controlled trial was conducted at the Shiraz University of Medical Sciences and approved by the Research and Ethics Committee of Shiraz University of Medical Sciences. A total of 96 hemodialysis patients were randomly selected from Namazi and Sadra hemodialysis units in Shiraz, Iran, if they were 20 to 60 years old and on maintenance hemodialysis at least 2 times weekly for at least 1 year. The exclusion criteria were smoking, pregnancy, acute inflammatory or cardiovascular disease, currently active infection, hepatic or rheumatic disorders, and receiving antioxidant (such as vitamin C, vitamin E, or omega-3), thyroxin, anti-coagulant, or oral contraceptive medications. The dosage and type of regular medications were kept consistent and the participants followed their regular diet during the period of the study. They were divided into 4 groups ($n = 24$ in each group) with balanced block randomization method, to receive ALA (600 mg), vitamin E (400 IU), ALA and vitamin E (combined; 600 mg and 400 IU, respectively), and placebo. However, 11 patients were excluded from the study, and finally data from 85 patients (45 men and 40 women) were collected and analyzed.

Laboratory Measurements

Five-milliliter blood samples were collected for measurement of biochemical markers, before the dialysis session at baseline and after 2 months. Plasma was prepared by blood centrifugation (3000 g, 10 minutes) and stored at -70°C until required.

Malondialdehyde measurement was performed by the spectrophotometric method.¹⁴ Briefly, 500 μL of blood sample was added to 2 mL of thiobarbituric acid and incubated for 15 minutes at 100°C . After cooling and centrifugation, the absorbance of supernatant was measured at 532 nm. The high-sensitivity C-Reactive protein (HS-CRP) was measured using an enzyme-linked immunosorbent assay kit (IBL-America, Minneapolis, MN, USA). Interleukin-6 was measured using a radioimmunoassay method (DIASource, Louvain-La-Neuve, Belgium).

Nutritional Assessment

Quantitative Subjective Global Assessment (SGA) form¹⁵ and 24-hour dietary recall questionnaire for 3 days per week were filled for each patient by the principle investigator before and after the intervention. Dietary components (energy, carbohydrate, protein, and fat) were analyzed by Food Processor Nut4 and compared with the Dialysis Outcomes Quality Initiative guidelines. Also, anthropometric measurements, including weight and height, were performed after dialysis session and the body mass index (BMI) was calculated.

Statistical Analyses

The SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, Ill, USA) was used for all statistical analyses. The results are expressed as mean \pm standard deviation for all continuous data. After confirming normality by the 1-sample Kolmogorov-Smirnov test, the Wilcoxon signed rank test and the paired sample t test were used, where appropriate. The differences between the four groups were assessed by the 1-way analysis of variance. A P value less than .05 was considered significant.

RESULTS

The four groups were comparable with respect to sex distribution, age, weight, height, BMI, kidney failure duration, hemodialysis duration,

nutritional status, fasting blood glucose, and insulin levels before supplementation intervention (Table 1). After the 2-month supplementation, there were no significant differences in dietary intakes and anthropometric measurements between the groups, but there was an increase in energy intake of the supplemented groups. Also, weight and BMI of patients in the vitamin E and combined supplementation groups increased, but it was not significant (Table 1).

A significant improvement in SGA score was observed in the vitamin E, ALA, and combined supplementation groups in comparison to the placebo one ($P < .001$, $P = .001$, and $P = .005$, respectively; Table 2).

Plasma levels of malondialdehyde, interleukin-6, and HS-CRP at baseline and after supplementation at 2-month are summarized in Table 3. There were no significant differences at baseline levels of these markers among the groups. Combined administration of ALA and vitamin E for 2-months reduced the plasma level of malondialdehyde from a median of $4.9 \pm 1.6 \mu\text{mol/L}$ to $4.5 \pm 1.3 \mu\text{mol/L}$, but it was not significant. There was a decrease in the level of HS-CRP of all interventional groups, but it was not significant. Supplementation of vitamin E and combined supplementation of vitamin E and ALA significantly reduced interleukin-6 concentration in comparison to the placebo group.

Table 1. Characteristics of Hemodialysis Groups at Baseline*

Parameter	Vitamin E (n = 17)	ALA (n = 20)	Vitamin E + ALA (n = 24)	Placebo (n = 24)
Sex				
Female	6	6	13	15
Male	11	14	11	9
Age, y	44.8 ± 12.7	48.8 ± 11.2	53.2 ± 9.8	48.9 ± 12.5
Weight, kg	67.4 ± 19.9	66.9 ± 18.0	67.4 ± 13.3	61.5 ± 15.9
Height, cm	164.0 ± 11.8	170.0 ± 10.2	162.2 ± 12.9	158.4 ± 12.1
Body mass index, kg/m ²	25.4 ± 6.5	23.4 ± 5.2	26.2 ± 7	25.5 ± 12.1
Kidney failure duration, y	3.9 ± 4.6	3.7 ± 3.6	4.1 ± 2.8	6.0 ± 5.1
Dialysis duration, y	16.5 ± 4.8	17.1 ± 5.5	16.2 ± 5.2	19.1 ± 5.9
Triglyceride, mg/dL	162.0 ± 98.2	126.2 ± 59.8	193.1 ± 123.5	133.5 ± 60.9
Cholesterol, mg/dL	140.0 ± 57.8	132.8 ± 42.7	144.4 ± 38.7	140.0 ± 51.3
LDLC, mg/dL	97.7 ± 38.4	91.7 ± 32.3	93.2 ± 27.2	92 ± 30.9
HDLC, mg/dL	34.8 ± 10.2	36.7 ± 13	37.4 ± 12.4	40.5 ± 12.5
Fasting blood glucose, mg/dL	109.4 ± 34.8	125.5 ± 84.6	124.1 ± 42.3	108 ± 30.8
Insulin, $\mu\text{mol/L}$	5.0 ± 3.0	9.1 ± 7.0	10.0 ± 9.2	8.3 ± 5.3
Energy, kcal	1375 ± 658	1319 ± 531	1083 ± 424	1094 ± 507
Protein, %	14.7 ± 2.3	17.2 ± 6.0	16.2 ± 4.3	15.6 ± 6.0
Carbohydrate, %	59.4 ± 11.0	58.8 ± 10.3	62.4 ± 11.0	58.6 ± 6.0
Fat, %	25.7 ± 12.0	23.8 ± 7.1	21.8 ± 8.2	25.6 ± 6.4

*ALA indicates alpha-lipoic acid; LDLC, low-density lipoprotein cholesterol; and HDLC, high-density protein cholesterol.

Table 2. Changes in Dietary Factors and Subjective Global Assessment Score in Hemodialysis Patients Before and After 2-month Supplementation*

Parameter	Vitamin E (n = 17)		ALA (n = 20)		Vitamin E + ALA (n = 24)		Placebo (n = 24)	
	Before	After	Before	After	Before	After	Before	After
Weight, kg	67.4 ± 19.9	68.1 ± 19.6	66.9 ± 18.0	66.3 ± 17.9	67.4 ± 13.3	68.0 ± 13.5	61.5 ± 15.9	61.0 ± 16.4
Body mass index, kg/m ²	25.0 ± 6.5	25.3 ± 6.5	23.0 ± 5.2	22.8 ± 5.2	26.0 ± 7.0	26.2 ± 7.1	24.4 ± 5.4	24.2 ± 5.7
SGA score	16.5 ± 4.8 [§]	15.7 ± 4.5	17.1 ± 5.5 [§]	16.6 ± 5.0	16.2 ± 5.2 ^{†§}	15.9 ± 5.3	19.1 ± 5.9 [†]	20.0 ± 6.6
Energy, kcal	1375 ± 658	1469 ± 659	1319 ± 531	1400 ± 520	1083 ± 424	1186 ± 498	1094 ± 507	1042 ± 537
Protein, %	14.7 ± 3.2	13.8 ± 3.2	17.2 ± 6.1	17.7 ± 5.9	16.2 ± 4.3	17.0 ± 4.5	15.6 ± 6.0	15.1 ± 3.8
Carbohydrate, %	59.4 ± 11.0	60.1 ± 10.9	58.8 ± 10.3	59.6 ± 10.6	62.4 ± 11.0	59.7 ± 12.4	58.6 ± 8.4	59.6 ± 9.0
Fat, %	25.7 ± 12.0	26.4 ± 11.8	23.8 ± 7.1	22.4 ± 6.9	20.0 ± 9.0	21.8 ± 8.2	25.6 ± 6.4	24.1 ± 7.0

*ALA indicates alpha-lipoic acid and SGA, Subjective Global Assessment.

[†] $P < .05$ for comparison of before and after values

[§] $P < .05$ for comparisons between groups by 1-way analysis of variance

Table 3. Changes in Oxidative Stress and Inflammatory Markers in Hemodialysis Patients Before and After 2 months of Supplementation

Parameter	Vitamin E (n = 17)		ALA (n = 20)		Vitamin E + ALA (n = 24)		Placebo (n = 24)	
	Before	After	Before	After	Before	After	Before	After
Malondialdehyde, $\mu\text{mol/L}$	4.4 \pm 1.6	4.7 \pm 1.2	3.9 \pm 1.2	4.6 \pm 1.3	4.9 \pm 1.6	4.5 \pm 1.3	4.4 \pm 1.6 [†]	6.2 \pm 5.3
HS-CRP, mg/L	10.7 \pm 7.9	8.7 \pm 8.4	8.4 \pm 7.8	5.9 \pm 5.7	7.5 \pm 6.8	5.9 \pm 5.5	6.9 \pm 6.2	7.1 \pm 6.2
Interleukin-6, pg/mL	43.6 \pm 33.0 ^{†§}	33.6 \pm 30.7	36.3 \pm 28.1 [§]	28.8 \pm 19.3	41.3 \pm 33.5 ^{†§}	30.3 \pm 25.6	41.1 \pm 37.5	52.0 \pm 42.0

*ALA indicates alpha-lipoic acid and HS-CRP, high-sensitivity C-reactive protein.

[†]P < .05 for comparison of before and after values

[§]P < .05 for comparisons between groups by 1-way analysis of variance

DISCUSSION

As documented, malondialdehyde levels as an oxidative stress marker is increased in hemodialysis patients. The mean malondialdehyde in this study was 4.4 $\mu\text{mol/L}$ that is high in comparison to the reported amount for healthy people (0.58 $\mu\text{mol/L}$).^{16,17} Elevated oxidative stress in hemodialysis patients is related to some factors such as consumption of water or fat soluble antioxidants, increase in metals like copper, defect of anti-oxidative cofactors, activated leucocytes, uremic toxins, acute or chronic infections, and diet restrictions.^{3,18-20} In this trial, ALA or vitamin E could not reduce malondialdehyde when they were used alone. Probably, supplementation with these doses (400 IU of vitamin E and 600 mg of ALA) was inadequate. On the other hand, with combined supplementation, we did not observe a significant reduction. It seems that the short period of intervention can be an explanation for it.

Alpha-tocopherol detoxifies lipid peroxy radicals. At the same time, an α -tocopheroxyl radical is generated. This can be converted to tocopherol by vitamin C.^{21,22} Alpha-lipoic acid can interact with other antioxidants like ascorbate and has the ability to regenerate α -tocopherol directly or indirectly; thus, lipoic acid and its reduced form have a central position in anti-oxidative system, and also vitamin E plays a main role in reduction of oxidative stress.²³ In studies of vitamin E supplementation, it has been suggested that effectiveness of vitamin E in lipid peroxidation reduction may be dependent on the period of the study and its dose. Cristol and colleagues²¹ used 500 mg of vitamin E as supplement for hemodialysis patients for 6 months and reached significant results, while Mydlik and associates²⁴ did not find significant effects on malondialdehyde and total antioxidant capacity by 400 mg of vitamin E supplementation for 3

weeks. In Marangon and colleagues' study,²⁵ alone or combined supplementation with 600 mg of ALA and 400 IU of vitamin E did not have a significant effect on other oxidative factors such as oxidized LDLC lag time, urinary F₂-isoprostans, and plasma carbonil in healthy people. In Chang and associates' study,²⁶ supplementation with 600 mg of ALA for 12 weeks in diabetic hemodialysis patients did not affect oxidized LDLC. Khabbazi and colleagues²⁷ also could not find any significant results by supplementation with 600 mg of ALA in hemodialysis patients.

We observed an increase in malondialdehyde levels in vitamin E and ALA and placebo groups, but the enhancement level of vitamin E- or ALA-treated groups was less than the placebo group. Hence, we may suggest that ALA and vitamin E can lead to a decreasing trend of malondialdehyde in these patients. Oxidized LDLC induces inflammation and subsequently circulating adhesion monocytes and effects on releasing cytokines such as interleukin-6 and tumor necrosis factor- α from monocytes.²⁸ C-reactive protein and interleukin-6 can be used as predictors of mortality in hemodialysis patients.²⁹ The results demonstrated a significant reduction of interleukin-6 in all groups in comparison to placebo; thus, we may focus the anti-inflammatory properties of ALA and vitamin E. Vitamin E and ALA lead to reduction of the monocytes transfer to inflammatory sites by reducing expression of vascular cell adhesion molecule 1 and inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells activation.³⁰⁻³² The results of various studies are varied. Chang and colleagues²⁶ did not observe significant results in HS-CRP levels by 600 mg of ALA supplementation for 8 weeks in diabetic hemodialysis patients. However, HS-CRP reduction in Khabbazi and colleagues' study,²⁷ in which hemodialysis patients were supplemented

with 600 mg of ALA, was significant. It might be attributed to differences in genetic characteristics of patients. In our study, although reduction of interleukin-6 in vitamin E and ALA groups was significant but adding ALA to vitamin E might be more effective. As Phillips and colleagues have suggested,³³ combination of supplements is more important in trials.

Malnutrition, inflammation, atherosclerosis syndrome is a result of oxidative stress and inflammation.¹⁰ Most of the hemodialysis patients have a critical nutritional status; the prevalence of malnutrition in these patients is about 20% to 80%.³⁴ We used SGA method, which is known as a clinically valid method for nutritional assessment.³⁵ This study concluded that there was a significant improvement in malnutrition status in all supplemented patients in comparison to placebo. Also, we compared our study population's dietary intakes with Dialysis Outcomes Quality Initiative clinical practice guidelines. Although during dialysis, some amounts of proteins are lost and therefore the patients require more protein and adequate energy intake to maintain nitrogen balance compared to non-hemodialysis ones,^{36,37} it has been noted that protein and energy intakes in our hemodialysis patients are low. Some other studies have also indicated that hemodialysis patients have less energy and protein intakes.³⁴ Supplementation caused an increase in energy and protein intake although it was not significant. Body mass index of patients in vitamin E and vitamin E plus ALA groups increased in comparison to placebo. Also, we had a 0.5-kg reduction in the weight of patients receiving placebo. In a cohort study that analyzed 5058 malnourished patients' status, it was concluded that 1 unit reduction in BMI increases the risk of CVD mortality about 6%.³⁸ In an inflammatory status like what we see in hemodialysis patients, release of pro-inflammatory cytokines can be related to anorexia, malnutrition and weight loss.³⁹ Some studies revealed that patients with lower BMI have a 60% increase of mortality risk in comparison to the ones with higher BMI.⁴⁰ In this study, supplementation may affect malnutrition status directly or indirectly by affecting the inflammatory status. Decreased inflammation can be effective on appetite improvement and consequently increased nutrient intake, BMI and malnutrition improvement. Our study results

may confirm this subject, although we had some limitations such as blind administration of study interventions, small sample size, and short period of follow-up.

CONCLUSIONS

The results of this study reveal that combination of ALA and vitamin E can be a modulator of inflammatory and malnutrition status in hemodialysis patients; thus, new therapeutic strategies like ours are needed to prevent the CVD mortality and morbidity. However, further investigations will be required in this regard and also we suggest to examine the effect of these supplements on the other oxidative stress factors such as lag time oxidized LDLC, super oxide dismutase, and glutathione peroxidase.

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CONFLICT OF INTEREST

None declared.

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