**Original Article****Effect of Alpha-lipoic Acid Supplementation on Serum Lipid Profile in Women with Rheumatoid Arthritis**Elham Mirtaheri¹, Bahram Pourghassem Gargari^{2*}, Sousan Kolahi³, Mohammad Asghari-Jafarabadi⁴, Mehrzad Hajjaliloo³

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Background and Objectives: Alpha-lipoic acid (ALA) is considered as a potent antioxidant with anti-inflammatory functions. Moreover, a number of studies have revealed its lipid lowering properties. Therefore, we aimed to examine the effect of ALA on serum lipids in women with rheumatoid arthritis (RA), who have high mortality rate mainly due to accelerated atherosclerosis.

Materials and Methods: In the present study a total of 70 RA patients were randomly assigned into two groups (1:1) to receive either ALA (1200 mg/day) or placebo for 8 weeks. Fasting blood samples were obtained before and after the intervention to analyze serum lipid profile including triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C). International physical activity questionnaire (IPAQ) was assessed at baseline and final. Between-group comparisons were done using Student's t-test and ANCOVA at baseline and after 8 weeks, respectively. Paired t-test was used for within-group comparisons. Sign test and Mann-Whitney's test were used for intra- and inter-group comparisons of qualitative variables, respectively. $P < 0.05$ was considered as significant.

Results: Finally, 65 RA patients completed the trial. No statistically significant differences were observed in serum lipid levels within and between the groups before and after the study. There were no significant intra- and inter-group differences in physical activity levels at the beginning and in the end of the study.

Conclusions: In the present study, serum lipid profile was not significantly affected by ALA intervention. However, ALA supplementation aiming at prevention or treatment of dyslipidemia in RA patients should be further investigated.

Keywords: Lipoic acid, Supplementation, Rheumatoid arthritis, Women, Lipid profile

Introduction

Rheumatoid arthritis (RA) is a chronic systemic and articular inflammatory disease with inflamed, swollen and tender joints, resulting in functional disability and increased mortality associated with accelerated atherosclerosis (1, 2). RA affects around 1% of the world population (3), and is about three times more common in women than in men (4).

It has been demonstrated that atherosclerotic cardiovascular disease is the most common cause of death in RA patients, who die 5–15 years earlier compared with the general population. Mainly due to its chronic inflammatory component, RA itself could be considered as an independent cardiovascular (CV) risk factor; however, traditional CV risk factors also play an important role in this area (2, 5). Dyslipidemia is one of the important traditional risk factors of cardiovascular disease (6). RA is associated with an abnormal lipid profile pattern, particularly lower level of high density lipoprotein cholesterol (HDL-C). However, the

evidence in this area is relatively conflicting (7-9). The reported differences in lipid profiles between RA patients and healthy controls appear to stem from different studied RA populations, drugs, and stage of inflammation (5, 10). In fact, it seems that drugs prescribed in RA mediate changes in lipid profile levels mainly through the effect on inflammation (11). Inflammation alters lipid profile levels and lipid metabolism. Studies have revealed that TNF- α stimulates hepatic lipogenesis resulting in hypertriglyceridemia (12). Moreover, in chronic inflammatory states like RA, markers of inflammation (including CRP) appear to be inversely related to HDL-C levels (13, 14), which can lead to accelerated atherosclerosis (15). Therefore, from the nutritional point of view, complementary treatment using dietary modifications, supplements and nutraceuticals with lipid lowering effects

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seems to be a good strategy to reduce future CV risk in RA patients.

Alpha-lipoic acid (ALA) functions naturally as a necessary cofactor for mitochondrial alpha-keto-dehydrogenases (16). Furthermore, a growing body of evidence shows that orally supplied ALA could have other biochemical functions beyond its role as a metabolic cofactor. Apart from its direct antioxidant functions like reactive oxygen species (ROS) quenching (17) and indirect antioxidant and anti-inflammatory properties through affecting critical transcription factors (17-19), ALA has also been found to have lipid lowering effects (20-27). A number of studies, especially in animals fed a high cholesterol or high-fructose diet, have shown that ALA decreases serum lipid levels (20-24). However, the efficacy of ALA in dyslipidemia was controversial in other studies (25-27). Therefore, it seems there is still insufficient data in this area. Hence, taking into account the probable effects of weight and physical activity as confounding factors of serum lipid levels, for the first time, we evaluated the effects of oral ALA supplementation on the serum lipid profile of RA patients.

Materials and Methods

Study design and subjects: The present study is a randomized double-blinded placebo-controlled clinical trial, which was approved by the Ethics Committee of Tabriz University of Medical Sciences. It was also registered at the Iranian Registry of Clinical Trials' website (IRCT201205263140N5).

A sample size of 30 patients in each group was calculated which would give a power of 80% at the 5% significance level. To allow 15% dropout rate the sample size was increased to 35 patients per group

RA patients were recruited from the Rheumatology Clinic of Imam Reza Hospital in Tabriz (Iran) from February to July 2012. Finally, taking into consideration the inclusion and exclusion criteria, 70 women with RA were included in the trial. Oral and written informed consents to take part in the study were obtained from all participants.

The inclusion criteria comprised patients diagnosed as having RA based on the American College of Rheumatology criteria, women aged 20-50 years, being at remission, mild or moderate state of the disease graded on the basis of disease activity score-28, not changing the treatment protocol, and not taking antioxidant or anti-inflammatory supplements at least one month preceding the enrolment. The exclusion criteria were clinically having other kinds of rheumatic diseases, cancer, diabetes mellitus, endocrine disorders, thyroid disorders, vitamin or mineral deficiency, morbid obesity (defined as a body mass index (BMI) >40), uncontrolled hypertension (systolic blood pressure (SBP) >140, diastolic blood pressure (DBP) >90), renal failure, hepatic diseases, gastrointestinal disorders, other types of autoimmune or inflammatory diseases, smoking or being a passive smoker, pregnancy, lactation,

post-menopause, receiving hormone replacement therapy, taking oral contraceptive pills, changing treatment protocol and lifestyle during the study, taking antioxidant or anti-inflammatory supplements during the study, compliance with the supplement < 75%, and unwillingness to continue the study.

To our knowledge, this is the second study in which ALA supplementation was used for RA patients. In the previous study conducted by Bae et. al (28), ALA dosage of 900 mg/day for 4 weeks was used, and finally, they suggested studies with higher dose and duration of supplementation to affect the disease process. On the other hand, the results of studies on non-RA patients evaluating the lipid lowering effect of ALA at 600 mg/day dose were inconsistent. Overall, the ALA dose of 1200 mg/day for 8 week supplementation period, which is absolutely safe, was chosen for this study.

The participants were randomly allocated into two groups (1:1), which were matched for age and disease severity, and received 1200 mg/day oral ALA supplement or placebo for 8 weeks (2 capsules each day, every 12 hours, 30 minutes prior to breakfast and dinner, 600 mg purified ALA or maltodextrin per capsule).

ALA (manufactured by A&A Pharmachem Inc., Ottawa, Ontario, Canada) and maltodextrin (provided by Karen Pharma & Food Supplement Co., Tehran, Iran) were filled in identical capsules, and packaged in the similar bottles (120 capsules per bottle, by Karen Pharma & Food Supplement Co., Tehran, Iran). Since the study was double-blinded, the bottles containing ALA or placebo were coded by a person not involved in the study. Also a randomization list was generated using the Random Allocation Software in blocks of four in which the patients' codes were entered in chronological order.

At baseline, information on age, disease history, medications, etc. was collected using a demographic questionnaire through a face-to-face interview. To control any confounding factors, the patients were asked not to change their usual life style, dietary intake, physical activity, and medications during the intervention period. Also, before and after the study physical activity levels of the patients were assessed using the short form of the International Physical Activity Questionnaire (IPAQ) by an instructed interviewer (29). The patients were classified as having high, moderate or low physical activity levels according to the categorical scoring protocol of the short form of IPAQ (30).

Initial and final dietary intakes of the patients were assessed using a self-administered three-day dietary record. They were instructed how to fill out the dietary records by an expert nutritionist. They were also given necessary information on food groups and portion sizes. Dietary data were analyzed by the Nutritionist IV software's (First Databank, San Bruno, CA, USA) modified version for Iranian foods.

Body weight was measured using a balance scale (Seca, Germany) to the nearest 0.5 kg. Height was measured using a non-stretchable tape (Seca) to the nearest 0.5 cm. BMI was calculated through dividing the weight (kg) by the height squared (meters).

Disease activity score-28 (DAS-28) was calculated using high-sensitive C-reactive protein (hs-CRP), and the numbers of swollen and tender joints was determined by means of this formula: $DAS28 = [0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.36 * \ln(\text{hs-CRP} + 1)] * 1.10 + 1.15$ (TJC28: the number of tender joints from 28 joints, SJC28: the number of swollen joints from 28 joints).

To evaluate compliance with the intervention, unused capsules left in the bottles were counted after 8 weeks. Compliance with the treatment was calculated using this formula: Compliance rate = [(number of delivered capsules - number of left capsules in the bottle) / number of delivered capsules] * 100.

Patient visits were at the beginning and in the end of the study. To control any probable adverse event during the trial period, all subjects were monitored by phone call every 10 days.

Blood sampling and biochemical assays: Before and after the 8-week supplementation period, 10 mL venous blood samples were taken after 10-12 hours fasting at room temperature. Then they were centrifuged for 15 minutes at 1500 g to obtain serum samples, which were stored at -20°C until biochemical analysis.

Serum concentrations of lipid profile components (including TC, TG and HDL-C) were measured using enzymatic method with commercially available kits (Pars

Azmun Co., Tehran, Iran) according to the manufacturer's protocol; the results were stated as milligram per deciliter (mg/dL). Serum LDL-C was calculated according to the Friedewald formula (31).

Statistical analyses: Statistical analyses were done using Statistical Package for the Social Sciences (SPSS), version 13 (SPSS Inc., Chicago, IL, USA). P-value < 0.05 was considered as significant. The quantitative and qualitative variables were displayed as mean ± standard deviation (M±SD) and frequency (%) of the patients, respectively. The Kolmogorov-Smirnov's test was used to test the normality of the variables. Leven test was used to test the homogeneity of the variables. For intra- and inter-group comparisons of the qualitative data, the Sign and Mann-Whitney's tests were used, respectively. At baseline, comparisons of mean values between the groups were done using the independent t-test. Paired t-test was used for within-group comparisons of the mean values. At the end of the study, between-group comparisons were done using the ANCOVA test after adjustment for basic measurements and some confounding factors (BMI, calorie intake and disease duration).

Results

Baseline characteristics: Figure 1 illustrates the study flow diagram. A total of 135 RA patients were screened, of whom 70 were eventually included in the study. The patients were randomized 1:1 to receive ALA or placebo for 8 weeks. Finally, 33 patients in the ALA group and 32 patients of the placebo group completed the trial, and no side effects were reported during and after the intervention.

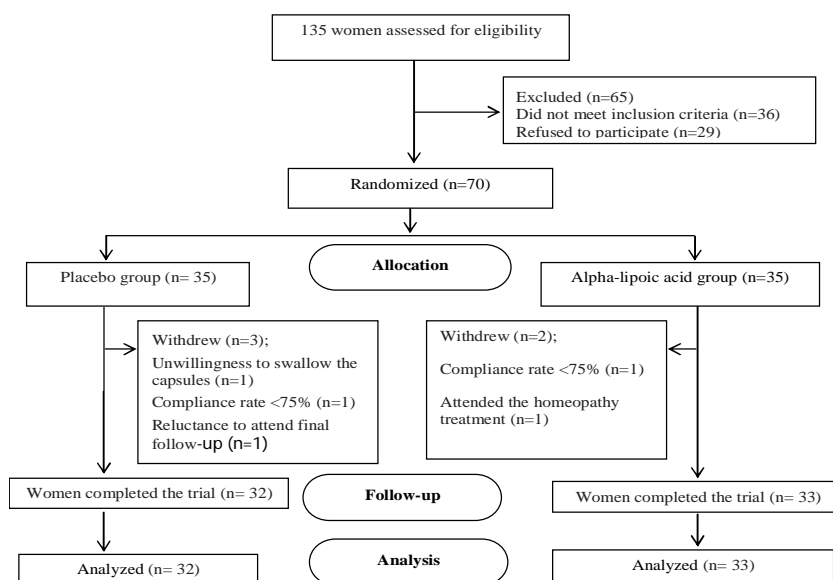


Figure1. Flow diagram of the study

Table 1 represents the baseline patient characteristics and medications, which were not significantly different between the ALA and placebo-treated groups.

There were no statistically significant differences in the doses and types of drugs between the two groups at the beginning of the study. Also doses and types of drugs remained unchanged throughout the supplementation period.

Outcome measures: Table 2 indicates the initial and final physical activity levels of the patients. Physical activity assessments showed no significant inter- and intra-group changes.

No significant within-group differences in dietary intakes were observed. Similarly, between-group comparisons did not show any significant differences before and after the study (data not shown).

Table 3 shows the serum lipid profile of ALA and placebo groups and their comparison before and after the intervention. As shown in Table 3, lipid profile analysis between the basal and 8th week values revealed that ALA supplementation did not result in any statistically significant changes in serum lipids compared with the placebo group. Similarly, no significant within-group changes were observed.

Table 1. Baseline characteristics of the studied subjects

Characteristic	Placebo group (n= 32)	ALA group (n=33)	P-value
Age (years)	38.28±8.63*	36.09±8.77*	0.306 [†]
Height (m)	1.58± 0.06*	1.56± 0.07*	0.353 [†]
Body weight (kg)	72.52±12.60*	70.57±15.2*	0.576 [†]
Body mass index (kg/m ²)	29.02±4.71*	29±6.4*	0.986 [†]
DAS-28	2.14±.72*	2.1±.76*	0.850 [†]
Disease duration (years)	6.78±4.72*	7.26±4.9*	0.897 [†]
Prednisolone treatment, no. (%)	28 (87.5%)	29 (87.9%)	0.980
Methotrexate treatment, no. (%)	29 (90.6%)	28 (84.8%)	0.214
Hydroxychloroquine, no. (%)	21 (65.6%)	21 (63.6)	0.949
Sulfasalazine, no. (%)	2 (6.3%)	1 (3%)	0.317
Calcium & Vitamin D supplement, no. (%)	27 (84.4%)	25 (75.8%)	0.067
Folic acid supplement, no. (%)	22 (68.8%)	22 (66.7%)	0.573

Except where indicated otherwise, values are the number (%) of patients.

*Refers to values, which are the mean ±SD.

Except where indicated otherwise, p-value was calculated using Mann-Whitney's test.

[†]Refers to p-values calculated using Student's t-test.

ALA = Alpha-lipoic acid.

DAS-28 = Disease activity score in 28 joints.

Table 2. Within- and between-group comparative analysis of physical activity levels of the studied groups

Variable	Time	Placebo group (n= 32)			ALA group (n=33)			P-value [†]
		Low	Moderate	High	Low	Moderate	High	
Physical activity level, Frequency (%)	Baseline	21 (65.6%)	11 (34.4%)	0	27 (81.8%)	4 (12.1%)	2 (6.1%)	0.201
	8 Weeks	25 (78.1%)	7 (21.9%)	0	26 (78.8%)	7 (21.2%)	0	0.949
	<i>P-value</i> [‡]		0.125		1			

Values are frequency (%) of the patients.

[†]P-value calculated using Mann-Whitney's test.

[‡]P-value was calculated using Sign test.

ALA = Alpha-lipoic acid.

Table 3. Laboratory parameters of the studied patients. Within- and between-group comparative analysis of the serum levels of lipid profile

Variables		Placebo group (n= 32)	ALA group (n= 33)	P-value †
TG (mg/dL)	Baseline	119.9±52.6	117.27±78.73	0.878
	8 weeks	119.87±53.24	114.24±65.56	0.724
	Mean change (95% CI)	-0.03 (-10.65, 10.59)	-3.03 (-12.4, 6.33)	
	P-value‡	0.995	0.512	
TC (mg/dL)	Baseline	178.34±29.06	167.73±33.6	0.188
	8 weeks	184.28±36.76	168.03±29.04	0.285
	Mean change (95% CI)	5.93 (-4.95, 16.82)	0.3 (-10.33, 10.93)	
	P-value‡	0.275	0.954	
HDL-C (mg/dL)	Baseline	48.43±13.43	46.09±13.53	0.497
	8 weeks	47.09±14.36	43.04±13.94	0.484
	Mean change (95% CI)	-1.33 (-6.24, 3.56)	-3.04 (-7.67, 1.57)	
	P-value‡	0.581	0.188	
LDL-C (mg/dL)	Baseline	104.95±32.08	96.51±25.71	0.27
	8 weeks	110.38±22.56	102.32±26.61	0.57
	Mean change (95% CI)	5.43 (-5.08, 15.94)	5.81 (-1.88, 13.51)	
	P-value‡	0.299	0.133	

Values are the mean ± SD.

†P-value was calculated using Student's t-test at baseline, or ANCOVA after 8 weeks.

‡P-value was calculated using paired t-test.

ALA = Alpha-lipoic acid.

TG = triglyceride, TC = total cholesterol.

HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.

Discussion

The results of this study showed no significant within- and between-group changes in serum lipid profile levels after 8 weeks of ALA supplementation. Due to the inflammatory nature of their disease and being affected by traditional risk factors of atherosclerotic CV disease like dyslipidemia, the RA patients are susceptible to develop CV disease (5, 32). Therefore, prevention or treatment of dyslipidemia as a part of cardiovascular risk management might be one of the useful approaches to limit excess mortality rate in these patients. In this regard, adjuvant therapies and dietary approaches have received more attention during recent years.

A number of studies provided evidence suggesting that ALA supplementation acts as a potent anti-lipidemic agent, which lowers the plasma level of TG, TC and LDL-C, and elevates HDL-C (23, 33, 34). However, to our knowledge, this is the first clinical trial aimed at investigating the effects of ALA on lipid profile in RA patients.

Our findings are in agreement with the results of a study on a rat model of diabetes by Salama et al. (35) in which the decrease in TG and TC levels after ALA supplementation (100 mg/kg for 30 days) was insignificant. In a randomized double-blinded placebo-controlled clinical trial involving patients with type 2

diabetes mellitus, Oliveira et al. (26) found no improvement after 4 months in the lipid fractions in the groups receiving ALA (600 mg/day) and Vitamin E (800 mg/day), alone or in combination. However, the observed differences in the lipid profile were not significant. To some extent, our evidence is consistent with the outcomes provided by Khabbazi et al. (27), who indicated that 600 mg/day ALA treatment for 8 weeks in hemodialysis patients did not result in statistically significant alterations in their serum HDL-C, LDL-C, TC and TG levels as compared with the placebo group. They further showed that, despite other lipid profile parameters, the mean HDL-C concentrations increased significantly in the ALA supplemented group during the study. In another study, Salwa et al. (36) indicated that 600 mg/day ALA supplementation for 2 months in diabetic patients lowered the serum levels of TG and VLDL-C significantly, while serum levels of cholesterol, HDL-C and LDL-C did not show any significant improvements in comparison with the diabetic untreated group. On the other hand, there are studies reporting improvement in all lipid profile components by ALA supplementation. Seo and his colleagues (23) conducted a study on 3 groups of rats fed with high fat diet (HFD) and a normal control group. In two of the HFD groups, the diet was supplemented with

two dosages of ALA (0.25% and 0.5% of the diet). After 4 weeks significant decrease in serum TG and LDL-C, and significant increase in serum HDL-C were observed in the groups received ALA compared to the third HFD group. In the context of effect on TC levels, the 0.25% ALA group was not significantly different from the non-ALA HFD group, whereas the 0.5% ALA group showed a significant decrease in total cholesterol levels compared to the non-ALA HFD group. In another study on obesity-induced hypertriglyceridemic ZDF (fa/fa) rats, ALA supplementation (200 mg/kg body weight daily for 2 weeks) not only stopped the progression of hypertriglyceridemia, but also normalized serum TG levels (37). Similarly, Zhang et al. (24) through a study on obese subjects with impaired glucose tolerance (IGT) demonstrated that 2-week ALA treatment (600 mg intravenously once daily) led to significant decrease in the plasma levels of TG, TC, LDL-C and VLDL-C as compared to the control group. Also positive effects of ALA on serum lipid profile have been reported in some other studies (38-40).

Inconsistent findings of different studies may result from different types of studies, and physiological circumstances (e.g. different types of disease), as well as the dose, duration and way of administration of ALA. Elimination of gut role in ALA absorption (20-40%) and metabolism (17) could be a reason for different outcomes of studies with intravenous ALA administration compared to those with orally supplied ALA. In the context of lipid lowering effects of ALA reported in several animal studies, the dosage used in animal studies (e.g. 200 mg/kg) in comparison with human studies is often mega-dose of ALA, which could be considered as a justifying reason for differences between the results of animal and human studies.

The exact mechanisms by which ALA may affect blood lipids are still unclear. ALA can improve lipid profile through decreasing hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase activity, and/or by increasing lipoprotein lipase and lecithin cholesterol acyl transferase (LCAT) activities (31). Also ALA may normalize blood and liver TG by inhibition of hepatic lipogenic gene expressions and stimulation of TG-rich lipoproteins clearance (37, 41). It has recently been suggested that probably through activation of AMP-activated protein kinase, ALA causes blocking of acetyl-CoA carboxylase (ACC), leading to enhanced mitochondrial fatty acid β -oxidation (42). As another mechanism, it has been postulated that ALA, by its anti-inflammatory functions, may downregulate the endothelial lipase, which could result in improvement of HDL-C levels (27).

Inefficacy of ALA treatment in the present study may have resulted from the lipid levels of the studied patients.

In the present study, the average HDL-C levels in both groups were under the reference range of HDL-C for women (>50 mg/dL); this is in agreement with the results of studies, which revealed that chronic inflammation in RA appears to be inversely related to HDL-C levels (13, 14). However, TG, TC and LDL-C were within normal ranges. In this normal or nearly normal status, making significant improvement in lipid profile components using supplementation seems to be too difficult to achieve. Moreover, our sample size and duration of the intervention may have not been adequate enough to show the probable effects of ALA on lipids. Specially, regarding the available animal studies and Zhang et al.'s (24) study, higher doses of ALA supplementation may be needed to affect the serum lipid profile.

One of the limitations of the present study was that, despite some abnormalities started in HDL-C and, to some extent, in LDL-C, other lipid profile components were normal, and had not developed obvious dyslipidemia yet. This is probably due to the fact that the patients included in this study did not have active forms of RA (Disease activity scores ≥ 3.2 were considered as active form of RA), and the mean disease duration was not long enough to develop dyslipidemia. Lack of dyslipidemia could be considered as a reason for insignificant results of the study. The other limitation of this study was that serum concentrations of ALA were not assayed to confirm that the expected amount of ALA has been appeared in serum of patients. In addition, a group of healthy individuals was not incorporated in the study design to compare serum levels of ALA and lipid profile between the RA and healthy participants to achieve more reliable outcomes. Finally, due to some limitations, the study was not designed for longer duration with groups receiving different doses of ALA.

Conclusion: In the current study, no treatment benefits of ALA on the lipid profile levels in RA patients were observed. Effects of ALA supplementation on lipid profile should be further investigated in studies with larger sample size and longer duration in RA patients with established dyslipidemia.

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Conflicts of interest: There are no conflicts of interest. We are responsible for this paper's content.

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