Review

Alpha-lipoic acid supplementation affects serum lipids in a dose and duration-dependent manner in different health status

An updated systematic review and dose-response meta-analysis of randomized controlled trials

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Abstract: *Background*: Many studies have investigated the effect of alpha-lipoic acid (ALA) supplementation on lipid profile, and different results have been obtained from these studies. The current systematic review and dose-response meta-analysis was conducted to achive a strong conclusion about the effect of ALA supplementation on lipid profile including total cholesterol (TC), low- and high-density lipoprotein cholesterol (LDL, HDL) and triglycerides (TG). *Methods*: A systematic search was performed in PubMed, SCOPUS, ProQuest and Embase for randomized placebo-controlled human trials that examined the effect of ALA supplementation on lipid profile up to November 2020. The dose and duration of ALA supplementation for included studies were ranged between 300–1200 mg/d and 2–16 weeks respectively. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were used to evaluate the effect size. Cochran's Q and I^2 tests were also used to assess between-study's heterogeneity. In addition, subgroup analysis was performed to investigate potential sources of heterogeneity. Dose-response relationship was done using fractional polynomial modeling. *Results*: Among all eligible studies, 12 studies with a total number of 548 participants were selected. ALA caused a significant reduction on TC (WMD): −10.78 mg/dl, 95% CI: −20.81, −0.74, P=0.002), LDL (WMD: −10.88 mg/dl, 95% CI: −19.52, −2.24, P=0.014) and TG (WMD: −31.02 mg/dl, 95% CI: −49.63, −12.42, P<0.001). There was also a non-significant increaes in HDL concentrations. In addition, dose-response analysis showed a positive association between LDL ($P_{non\text{-}linearity}$=0.026), TG ($P_{non\text{-}linearity}$<0.001) and duration of intervention in a non-linear model. *Conclusion*: The present meta-analysis revealed the beneficial effects of ALA supplementation on TC, LDL and TG levels. Moreover, the beneficial effects of ALA supplementation on LDL and TG levels was duration-dependent.

Keywords: Alpha-lipoic acid, lipid profile, Cholesterol, Triglyceride, LDL, HDL, dose-response

Abbreviations

CVD: cardiovascular disease; ALA: Alpha-lipoic acid; LPL: lipoprotein lipase; LCAT: lecithin cholesterol acyltransferase; VLDL: very low-density lipoprotein; FAS: fatty acid synthase; ACC: acetyl-CoA carboxylase; RCT: randomized controlled trial; WMD: weighted mean difference; SD: Standard Deviation; CI: Confidence Intervals.

Introduction

Metabolic disorders are a set of pathophysiological conditions that result from metabolism abnormalities and energy imbalance [1]. Metabolic disorders increase cellular dysfunction, redox imbalance and lead to pre-oxidative status. Oxidative and inflammatory conditions are the basis of several diseases such as diabetes, cardiovascular complications, and tumor development. Therefore, investigating the clear link between oxidative stress and metabolic disorders can be effective and useful in the prevention and treatment of diseases [2]. Lipid profile management and lifestyle modification are effective in primary and secondary prevention of metabolic disorders such as cardiovascular diseases (CVD). Therefore, it is necessary to pay much attention to dietary supplements such as alpha-lipoic acid (ALA) and reveal their possible beneficial role in treatment of dyslipidemia [3, 4].

ALA, as a potent antioxidant, corrects lipid metabolism disturbances. As a sulfur containing compound, ALA is synthesized naturally in human body by lipoic acid synthase 11 in a very small amounts [5, 6]. ALA, also known as Thioctic acid, is chemically structured as 1, 2-dithiolane-3-pentanoic acid ($C_8H_{14}O_2S_2$); it has also two different enantiomers, including active isomer (R) and isomer (S). R-ALA, in the form of lipoyl lysine, is found in several animal foods in low amounts and daily consumption of ALA in these foods (e.g. heart, muscles, liver, and kidneys) is relatively low to achieve a healing effect [7]. Previous studies have proven the functions of ALA in neutralizing reactive oxygen species (ROS), regenerating endogenous antioxidants such as vitamins C, E, and glutathione (GSH), chelating metal ions, and repairing proteins that are damaged due to oxidation [6, 8].

Beside its anti-oxidative and anti-inflammatory properties, it is also involved in fat metabolism adipogenesis inhibition [4]. Evidence indicates that it exhibits favorable lipid-lowering responses through several mechanisms such as: inhibition of hypothalamic adenosine mono-phosphate (AMP)-activated protein kinase (AMPK) to reduce food intake (anti-obesity properties), stimulation of energy expenditure by regulating expression of uncoupling protein 1, inhibition of fatty acid synthesis, modulating hepatic βoxidation of fatty acids and decreasing hepatic lipogenesis [9]. In a study, ALA, caused a significant reduction in LDL and TC among high-cholesterol, high-fructose diet fed rabbits [10]. It seems that lipid lowering effects of ALA are generally, attributed to hepatic β-oxidation and free radical scavenging activities (Figure 1).

There are many RCT studies with inconsistent results about the effects of ALA administration on lipid profile. There is only one meta-analysis study that examined the effects of ALA supplementation on lipid profile with 11 trials [11]; while in the current study, as an updated systematic study and meta-analysis, we evaluated the effects of ALA supplementation on lipid profile in a dose-response manner.

Method

This study is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Table E1 in electronic supplementary material, ESM 1.

Search strategy

A systematic search on PubMed, SCOPUS, ProQuest, and Embase for randomized placebo-controlled human trials was performed with no language restrictions; the studies that examined the effect of ALA supplementation on lipid profile up to November 2020 were included. A sample search strategy for PubMed database was as follows: "Alpha-lipoic acid" OR "α lipoic acid" AND "serum lipids" OR "plasma lipids" OR "low-density lipoprotein cholesterol" OR "LDL" OR "high-density lipoprotein cholesterol" OR "HDL" OR "total cholesterol" OR "TC" OR "triglyceride" OR "TG". Hand-searching was performed using a reference list of all related articles, previous review studies, and meta-analysis. The study was carried out using the PICO (Population, Intervention, comparator, and outcome) design. PICO stands for Population (general adult populations), Intervention (supplementation with ALA), Comparison (with control or placebo groups), and outcomes (changes in TC, LDL, HDL and TG) (Table E2 in ESM 1).

Eligibility criteria and study selection

Published articles with the following criteria were included in the current study: (1) Randomized placebo-controlled trials (either crossover or parallel design) that were conducted among adults (18 years or older), (2) Studies that administered only ALA, and (3) Studies that reported TC, LDL, HDL and TG levels before and after the intervention. If several studies with the same data set were recognized, only the most complete one was included in this meta-analysis. The studies with observational, experimental and in vitro design, reviews, grey literature (comments, book chapters, letters, conference papers, and seminars) and the studies that were conducted among children and pregnant women were excluded. Search results and literature review uploaded to EndNote software (X8 version, for Windows, Thomson Reuters). Retrieved citations were merged and the duplicates were removed. Two independent authors evaluated and reviewed all of the selected articles according to their title, abstract and then full-text for possible eligibility. Finally, the articles which did not meet the eligibility criteria were excluded. The full text of the relevant manuscripts were retrieved and evaluated. Any disagreement between the researchers was discussed and resolved.

Data extraction

Two independent researchers screened the full text of selected eligible articles, and extracted the following characteristics: name of the first author, geographical area, year of publication, sample size, age and sex of participants, study design, the health status of participants, duration of intervention, ALA dosage, number of study participants in placebo and treatment groups, baseline BMI of participants

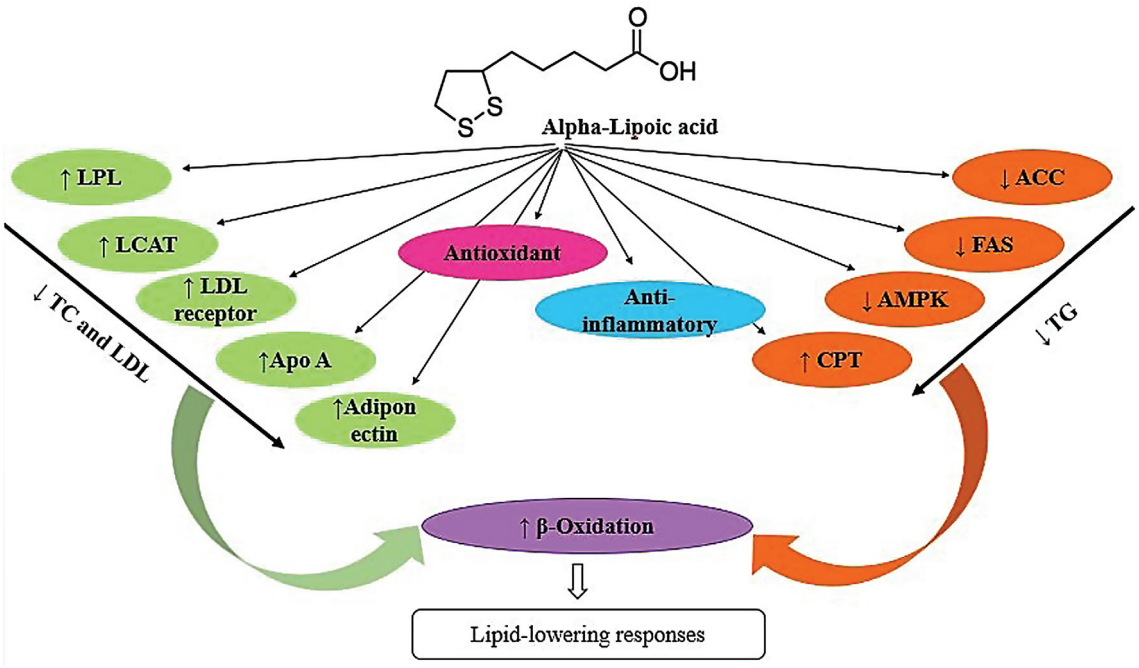

Figure 1. The role alpha-lipoic acid in fat metabolism (LPL: Lipoprotein lipase; LACT: Lecithin-cholesterol acyltransferase; LDL: Low density cholesterol; Apo A: Apo protein A; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; AMPK: AMP-activated protein kinase; CPT: Carnitine palmitoyl transferase I; TC: Total cholesterol; TG: Triglycerides).

and the outcomes (mean and standard deviation (SD) of the TC, LDL, HDL and TG).

Quality assessment

Two researchers separately evaluated the quality of selected studies according to the Cochrane risk-of-bias tool. This tool is composed of following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. According to the Cochrane tool, the studies were classified into three categories: "low", "high" or "unclear" risk of bias. The quality of each study is considered "good", "fair" and "weak" when it has at least 3, 2 and less than 2 low-risk bias items respectively. Detailed explanations of the study quality are shown in Figure 2. Moreover, the details of quality assessment of included studies are presented in Table E3 in ESM 1.

Data synthesis and statistical analysis

We examined the effect of ALA supplementation on TC, LDL, HDL and TG levels in mg to deciliter. To evaluate the overall effect sizes in the meta-analysis, the mean differences and SD of the lipid profile between the intervention and control groups were used. The effect size was defined as the mean weighted mean difference (WMD) and 95% CI. The non-linear potential effects of ALA duration and dosage of intervention on lipid profile were examined using fractional polynomial modeling. Cochrane Q and I-square (I^2) tests were used to determine the heterogeneity within and between the study. I^2 values of less than 25%, 25%–50% and more than 50% were considered as no heterogeneity, moderate heterogeneity and high heterogeneity levels. P-values less than 0.1 and/or I^2 more than 50% were representative of significant heterogeneities. Subgroup analysis was performed to identify the potential sources of heterogeneity. Sensitivity analysis was performed to evaluate the effect of each study on the overall outcome according to the duration of intervention, ALA dosage, and baseline values of lipid profile, health status, sample size, region, sex, and quality of the study. Also, Egger's and Begg's regression tests with corresponding funnel plots were used to evaluate the publication bias. Statistical analyzes were performed using software Stata version 13 and P-values less than 0.05 were considered statistically significant.

Results

Search results

A total of 847 studies identified through searching in electronic databases. After removing 467 duplicates and

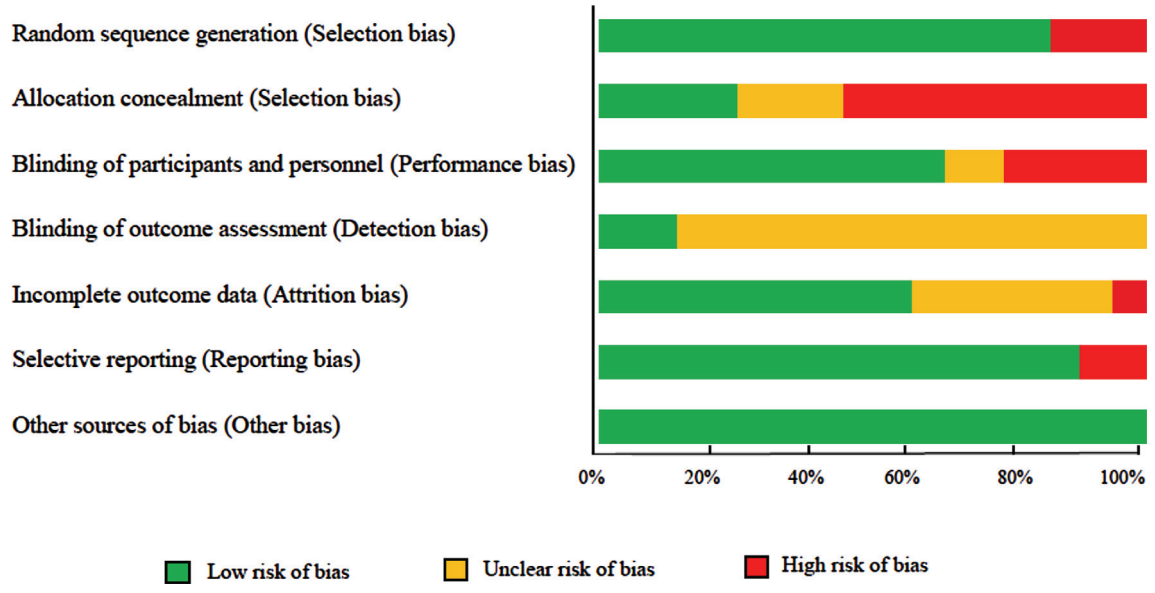

Figure 2. COCHRANE's tool for assessing risk of bias.

screening the remained studies, 428 studies were excluded according to title and abstract. Finally, 12 studies met the inclusion criteria and were included into the analysis. This process has been provided in Figure 3.

Study features

The study characteristics of 12 eligible articles are presented in Table 1. A total of 548 participants were included in the present meta-analysis aged between 14 and 70 years old. All studies were conducted among both genders except one study that included just men [12]. Included studies were randomized, double-blinded, placebo-controlled trials that were performed between 2008 and 2020 and the majority of included studies were conducted in Iran [8, 9, 13] and China [10, 14, 15]. The ALA dosage was ranged from 300 [15, 16] to 1200 [8] mg/day and the duration of supplementation varied from 2 [10] up to 16 [17] weeks. The included studies were mostly performed among apparently healthy individuals except some of them that were performed among patients with type 2 diabetes [8, 12, 15, 16, 18], stroke [9], schizophrenia [6], end stage renal diseases [13], age-related macular degeneration (AMD) [14] and obesity [10].

The results of the meta-analysis of the effects of ALA supplementation on TC

Overall, eleven study that included 518 participants evaluated the effect of ALA supplementation on TC level [6, 8, 9, 10, 13, 14, 15, 17, 18, 19]. The effect size and the forest plot of the related random effect analysis is presented in Figure 4A. According to the results ALA supplementation was associated with 10.78 mg/dl reduction in blood TC (WMD: −10.78 mg/dl, 95% CI: −20.81, −0.74, P=0.002; I^2=63.6%, P=0.002) (Figure 4A). According to the Table E4 in ESM 1, study duration, dose, sample size, geographical locations and quality of studies were identified as possible sources of heterogeneity. It has been shown that the studies with supplementation period of more than 10 weeks, lower doses of ALA administration, and those which were conducted in USA had 0% heterogeneity.

The results of the meta-analysis of the effects of ALA supplementation on LDL

Totally 518 individuals were included from 11 studies that evaluated the effect of ALA supplementation on LDL [6, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19]. The related forest plot is provided in Figure 4B. Significant reduction in LDL was attributed to ALA supplementation (WMD: −10.88 mg/dl, 95% CI: −19.52, −2.24, P=0.014; I^2=78.1%, P=0.000) (Figure 4B). According to the subgrouping analysis, study duration, dosage of intervention, sample type, health status, geographical locations and quality were potent heterogeneity sources (Table E5 in ESM 1).

The results of the meta-analysis of the effects of ALA supplementation on HDL

Similarly, 11 studied that evaluated the effect of ALA supplementation on HDL with 518 participants were analyzed [6, 8, 9, 10, 12, 13, 14, 15], 17, 18, 19] and effect size of included studies are shown in Figure 3C (WMD: 2.82 mg/dl, 95% CI: −0.69, 6.40, P<0.001; I^2=85.7%, p<0.001) (Figure 4C). The results of subgrouping (Table E6 in ESM 1) revealed that study duration, supplementation dosage, health status, sample size, location,

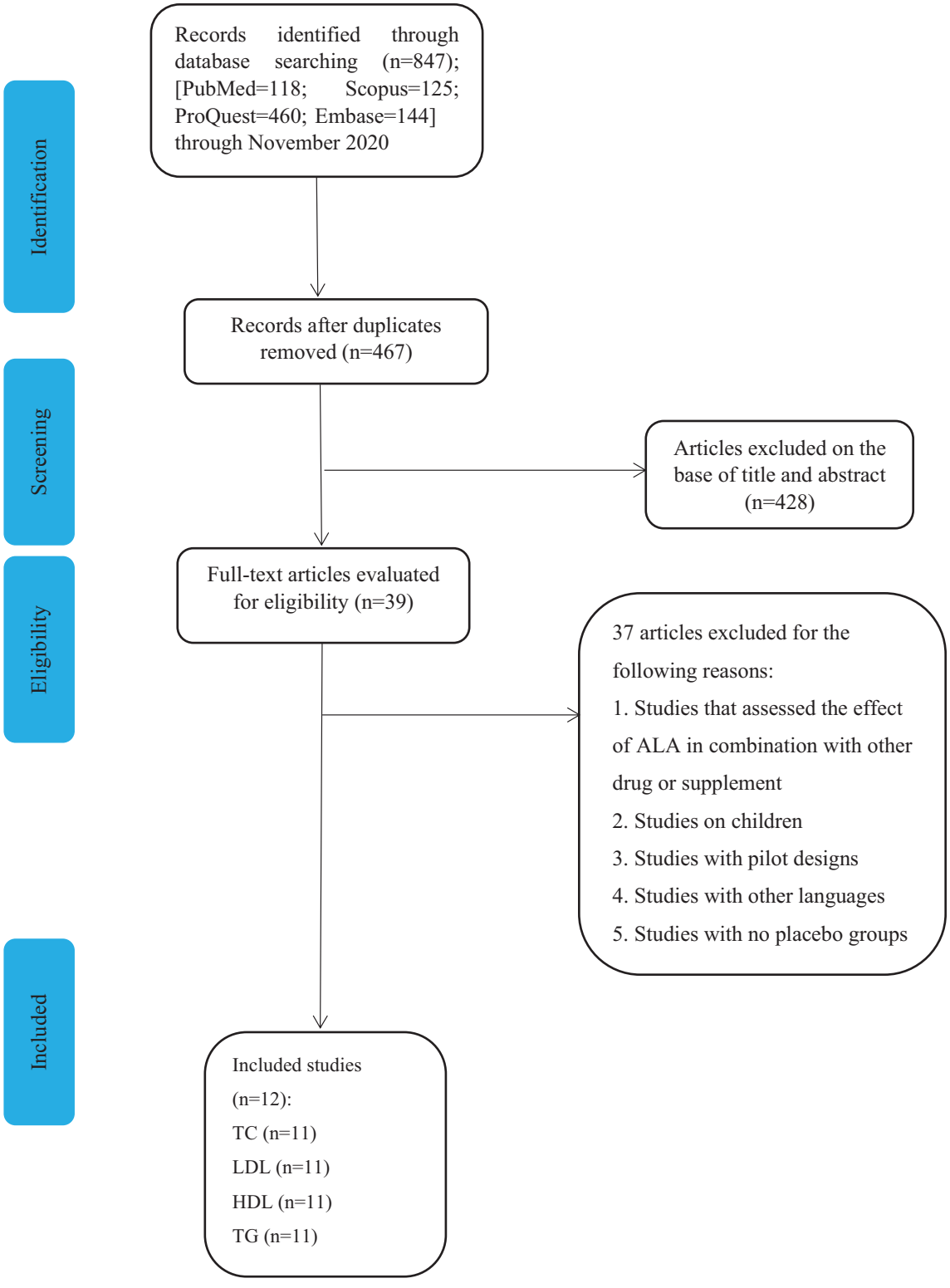

Figure 3. Flow diagram of study screening and selection process.

design and quality of the study were hetrogeneity sources. Furthermore, the studies that were performed among diabetic patinets or those that were performed in USA had reduced heterogeneity level.

The results of the meta-analysis of the effects of ALA supplementation on TG

Results indicated that ALA supplementation significantly reduced TG level (WMD: −31.02 mg/dl, 95% CI:

Table 1. General characteristics of included studies in the systematic review and meta-analysis

Journal/First author	Year/Country	Subjects	Sample size (IN/Cont)	Age range [(years) mean±SD)] (IN/CON)	Duration (week)	Intervention		Baseline BMI [(kg/m^2) ±mean±SD)] (IN/CON)	Time consumption	Design	Male %	Main results
						ALA dose mg/d	Placebo					
Oxid Med Cell Longev/ Baziar N [8]	2020/Iran	T_2DM	35/35	52.66±481/53.34±4.45	8	1200	Maltodextrin	25.4±1.25/24.93±1.26	30 minutes before meals	Double-blind, RCT	44.2	↓ Sig. TG in the ALA group (P<0.001)
Iran Red Crescent Med J/ Mohammadi V [9]	2017/Iran	Stroke	33/34	62.33±6.19/64.23±8.01	12	600	Wheat flour	165.68±8.95/165.23±9.29	1 hour before or 2 hours after lunch daily	Double-blind, RCT	Unclear	No significant differences in TC, LDL, and HDL in both groups. ↓ Sig. TG, TC and LDL ↑ Sig HDL in ALA group
Psychiatria Danubina/ Vidović B [6]	2014/Serbia	Schizophrenia	18/38	39.7±8.4/41.1±10.6	13	500	Unclear	26.7±5.4/24.9±3.2	30 min before meals	Controlled trial	35.7	↑ Sig. TG in patients group (p<0.05)
J Ren Nutr/Khabbazi T [13]	2012/Iran	ESRD on HD	31/32	53.83±13.29/54.04±13.96	8	600	Starch	25.46±4.18/26.16±4.75	After breakfast meal	Double-blind, RCT	68.2	↑ Sig. HDL in the ALA group
Ann Nutr Metab/ Sun YD [14]	2012/China	Age-related macular degeneration (AMD)	30/32	65.78±7.93/64.47±8.13	12	600	Unclear	24.5±7.9/25.1±9.2	Unclear	RCT	33.65	No significantly differences in HDL between 2 groups No significant differences in TC, TG, HDL and LDL in both groups.
J Clin Diagn Res/Udupa AS [16]	2012/India	T_2DM	25/25	53.5±1.4/53.8±2.1	12	300	Soft gelatin capsules	32.26±2.26/32.47±2.44	Unclear	Prospective, Double-blind, RCT, Single centered	53.85	↓ Sig. TC in ALA group.
Diabetes Res Clin Pract/ de Oliveira AM et al. [17]	2011/Brazil	T_2DM	26/26	38–75	16	600	Unclear	Unclear	Unclear	Double-blind, RCT		↓ Sig. TC in ALA group compared to placebo No significant differences in TC, HDL, LDL and TG
Obesity/Zhang Y [10]	2011/China	Obese patients with IGT	13/9	52.5±8.2/52.6±6.2	2	600	Normal saline	30.2±1.4/30.4±2.1	Unclear	Double-blind, RCT	45.4	↓ Sig. TG, TC, LDL
Am J Pharmacol Toxicol/ El-Nabarawy SK [12]	2010/Egypt	T_2DM	15/15	46.6±7.94	8	600	Unclear	30.02±1.85/28.74±2.43	Unclear	Controlled trial	100	↑ Sig. HDL in ALA group and compared placebo (P<0.01) ↑ Sig. TG, LDL in ALA group compared to control group
Arch Gerontol Geriatr/ Gianturco V [19]	2009/Italy	Non-insulin dependent diabetes mellitus	7/7	61±7/58±16	4	400	Unclear	Unclear	Unclear	Double-blind, RCT	57.1	↓ Sig. HDL in ALA group compared to control group (p<0.001) ↑ Sig HDL in ALA group compare to placebo
J Complement Integr Med/Lukaszuk JM [18]	2009/USA	T_2DM	13/7	21–65	13	600	Microcellulose	33.8±8.3/33.3±5.1	30 minutes before meals	RCT	50	No significant difference in TG, TC and LDL between two groups No significant differences in TC, HDL, LDL and TG between the groups
Clin Endocrinol/Xiang GD [15]	2008/China	IGT patients	21/21	51±8/51±6	Unclear	300	Sodium chloride	24·5±2·8/24·8±3.1	Before an oral glucose tolerance test (OGTT)	Double-blind, RCT	52.38	No significant difference in TC, LDL, HDL and TG between ALA group and placebo group at baseline.

ALA: alpha lipoic acid; IN: Intervention; CON: control; T_2DM: type 2 diabetes mellitus; ESRD: end stage renal disease; SD: standard deviation; HD: hemodialysis; IGT: impaired glucose tolerance; BMI: body mass index; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; RCT: randomized controlled trial; Sig.: significant.

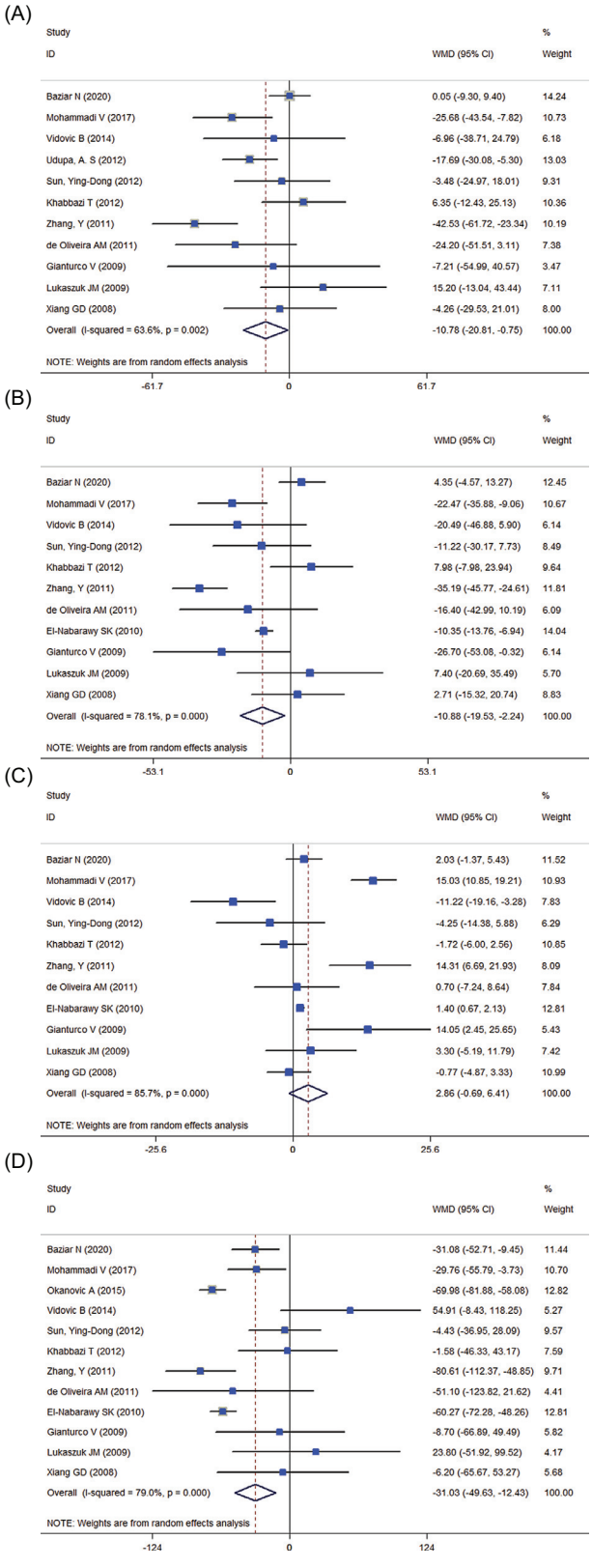

Figure 4. The forest plot showing the weighted mean difference (WMD) of the effect of ALA on cholesterol (A), LDL-C (B), HDL-C (C) and TG (D).

−49.63, −12.42, P<0.001; I^2=78.1%, p<0.001; Figure 4D). Moreover, duration of the study, ALA dosage, sample type, health status, sample size, design, location and quality of included studies were recognized as sources of heterogeneity (Table E7 in ESM 1).

The results of dose-response meta-analysis for the association between the dose and duration of ALA supplementation against lipid profile

The results of the association between ALA dosage and duration with lipid profile in a dose-responsive manner are presented in Figure 5 AH. Following dose-response analysis, ALA administration caused a decline in LDL ($P_{non\text{-}linearity}$=0.026) and TG ($P_{non\text{-}linearity}$<0.001) depending on the duration of the intervention in a non-linear model. No evidence of non-linearity for other parameters were observed.

Publication bias

Egger's and begg's tests were employed to identify publication bias for the included studies. No publication bias was reported for TC (Begg's test, P=0.815; Egger's test, P=0.743), LDL (Begg's test, P=0.815; Egger's test, P=0.925) and HDL (Begg's test, P=0.586; Egger's test, P=0.575) (Figure E1 in ESM 1). Although the results of Begg's test showed no publication bias for TG (P=0.217), but because of significant level for Egger's test (P=0.005), we performed fill and trim analysis (Figure E2 in ESM 1) and the effect size of random effect model was as follows: WMD: −54.106, OR: −73.084, −35.128; P<0.001.

Discussion

The statistical analysis revealed a favorable effect of ALA supplementationin on lipid profile. The findings indicated that ALA consumption caused a significant reduction in TC, LDL, TG levels among different health status. A non-significant increase in HDL values was also observed. In line with our meta-analysis, El-Farok et al [20] and Amom et al [21] reported that ALA consumption contributed to improvement of TC and LDL. It seems that cholestrol-lowering effcet of ALA is associated with a decreased level of plasma PCSK9, increased lipoprotein lipase (LPL), lecithin cholesterol acyl transferase (LCAT) and hepatic LDL receptor protein activities [22, 23, 24]. Another mechanism is the elevated level of apo-protein A and adiponectin syntheses which improve free fatty acid β-oxidation [9, 22]. Similarly, this finding was repeated in animal model carried out by Ide et al too [25]. In contrast, Sun et al [14] and Baziar et al [8] failed to show a significant effect of 600 and 1200 mg ALA consumption on TC and LDL levels [8].

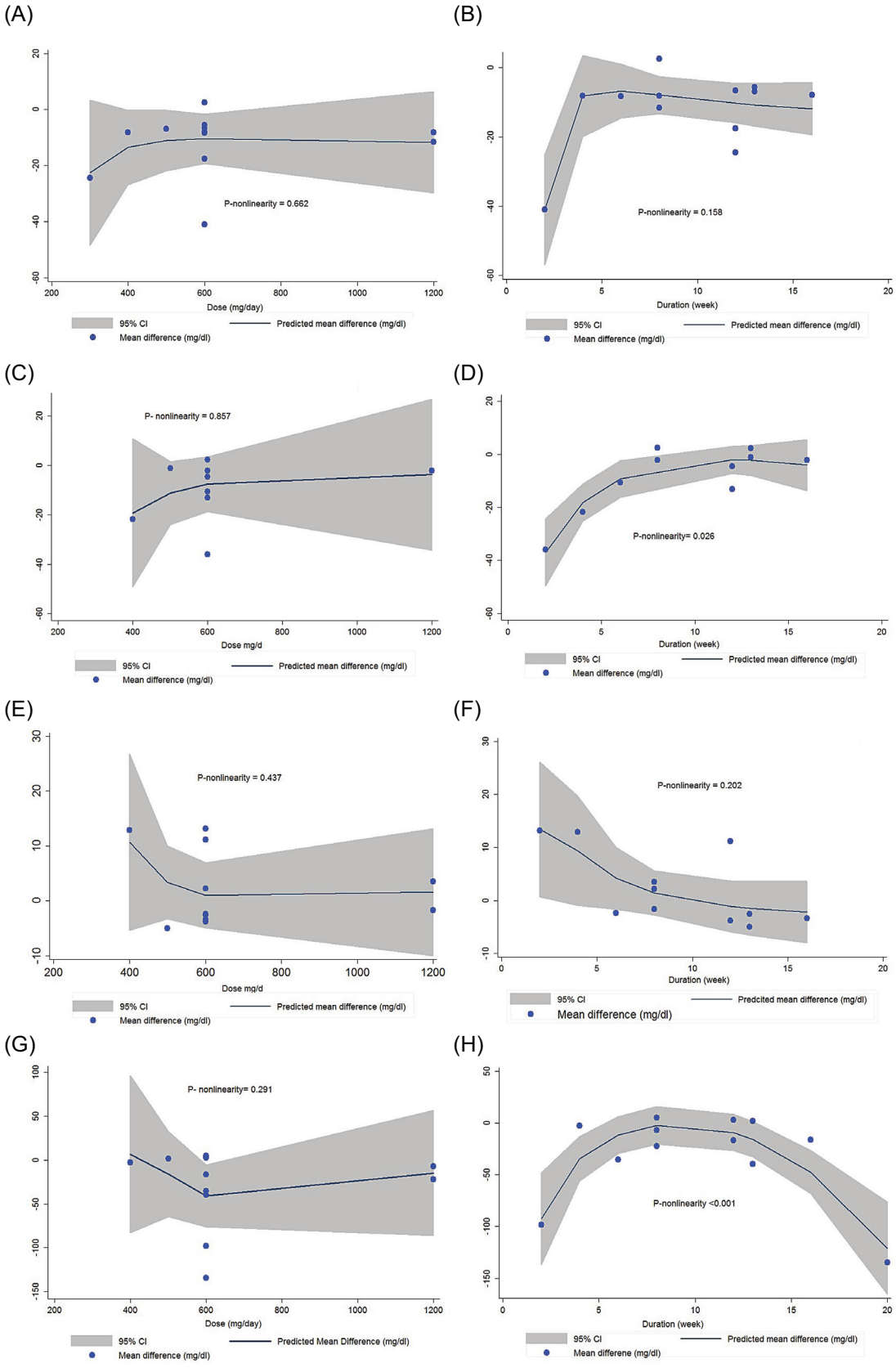

Figure 5. Dose-response association between the ALA dosage and duration with the study outcomes [TC (A, B); LDL-C (C, D) HDL-C (E, F) and TG (G, H)]. Linear relation (solid line) and 95% CI (gray area) of mean difference in study outcomes by 1 mg/d increment in ALA dosage or 1 week increment in ALA treatment duration.

Moreover, similar to our study, Mohammadi et al. showed a significant decreased level of TG by 600 mg ALA adminstration in patients with stroke [9]. Prior studies showed that ALA may protect the liver against TG accumulation through down-regulation of hepatic acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) expression; as a consequence, lipogenesis suppresses and expression of carnitine palmitoyl transferase Ia increases [26, 27]. Moreover, ALA administartion might be associated with inhibition of AMPK and ACC activity [28].

Our findings indicated a positive effect of ALA on serum HDL level which was not significant. Although several studies have shown a significant effect of ALA on increasing level of HDL [13], there are some studies that reported no significant change in HDL level due to ALA treatment [14]. The uderlying pathways involved in the effects of ALA on serum HDL is not clear. However, evidence indicates that inflammatory status may promote overexpression of endothelial lipase and redcued HDL level in mice [29, 30, 31].

These lipid modulating effects of ALA have been implemented through several mechanisms. So it seems logical to use it as a adjunct treatment in treating dyslipidemia. In addition, dose-responsive analysis revealed a significant association of LDL and TG level with the period of intervention in a non-linear model. It has been demonstrated that ALA supplemetation, up to 12 week, can improve LDL level while intervention period of more than 12 weeks has not beneficial effects in reducing LDL.

The current meta-analysis is the first comprehensive, dose-responsive and up to date study that evaluated the effects of ALA administration on lipid profile. The results were also subgrouped according to numerous factors including health status, sample type, age, gender and the study quality for finding the possible heterogeneity sources. However, the significant heterogeneity of the included studies limits the generalizability of our results.

Conclusion

The current study showed that ALA supplementation may have positive significant effects on LDL and TG concentrations. So it can be suggested as a add-on treatment in therapeutic protocol of patients with lipid disorders. Also, duration of supplementation with this compound is crucial to exert its beneficial effects on LDL and TG levels. Conducting additional studies with larger sample sizes in different populations is needed to shed the light in this concept.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000732

ESM 1. PRISMA Checklist (Table E1), Search strategies and the number of records according to different electronic database (Table E2), Quality of bias assessment of the included studies according to the Cochrane guidelines (Table E3), Results of subgroup analyses for the effects of ALA on serum TC concentrations according to intervention or participant characteristics (Table E4), Results of subgroup analyses for the effects of ALA on LDL-C concentrations according to intervention or participant characteristics (Table E5), Results of subgroup analyses for the effects of ALA on HDL-C values according to intervention or participant characteristics (Table E6), Results of subgroup analyses for the effects of ALA on TG values according to intervention or participant characteristics (Table E7), Begg's funnel plot (with pseudo 95% CIs) of the WMD versus the se (WMD) for studies evaluating the association between ALA supplementation and (A) TC (B) LDL-C (C) HDL-C and (D) TG values. CI, confidence interval; WMD, weighted mean difference (Figure E1), Filled funnel plot with pseudo 95% confidence limits for studies evaluating the association between ALA supplementation and TG values (WMD: −54.106, CI: −73.084, −35.128; P<0.001) (Figure E2).

References

1. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci. 2011;7(7): 1003–16.
2. Rani V, Deep G, Singh RK, Palle K, Yadav UCS. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. Life Sci. 2016;148:183–93.
3. Drakopoulou M, Toutouzas K, Stathogiannis K, Synetos A, Trantalis G, Tousoulis DT. Managing the lipid profile of coronary heart disease patients. Expert Rev Cardiovasc. 2016;14(11):1263–71.
4. Mahmoudinezhad M, Vajdi M, Farhangi MA. An updated systematic review and dose-response meta-analysis of the effects of Alpha-Lipoic acid supplementation on glycemic markers in adults. Nutrition. 2020;111041–85.
5. Vajdi M, Abbasalizad Farhangi M. Alpha-lipoic acid supplementation significantly reduces the risk of obesity in an updated systematic review and dose response meta-analysis of randomised placebo-controlled clinical trials. Int J Clin Pract. 2020;74(6):e13493–e507.
6. Vidović B, Milovanović S, Đorđević B, Kotur-Stevuljević J, Stefanović A, Ivanišević J, et al. Effect of alpha-lipoic acid supplementation on oxidative stress markers and antioxidative defense in patients with schizophrenia. Psychiatr Danub. 2014;26(3).

7. Rochette L, Ghibu S, Muresan A, Vergely C. Alpha-lipoic acid: molecular mechanisms and therapeutic potential in diabetes. Can J Physiol Pharmacol. 2015;93(12):1021–7.
8. Baziar N, Nasli-Esfahani E, Djafarian K, Qorbani M, Hedayati M, Mishani MA, et al. The beneficial effects of alpha lipoic acid supplementation on Lp-PLA2 mass and its distribution between HDL and apoB-containing lipoproteins in type 2 diabetic patients: A randomized, double-blind, placebo-controlled trial. Oxid Med Cell Longev. 2020;2020:1–13.
9. Mohammadi V, Khorvash F, Feizi A, Askari G. Does alpha-lipoic acid comsumption improve lipid profile in patients with stroke? A randomized, double blind, placebo-controlled clinical trial. Iran Red Crescent Med J. 2017;19(8):e58765–e71.
10. Zhang Y, Han P, Wu N, He B, Lu Y, Li S, et al. Amelioration of lipid abnormalities by α-lipoic acid through antioxidative and anti-inflammatory effects. Obesity. 2011;19(8):1647–53.
11. Mousavi SM, Mokhtari P, Asbaghi O, Rig S, Persad E, Jayedi A, et al. Does saffron supplementation have favorable effects on liver function indicators? A systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2021:1–13.
12. El-Nabarawy SK, Mohamed MAE, Ahmed MM, El-Arabi GH. α-Lipoic acid therapy modulates serum levels of some trace elements and antioxidants in type 2 diabetic patients. Am J Pharmacol Toxicol. 2010;5(3):152–8.
13. Khabbazi T, Mahdavi R, Safa J, Pour-Abdollahi P. Effects of alpha-lipoic acid supplementation on inflammation, oxidative stress, and serum lipid profile levels in patients with end-stage renal disease on hemodialysis. J Ren Nutr. 2012;22(2): 244–50.
14. Sun YD, Dong YD, Fan R, Zhai LL, Bai YL, Jia LH. Effect of (R)-α-lipoic acid supplementation on serum lipids and antioxidative ability in patients with age-related macular degeneration. Ann Nutr Metab. 2012;60(4):293–7.
15. Xiang GD, Sun HL, Zhao LS, Hou J, Yue L, Xu L. The antioxidant alpha-lipoic acid improves endothelial dysfunction induced by acute hyperglycaemia during OGTT in impaired glucose tolerance. Clin Endocrinol. 2008;68(5):716–23.
16. Udupa AS, Nahar PS, Shah SH, Kshirsagar MJ, Ghongane BB. Study of comparative effects of antioxidants on insulin sensitivity in type 2 diabetes mellitus. J Clin Diagnostic Res. 2012;6(9):1469–73.
17. de Oliveira AM, Rondó PHC, Luzia LA, D'Abronzo FH, Illison VK. The effects of lipoic acid and α-tocopherol supplementation on the lipid profile and insulin sensitivity of patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Diabetes Res Clin Pract. 2011;92(2):253–60.
18. Lukaszuk JM, Schultz TM, Prawitz AD, Hoffman E. Effects of R-alpha lipoic acid on HbA1c, lipids and blood pressure in Type-2 diabetics: A preliminary study. JCIM. 2009;6(1):1–16.
19. Gianturco V, Bellomo A, D'ottavio E, Formosa V, Iori A, Mancinella M, et al. Impact of therapy with α-lipoic acid (ALA) on the oxidative stress in the controlled NIDDM: a possible preventive way against the organ dysfunction? Arch Gerontol Geriatr 2009;49:129–33.
20. El-Farok DHM, El-Denshry ES, Mahmoud M, Asaaf N, Emam M. Lipid lowering effect of ginseng and alpha-lipoic acid in hypercholesterolemic patients. Glob J Pharmacol. 2013;7(3):298–306.
21. Amom Z, Zakaria Z, Mohamed J, Azlan A, Bahari H, Baharuldin MTH, et al. Lipid lowering effect of antioxidant alpha-lipoic acid in experimental atherosclerosis. J Clin Biochem Nutr. 2008;43(2):88–94.
22. Ichikawa T, Liang J, Kitajima S, Koike T, Wang X, Sun H, et al. Macrophage-derived lipoprotein lipase increases aortic atherosclerosis in cholesterol-fed Tg rabbits. Atherosclerosis. 2005;179(1):87–95.
23. Zhao Y, Jing Z, Lv J, Zhang Z, Lin J, Cao X, et al. Berberine activates caspase-9/cytochrome c-mediated apoptosis to suppress triple-negative breast cancer cells in vitro and in vivo. Biomed Pharmacother. 2017;95:18–24.
24. Amirkhizi F, Hamedi Shahraki S, Hosseinpour Arjmand S, Ebrahimi-Mameghani M. The effect of alpha-lipoic acid on liver function and metabolic marker in obese patients with non-alcoholic fatty liver disease: A double-blind randomized controlled trial. IRCMJ. 2018;20(3):e65925–e37.
25. Ide T, Azechi A, Suzuki N, Kunimatsu Y, Nakajima C, Kitade S. Effects of dietary α-lipoic acid enantiomers on hepatic fatty acid metabolism in rats. J Funct Foods. 2013;5(1):71–9.
26. Chen WL, Kang CH, Wang SG, Lee HM. α-Lipoic acid regulates lipid metabolism through induction of sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase. Diabetologia. 2012;55(6):1824–35.
27. Carrier B, Rideout TC. Anti-obesity and lipid-lowering properties of alpha-lipoic acid. J Hum Nutr Food Sci. 2013;1:1002–8.
28. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8(11):1288–95.
29. Jahangiri A. High-density lipoprotein and the acute phase response. Curr Opin Endocrinol Diabetes Obes. 2010;17(2): 156–63.
30. Kaysen GA. Biochemistry and biomarkers of inflamed patients: why look, what to assess. Clin J Am Soc Nephrol. 2009;4(Supplement 1):S56–S63.
31. Jaye M, Lynch KJ, Krawiec J, Marchadier D, Maugeais C, Doan K, et al. A novel endothelial-derived lipase that modulates HDL metabolism. Nat Genet. 1999;21(4):424–8.

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Conflict of interest
The authors declare that there are no conflicts of interest.

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