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Review

Alpha-lipoic acid supplement in obesity treatment: A systematic review and meta-analysis of clinical trials

Nazli Namazi [a], Bagher Larijani [b, **], Leila Azadbakht [c, d, e, *]

[a] Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[b] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[c] Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[d] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[e] Department of Community Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

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SUMMARY

Background & aims: Previous studies have supported positive roles of antioxidant supplements on weight-loss. One antioxidant supplement is Alpha-lipoic acid. However, recommending ALA as an anti-obesity supplement remains controversial. Accordingly, the purpose of the present study was to perform a meta-analysis on the effects of ALA supplement on anthropometric indices among adult subjects.
Methods: We searched five electronic databases till September 2016. Placebo-controlled clinical trials were included. Weighted Mean Difference (WMD) was pooled using a random-effects model.
Results: Findings of 12 included trials indicated that ALA supplement reduced body weight (WMD: −0.69 kg; 95% CI: −1.27, −0.10; $I^2 = 0\%$) and BMI (WMD: −0.38 kg/m^2; 95% CI: −0.53, −0.24; $I^2 = 0\%$) significantly compared to the placebo group. However, its effects on Waist Circumference (WC) was not significant (WMD: −0.30 cm; 95% CI: −1.18, 0.58; $I^2 = 17.8\%$). Stratification by health status indicated that ALA decreased WC in unhealthy subjects (WMD: −2.00 cm; 95% CI: −4.19, 0.19; $I^2 = 1.3\%$) more than healthy individuals (0.03 cm; 95% CI: −0.69, 0.75; $I^2 = 0\%$).
Conclusions: The present study revealed that supplementation with ALA slightly but significantly decreased body weight and BMI. Safe dosage for ALA is up to 1200 mg/day. However, it seems that ALA cannot be cost-effective. Further studies are needed to clarify the effects of ALA on metabolic parameter in unhealthy obese individuals.

1. Introduction

The increasing prevalence of obesity affects different populations throughout the world [1]. Obesity can trigger the development of several non-communicable diseases (NCDs) including type 2 diabetes, cardiovascular diseases, stroke and some types of cancer [2]. Furthermore, it brings a high cost to societies [3], results in reduced quality of life [4] and increases mortality and various morbidity rates [5]. Obesity-related complications necessitate the development of effective treatment strategies to decrease risk for obesity associated disorders [6].

Common treatments (calorie restricted diets and exercise) for managing body weight have been shown to be relatively unsuccessful over a long time period [7–11]. To increase compliance and adherence of obese subjects to calorie restricted diets and healthy dietary recommendations, complementary therapies such as anti-obesity supplements can be useful [6]. The pharmaceutical industry has attempted to develop effective weight loss products with no common serious side effects to human health and well-

Abbreviations: ALA, alpha lipoic acid; AMPK, AMP-activated protein kinase; BMI, body mass index; CI, confidence interval; PPAR, peroxisome proliferator-activated receptor; RCT, randomized clinical trial; NCDs, non-communicable diseases; SD, standard deviations; WC, waist circumference; WMD, weighted mean difference.

* Corresponding author. Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, PO Box: 1416643931, Tehran, Iran. Fax: +98 2188984861.
** Corresponding author. Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, PO Box: 1411413137, Tehran, Iran. Fax: +98 2188220052.
E-mail addresses: larijanib@tums.ac.ir (B. Larijani), azadbakhtleila@gmail.com (L. Azadbakht).

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being [12]. Since taking anti-obesity medications and supplements has become increasingly popular among obese subjects, it is important to evaluate the efficacy of available anti-obesity products [13]. Evidence has supported beneficial effects of several antioxidants supplements such as phenolic compounds (eg. quercetin, myricetin, catechin, procyanidin, reserveratol), some vitamins and minerals (eg. vitamin C, vitamin E, zinc, selenium) on weight-loss and obesity complications [14,15]. Investigations on anti-obesity characteristic of antioxidants have indicated that they can inhibit adipocyte differentiation, reduce fat absorption from gastrointestinal tract, suppress lipogenesis and cause apoptosis in adipocytes [16]. Based on a review study, antioxidants can affect several receptors and enzymes including peroxisome proliferator-activated receptors (PPAR), adenosine mono phosphate activated protein kinase (AMPK), and mitogen-activated protein [16,17].

Antioxidant supplements have shown different efficacy on obesity management. For instance, a meta-analysis demonstrated that green tea catechin vs. placebo had a slight reduction (0.14 kg) effect on body weight with no serious side effects. However, some studies reported mild gastrointestinal problems following catechin consumption [18]. Based on a clinical trial, zinc supplementation decreased body weight (1.7 kg) in obese children with no adverse effects after 8 weeks [19]. According to a systematic review, there are limited clinical trials with contrary results on resveratrol, quercetin and hesperidin supplements in which their anti-obesity effects were examined. The most reduction rate in body mass index (BMI) following taking aforementioned supplements was 1.3, 0.5, 0.2 kg/m^2, respectively and they were well-tolerated [20].

Another antioxidant supplement that has generated interest is α-lipoic acid [21]. Alpha lipoic acid, or thiocitic acid, is an antioxidant compound which contains sulfur and eight carbons, and is a cofactor for mitochondrial respiratory enzymes [22]. The human body can synthesize small amounts of ALA [23]. ALA can scavenge free radicals, activate antioxidant systems, and also affect inflammatory markers [22]. It also has unique characteristic. The solubility rate of ALA in fat and water is similar. Moreover, it has been reported that lipoate/dihydrolipoate system has a low redox potential power. Therefore, ALA can play as a reduction for oxidized forms of components with antioxidant properties and neutralize reactive oxygen species. Thus, it called as antioxidant of antioxidants. Additionally, most of clinical trials reported that ALA is safe and well-tolerated [24]. Apart from its role in metabolic processes, ALA can improve metabolic disorders, neuron degeneration, rheumatoid arthritis, diabetic polyneuropathy, and body weight [21].

ALA can promote body weight and fat mass loss through its ability to suppress hypothalamic AMP-activated protein kinase (AMPK) and decrease dietary energy intake [25,26], reduce lipoprotein lipase activity [23], increase energy expenditure [22,27], lipolysis [28], and insulin sensitivity [29] and inhibit lipogenesis [28]. Furthermore, clinical trials have revealed that ALA is safe and no serious adverse effects have been reported yet [30,31].

Despite reported anti-obesity characteristics of ALA in some clinical trials [22,28,30,32], several studies did not show positive effects of ALA on weight reduction [33–35]. Therefore, taking an ALA supplement to promote weight loss remains controversial. Discrepancies in findings might be the result of differences in study design, characteristics of study samples, dosage and duration of the studies. To the best of our knowledge, no systematic review and meta-analysis study evaluates anti-obesity effects of ALA. Accordingly, the aim of the present study was to summarize the effects of ALA on body weight, BMI, waist circumference (WC), and its efficacy in adult subjects, using data from randomized clinical trials (RCT).

2. Materials and methods

2.1. Databases and search strategy

The present meta-analysis was conducted and reported based on the PRISMA guideline [36]. We searched PubMed/Medline (www.pubmed.com), Scopus (www.scopus.com), Web of Science (webofknowledge.com), the Cochrane Library (www.cochranelibrary.com) and Google Scholar (scholar.google.com) electronic databases.

2.2. Study selection

Search terms included synonyms for exposure and outcomes as follows: “alpha-lipoic acid” OR “alpha lipoic acid” OR “α-lipoic acid” OR “α lipoic acid” OR “thiocitic acid” were combined with terms related to obesity: “Obesity” OR “weight” OR “energy intake” OR “appetite” OR “dietary intake” OR “fullness” OR “hunger” OR “satiety”. Strategy search in PubMed database was as follows: (“alpha-lipoic acid”[tiab] OR “alpha lipoic acid”[tiab] OR “alpha-lipoic acid”[tiab] OR “alpha lipoic acid”[tiab]) AND (obesity[tiab] OR weight[tiab] OR appetite[tiab] OR “energy intake”[tiab] OR “dietary intake”[tiab] OR “food intake”[tiab] OR “fullness”[tiab] OR “hunger”[tiab] OR “satiety”[tiab]) AND (“1900/01/01”[PDAT]: “2016/09/31”[PDAT]). Key terms were used in the primary search strategy and in a subsequent medical subheading (MESH) and free terms search. To identify publications not found from mentioned databases, the reference lists of all eligible papers were investigated.

All studies found from electronic databases and reference lists were entered into endnote software (EndNote X6, Thomson Corporation, Stamford, USA) and duplicate studies were removed. Two reviewers independently searched and entered studies to the Endnote program. After screening possible related studies by title and abstract based on inclusion and exclusion criteria, full texts of eligible studies were evaluated by each reviewer independently and reached consensus by discussion. Discussion about including a paper was based on pre-determined inclusion and exclusion criteria (see Section 2.3). If there was any disagreement in making decision about the methodological quality score of a paper or any discrepancy in data extraction, reviewers referred to a full text of paper and re-assessment it. Where the two reviewers did not get a consensus, they consulted with other reviewer and he (B.L) helped to make a decision.

2.3. Inclusion and exclusion criteria

The search was restricted to placebo-controlled clinical trials (either parallel or cross-over designs) with no language restriction till September 2016. Studies that evaluated taking ALA in adults and had placebo group were included. Other types of human studies (cross-sectional, cohort studies), animal, *In vitro* studies, grey literatures (book chapters, abstracts in conferences, interviews) and review papers were not included. Primary outcomes were body weight and BMI; therefore clinical trials which report at least one of these two parameters were included. Studies on the effects of ALA in combination with other component were also excluded.

2.4. Data extraction

Two independent reviewers extracted data from the full-text papers of eligible studies. Based on a pre-designed extracted sheet, essential data were collected. Discrepancies in decisions between two reviewers were resolved by discussion. Name of the first author, publication year, gender, age, sample size per comparison group, duration of study, sample characteristics, study

design and blinding, number of subjects lost to follow-up, daily dosage, type of ALA, outcomes, body weight, BMI and WC before and after the intervention, and adverse effects were extracted. Four studies did not report Mean ± SD of body weight, BMI or WC after the intervention; therefore we contacted the corresponding authors via e-mail to obtain sufficient data. Summary of included studies is presented in Table 1.

2.5. Quality assessment (risk of bias assessment)

To evaluate study quality, the Jadad checklist [37] was filled out by two independent reviewers for each eligible paper. The Jadad checklist consists of three main items (randomization, blinding, and description of dropouts). Clinical trials with score of 3 or more were considered as high quality studies.

2.6. Data analysis

All data were presented as weighted mean differences (WMDs) and standard deviations (SD) to present the size of ALA effect on anthropometric indices. Body weight and BMI were considered as primary outcomes, and WC and adverse effects of ALA were considered as secondary outcomes to examine the differences between ALA and placebo groups. Meanwhile there were differences in the study groups of the eligible studies and the treatment effects could likely vary based on disease background, WMDs were pooled in consideration with random-effects model using DerSimonian & Laird. The heterogeneity was examined using the I square (I^2) index. I^2 values less than 25%, between 25 and 50%, between 50 and 75% and over 75% were considered as low, moderate, severe and highly severe heterogeneity, respectively [38]. Subgroup analysis and meta regression were conducted to identify causes of between-study heterogeneity or the effects of different parameters on the effect size.

Potential clinical sources of observed heterogeneity were assessed based on the following categories: Baseline BMI, study duration, mean age, dosage, healthy status, adjusting for confounding factors and study quality (total score, randomization, blinding, drop out). The existence of publication bias was checked with visual evaluation of funnel plot for mean differences against study sample size and confirm with the Egger's regression model. Fill and trim was used for correcting effect size whenever a publication bias was existed. To examine the effect of each clinical trial on the pooled effect size, sensitivity analysis was conducted. Furthermore, the Jadad scoring was used to assess selection, performance, and detection and attrition bias in each included trial. All data analyses were carried out using Stata 12.0 software (StataCorp LP, College Station, TX).

3. Results

3.1. Study characteristics

After a primary search, we identified 2067 publications (including 1220 duplications) and three studies were found from Google Scholar and reference lists. In the title and abstract assessment step, 788 irrelevant publications were found and excluded. In the next step, the eligibility of 62 full texts was examined. After excluding 50 publications, finally 12 clinical trials were included in the systematic review and meta-analysis (Fig. 1). Reasons for excluding studies in the step of full text evaluation were as follows: irrelevant ($n = 21$), combination with other interventions ($n = 3$), study on adolescent ($n = 1$), multiple publications ($n = 5$), studies with no placebo group ($n = 4$), studies with missing data ($n = 1$) or not including primary endpoints ($n = 15$). To obtain missing data, we contacted the authors via email and three of six authors replied. The aims of one study, that their authors did not reply, were not changes in anthropometric indices. The baseline value for BMI was reported in the paper. However, the changes from baseline or values after the intervention were not reported. Therefore it was excluded. Two studies [29,39] reported just BMI and the authors did not reply to our emails about the body weight of participants at baseline and at the end of study. Therefore, just BMI was extracted from these two studies.

Characteristics of the 12 eligible trials are summarized in Table 1. Most studies were conducted in Asian countries ($n = 9$) [22,29,30,32–34,39–41] and the remaining studies were performed in Spain [28], New Zealand [42] and Germany [43]. Participants were in the age range of 37 and 62 years. Most included clinical trials evaluated the effects of ALA in both genders ($n = 9$). Two studies included women only [28,33] and one study examined men [22]. Baseline BMI of participants in each study showed that all trials except one [41] examined overweight and obese subjects (BMI > 25 kg/m^2). All papers assessed the effects of ALA alone except the study by Huerta et al. [28]. They recommended calorie restricted diets (−30% total energy expenditure) to both intervention and placebo groups. Most studies were conducted on unhealthy subjects ($n = 10$) and just two studies examined the effects of ALA on healthy obese individuals [28,32].

Ranges of recommended dosage for ALA varied between 300 and 1800 mg/day, and duration of treatment was between 8 and 48 weeks. In most studies, it was recommended to take ALA before meals. All trials except two [29,41], reported the effect of oral supplementation with ALA. In two mentioned studies, ALA recommended intravenously in subjects with impaired glucose tolerance. Most studies reported crude values for the effect size, while few studies ($n = 4$) [28,33,40,41] presented adjusted effect sizes for confounding factors.

Only in three included studies [28,30,32], anthropometric indices were considered as primary outcomes. For anthropometric indices, all studies measured body weight, height, and WC, and they were not based on self-reported information. However, the method for WC measurement was not explained. Therefore, the effect of the WC measurement on the overall effect size remained unclear.

The number of studies in which each primary outcome included was as follow: Body weight ($n = 9$) [22,28,30,32–34,40,42,44], BMI ($n = 10$) [22,28,30,32,33,39–44], WC ($n = 5$) [22,28,29,32,33]. Apart from the aforementioned anthropometric indices, some clinical trials reported additional indices such as body fat mass, hip circumference and waist to hip ratio. Meanwhile, these indices were reported in a few studies, this did not allow meta-analysis and, thus they were not considered in the current meta-analysis.

3.2. Study quality and risk of bias findings

Quality score of each clinical trial is presented in Table 2. The eligible papers had the quality score of 1–5 out of 5. Of 12 trials, 9 studies had high quality (score ≥ 3) [22,28–30,32,33,40,42,44]. All studies except one [39] were randomized, and the randomization method was explained in five studies [22,32,33,40,42]. Blindness was reported in nine studies [22,28–30,32,33,40,42,44], and in four studies, presented information indicated that blinding was sufficient [32,33,40,42]. All studies except two [22,34], reported numbers of participants that dropped out and their reasons. Most studies had randomization design. Therefore, selection bias cannot be considerable. However, blinding was not performed for all studies. Therefore, performance bias and detection bias existed. Dropout rates in one study [44] were noticeable, and attrition bias might also exist.

Table 1
Summaries of clinical trials included in the meta-analysis.

Author/year	Subject (gender)	Mean age (year)	Mean BMI (kg/m^2)	Sample size	Sample after drop out	Study design (blinding)	Other intervention	Dosage (mg/day)/ number & form	Time consumption	Duration (wk)	Side effect (withdrawal)	Outcomes
Kim et al., 2016	Overweight Stable patients with schizophrenia M/F	40	28.4	22	20	R/P Double	No	1200–1800 Mean: 1620 ± 290 6 capsules (divided in 3 times)	30 min before each main meal	12	Skin eruption ($n = 1$)	↓Body weight ↓Visceral fat -BMI -Abdominal fat -Subcutaneous fat
Huerta et al., 2016	Overweight and obese healthy women	38.5	32.8	54	42	R/P Double	Hypocaloric diet (−30% TEE)	300/3 capsules (divided in 3 times)	30 min before each main meal	10	Not reported	↓Body weight ↓BMI ↓WC ↓HC ↓Energy intake
Gargari et al., 2015	Women with rheumatoid arthritis	37	29	70	65	R/P Double	No	1200/2 capsules (divided in 2 times)	30 min before breakfast & dinner	8	Not reported	-Body weight -WC
Mohammadi et al., 2015	Men with spinal cord injury	38	27.8	58	58	R/P Double	No	600/1 capsule	30 min before breakfast	12	Not clear	↓Body weight ↓BMI ↓WC ↓Fat and energy intake
Okanovi, 2014	Obese with T2D M/F	62	31	60	60	No explanation	No	600/1 capsule	Not reported	20	Not clear	↓BMI
Manning et al., 2013	Metabolic syndrome subjects M/F	56	31	74	74	R/P Double	No	600/1 capsule	30 min before food (not clear)	48	Not reported	-Body weight -BMI
Khabbazi et al., 2012	Patients with renal disease M/F	54	25.5	63	52	R/P Double	No	600/1 capsule	30 min before breakfast	8	Not clear	-Body weight -BMI
Ansar et al., 2011	Type 2 diabetes M/F	50.5	28	57	47	R/P Double	No	300/3 capsules (divided in 3 times)	30 min before each main meal	8	Not clear	-Body weight
Koh et al., 2011	Obese subjects M/F	41	33	360	228	R/P Double	No	1200 (6 tablets) 1800 (9 tablets) divided in 3 times	30 min before each main meal	20	1200/1800 Fever: 1 Epigastric soreness: 3; Itching sensation: 3	↓Body weight ↓BMI ↓WC ↓Fat mass
Zhang et al., 2010	Obese subjects with impaired glucose tolerance M/F	52	30	35	22	R/P Double	No	600/intravenously (with 250 mL normal saline)	Once a day (time was not reported)	2	Not clear	-BMI -WC
Xiang et al., 2010	Subjects with impaired fasting glucose M/F	59	23.3	60	60	R/P Double	No	600 Intravenously (with 250 mL 0.9% sodium chloride)	Once a day (time was not reported)	3	Not clear	-BMI
Ziegler et al., 1997	Type 2 diabetes M/F	58	–	73	56	R/P Double	No	800 (4 tablets)	Not reported	16	Not clear	-Body weight

BMI: body mass index; WC: waist circumference; HC: hip circumference, HTN: hypertension; DM: diabetes mellitus; R/P: randomized/placebo; TEE: total energy expenditure.

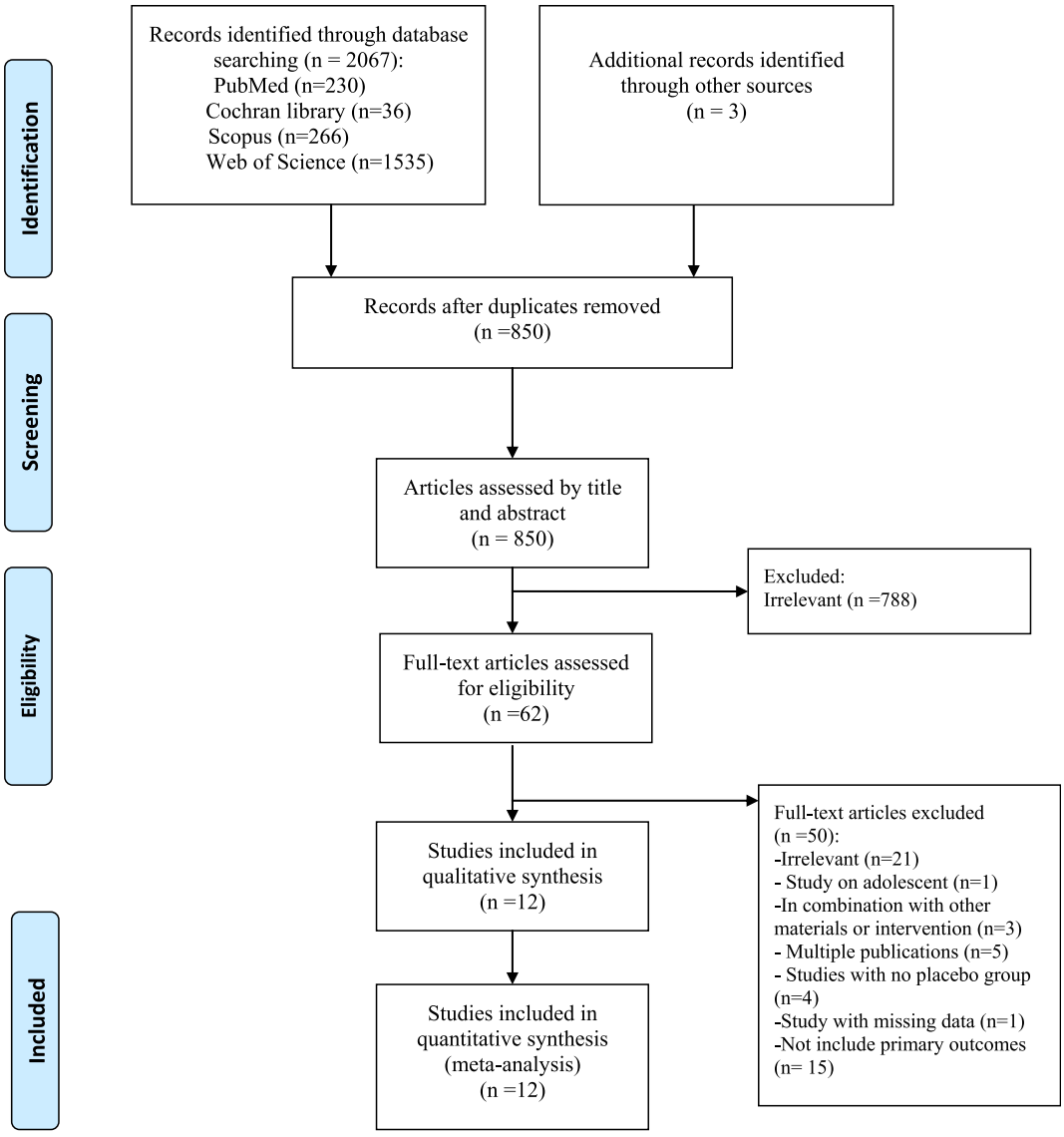


Fig. 1. Selection steps of included clinical trials.

3.3. Systematic review findings

Based on the current systematic review, four studies reported positive effects of ALA on weight loss [22,28,30,32]. However, five studies found that ALA cannot reduce weight considerably [33,34,40,42,44]. For BMI changes, four studies reported a significant reduction in BMI in the ALA group compared to the placebo group [22,28,32,39]; nevertheless BMI changes in several trials were not significant [22,29,30,32,40–42]. Few studies assessed the effects of ALA on WC [22,29,32,33,45]. Among them, three trials reported favorable effects of ALA on reduction in WC [22,28,32]. Differences in baseline values, individual characteristics, disease history, dosage and duration of study are possible factors that affect such variants.

Table 2
Metholodological quality scores for included studies using Jadad scale.

Study	Randomization	Blinding	Description of withdrawal	Total score
Kim et al., 2016	1	1	1	3
Huerta et al., 2015	1	1	1	3
Gargari et al., 2015	2	2	1	5
Mohammadi et al., 2015	2	1	0	3
Okanovi et al., 2014	0	0	1	1
Manning et al., 2013	2	2	1	5
Khabbazi et al., 2012	2	2	1	5
Ansar et al., 2011	1	0	0	1
Koh et al., 2011	2	2	1	5
Zhang et al., 2010	1	1	1	3
Xiang et al., 2010	1	0	1	2
Ziegler et al., 1997	1	1	1	3

3.4. Adverse effects

In two trials, side effects for supplementation with ALA were reported [30,32]. In the study by Koh et al., four subjects withdrew due to itching and urticaria. In addition, four subjects reported fever and did not complete the study. It was observed in three and one subjects who consumed 1800 and 1200 mg/day ALA, respectively. Epigastria soreness was also reported in subjects taking dosage of 1200 mg/day. However, only significant differences were observed in itching sensation between the ALA and placebo groups [32]. In the study by Kim et al., one subject withdrew due to skin

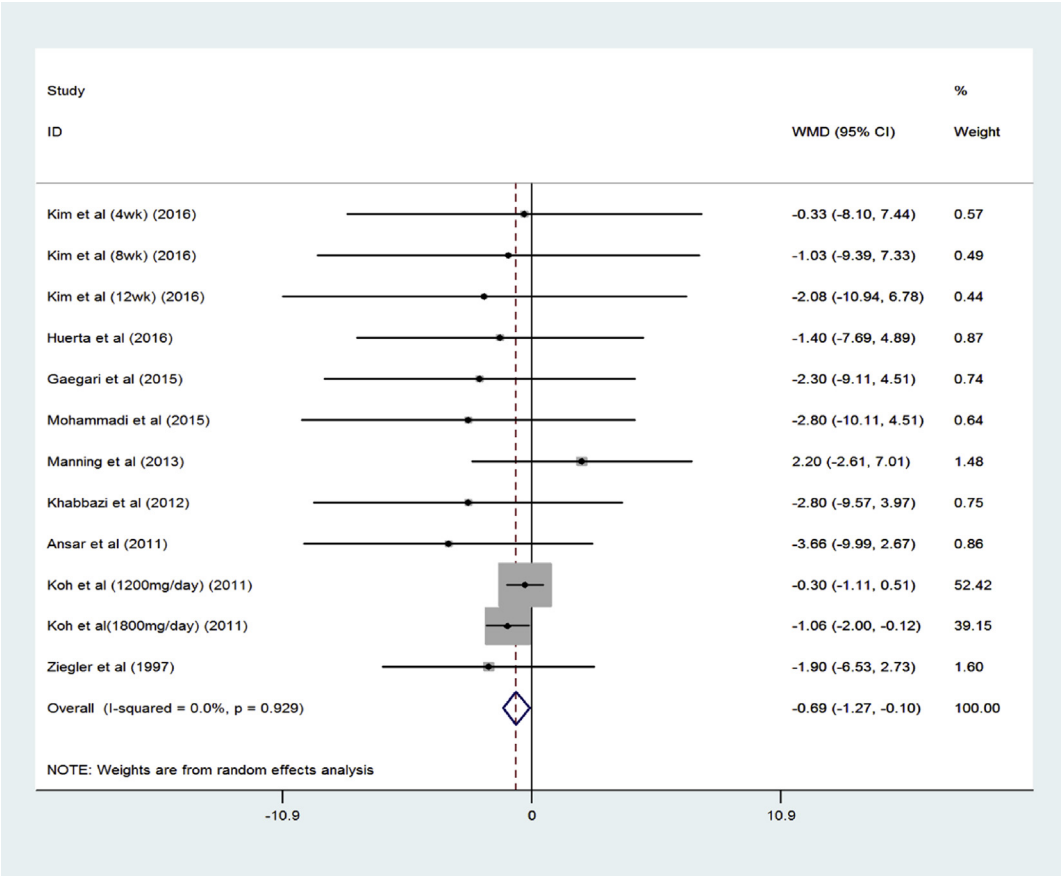


Fig. 2. Forest plot of weighted mean difference (WMD) in body weight between supplementation with alpha-lipoic acid and placebo group.

symptom after taking a mean daily dosage of 1620 mg. Furthermore, gastrointestinal disorders were reported [30]. However, reported problems were mild and no one withdrew due to these adverse effects. Among 12 included trials, three studies did not report side effects for ALA [28,33,42] and in the remaining studies, the adverse effect of ALA was unclear [22,29,34,39,40,44,46].

3.5. Quantitative synthesis

3.5.1. Body weight

This meta analysis was performed on 12 datasets of the 9 included studies. One study evaluated the effects of ALA over three periods of time (after 4, 8 and 12 weeks) [30] and one study assessed two different dosages of ALA (1200 and 1800 mg/day) compared to the placebo group [32]. Therefore, the meta-analysis overall consisted of 12 effect sizes.

The pooled WMD for the effects of ALA on body weight compared to the placebo group was −0.69 kg (95% CI: −1.27, −0.10; $p = 0.02$) with a minimum heterogeneity ($I^2 = 0\%$) (Fig. 2).

To examine the effect of each study on the pooled effect size, we conducted a sensitivity analysis. There were two studies with different design or measurement tools. One study evaluated the effects of ALA supplement along with a low-calorie diet compared to placebo and calorie restricted diet [28]. Sensitivity analysis showed that this clinical trial did not alter the overall effect size (WMD: −0.67 kg; 95% CI: −1.2, −0.09). Besides in another trial due to study sample (men with spinal cord injury), weight measurement was different from other studies [22]. However, based on sensitivity analysis this trial did not modify the pooled effect size (WMD: −0.67 kg; 95% CI: −1.2, −0.08). Furthermore sensitivity analysis revealed that Ziegler et al., study with considerable dropout ($n = 17$) [44] did not have noticeable effect on the overall weight changes (WMD: −0.66 kg; 95% CI: −1.2, −0.07).

For evaluation of the effects of study quality (score of <3, ≥3), baseline BMI (25–30 kg/m^2, ≥30 kg/m^2), age (<41, ≥41 years), adjustment for confounding factors (yes, no), study duration (<10 wk, ≥10 wk), healthy status (healthy, unhealthy), and dosage (>600 mg/day, ≤600 mg/day) on body weight, subgroup analysis was performed. Subgroup analysis for the total score of study quality indicated that studies with low quality reported greater weight loss following ALA supplementation compared to high quality studies (WMD: −1.98 vs. −0.61 kg, respectively).

High quality studies indicated significant but slight weight loss following supplementation with ALA (95% CI: −1.21, −0.01). There were no considerable differences between overall effect size and subtotal effect size (high quality studies). Furthermore, the effects of each main item of the Jadad scale (randomization, blinding and drop out) were examined. Findings indicated that both randomization (score of 2, less than 2) and blinding (score of 2, less than 2) affected the effect size. WMD in studies with score of less than 2 for each randomization and blinding item were −1.87 and −1.98 kg, respectively compared to the overall effect size (WMD: −0.69 kg; 95% CI: −1.27, −0.10).

Subgroup analysis indicated that weight reduction in overweight subjects was more than obese individuals (WMD: −2.3 vs. −0.59 kg, respectively). Our findings indicated that supplementation with ALA for less than 10 weeks was more efficient for weight loss. Weight loss in studies that lasted less than 10 weeks (WMD: −2.24 vs. −0.63 kg, respectively) was more than studies followed for longer period. However, the effects of study duration on the

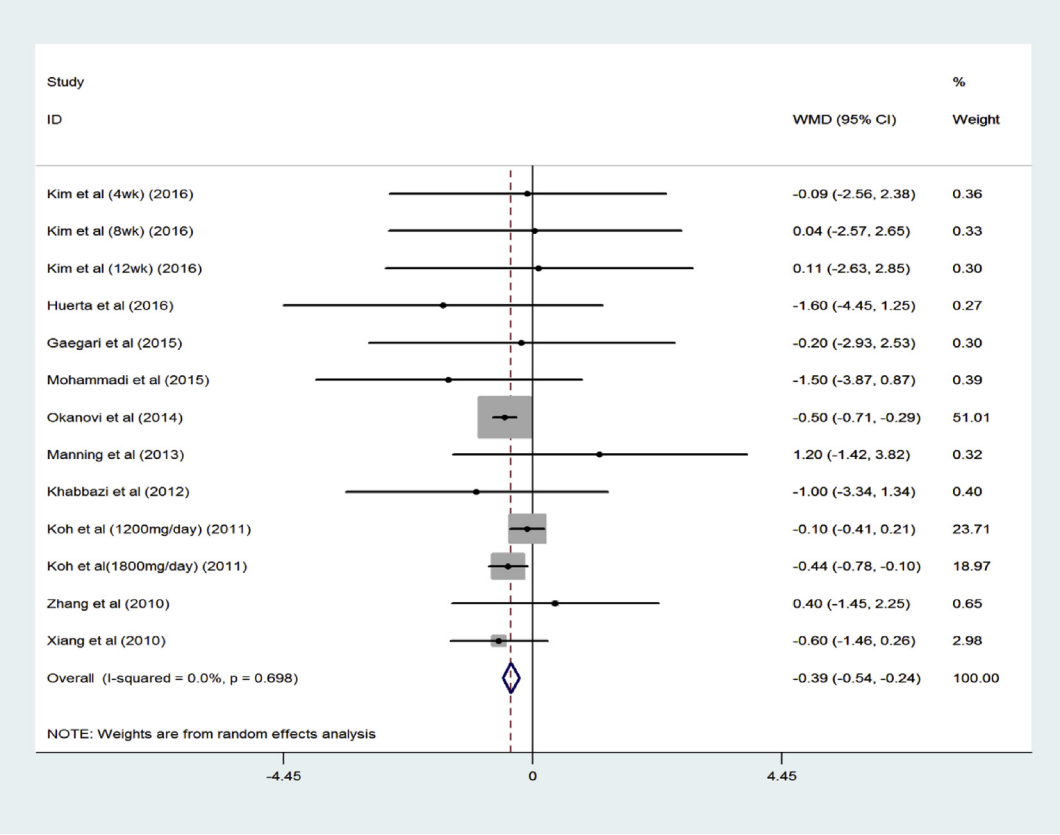


Fig. 3. Forest plot of weighted mean difference (WMD) in body mass index between supplementation with alpha-lipoic acid and placebo group.

effect size were not significant ($p = 0.13$). Subgroup analysis based on health status indicated that weight loss in unhealthy subjects was more than that of healthy individuals (WMD: −1.34 vs. −0.63 kg, respectively). ALA dosage equal or less than 600 mg/day indicated more weight reduction compared to dosages more than 600 mg/day (WMD: −1.08 vs. −0.67 kg). However, a dose–response analysis failed to indicate a significant association between dosage of ALA and reduction in body weight (coefficient of correlation = −0.00031, $p = 0.74$). None of seven mentioned subgroup analysis influenced the effect size significantly.

3.5.2. BMI

The quantitative analysis of BMI values (13 datasets) indicated a significant reduction in BMI in the ALA group compared to the placebo group (−0.39 kg/m^2; 95% CI: −0.54, −0.24; $I^2 = 0\%$) (Fig. 3). To identify the effects of study characteristics on the effect size, subgroup analysis was conducted based on the study quality, baseline BMI, mean age, and adjustment for confounding factors, health status, duration, and dosage. Subgroup analysis indicated that none of mentioned parameters had considerable or significant affect on the effect size.

3.5.3. Waist circumference

A forest plot of six datasets indicated nonsignificant reduction in WC after taking ALA supplement compared to the placebo (WMD: −0.30 cm; 95% CI: −1.18, 0.58; $I^2 = 17.8\%$) (Fig. 4). The effects of study duration, dosage, and participant's characteristics (baseline BMI, mean age, and health status) on the effect size were assessed. None of mentioned parameters affect the pooled effect size significantly. However, after subgroup analysis for health status, supplementation with ALA decreased WC in unhealthy subjects (WMD: −2.00 cm; 95% CI: −4.19, 0.19; $I^2 = 1.3\%$; $p = 0.36$) more than healthy individuals (WMD: 0.03 cm; 95% CI: −0.69, 0.75; $I^2 = 0\%$; $p = 0.29$). Health status subgroup also decreased the observed heterogeneity more than other subgroups.

3.6. Publication bias

The funnel plot for the effects of ALA on body weight revealed a symmetric pattern (Fig. 5a) that suggested no publication bias in the meta-analysis for body weight. Besides, the Eggers regression plot confirmed that no publication bias existed for body weight ($p = 0.11$). Funnel plot for the effects of ALA on BMI value indicated scare studies at the middle of the plot that revealed an asymmetry (Fig. 5b). Eggers regression also confirms the publication bias ($p = 0.001$). Therefore, the publication bias was corrected with trim & fill. After correction effect size (WMD: −0.38 kg/m^2; 95% CI: −0.53, −0.24), one study was added as shown in square (Fig. 6). Since a few studies reported WC, for evaluation publication bias, Eggers regression was performed directly. Eggers regression indicated that there is no publication bias for WC ($p = 0.28$).

4. Discussion

The present meta-analysis indicated that supplementation with ALA can decrease body weight and BMI. However, ALA did not decrease WC compared with the placebo group.

Results of this systematic review were in line with the previous narrative review [47]. Supplementation with ALA had beneficial effect on body weight based on the mentioned review. The

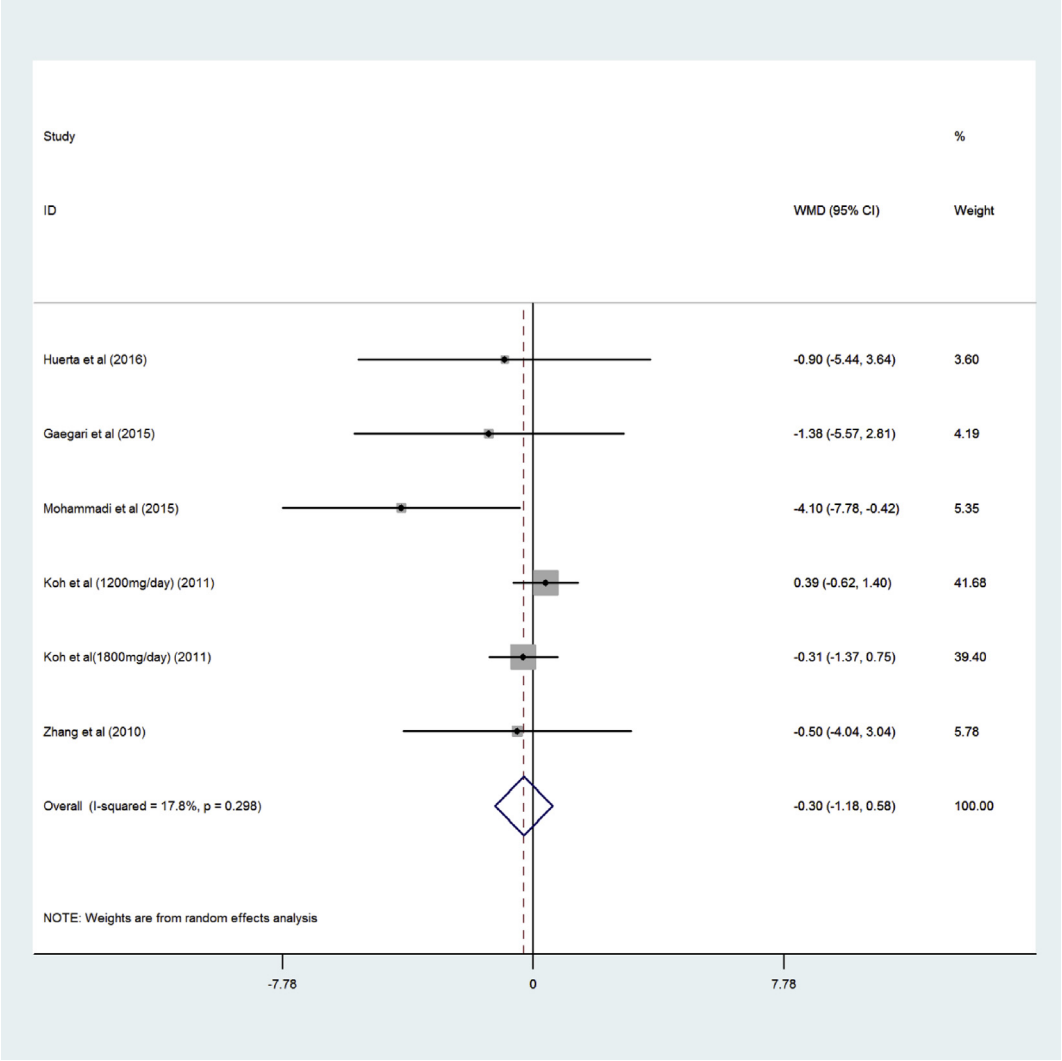
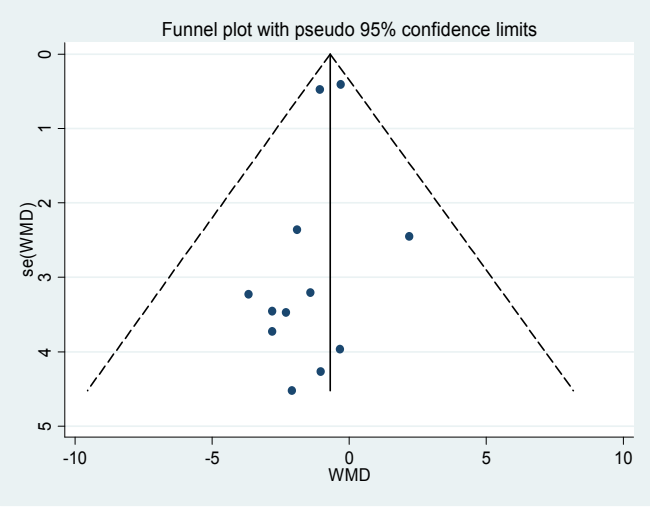


Fig. 4. Forest plot of weighted mean difference (WMD) in waist circumference between supplementation with alpha-lipoic acid and placebo group.

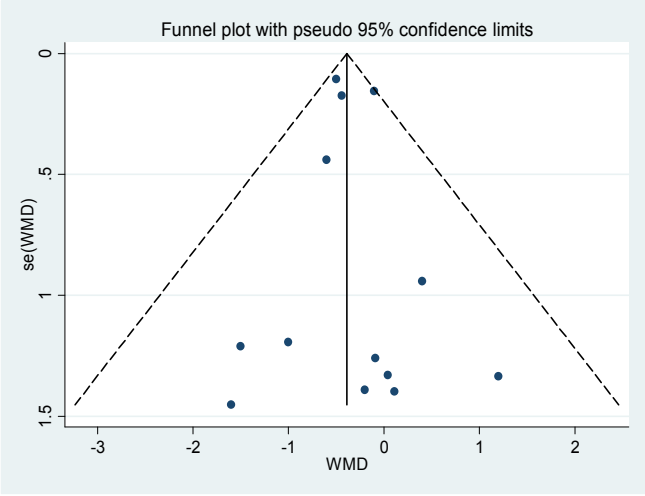
observed reduction in body weight following supplementation with ALA was too slight from a clinical point of view. Meanwhile, all studies evaluated the effects of ALA with no other weight loss intervention, the present systematic review revealed a pure effect of ALA. Our findings revealed that supplementation with ALA on body weight in overweight subjects was more effective than obese individuals. Although from a clinical point of view, −2.2 kg weight loss after approximately 9 weeks is not considerable. As it is presented in the current study, weight loss in unhealthy subjects is more than healthy subjects. Hence ALA is an antioxidant supplement, it can improve metabolic status and prevent NCDs [48,49]. However, due to the results of the present study, we cannot draw a conclusion about the efficacy of ALA supplementation on metabolic disorders. Based on our findings, for recommending ALA as an anti-obesity supplement, low dosage (<600 mg/day) for a short period of time (<10 weeks) is suggested for overweight subjects.

From a clinical point of view, changes in BMI value were slight. Even after correcting the effect size using trim & fill, changes in the pooled effect size were too slight. Due to different disease backgrounds and insufficient studies on each gender, the effects of these parameters on the influence of ALA on obesity management remained unclear.

Waist circumference is a better indicator compared to other anthropometric indices for predicting incidence of CVDs, metabolic syndrome, type 2 diabetes, and specific cause mortality [50]. Limited studies reported WC changes following ALA supplementation. Based on our findings, the effect of ALA on WC was not significant and also from a clinical point of view, ALA cannot be a good choice for reduction in visceral adiposity. WC reduction of approximately −0.3 cm through a period ranging from 2 to 20 weeks is too slight. It seems that there is no narrative systematic review to summarize the effects of ALA on abdominal obesity and comparison of our results was not possible. WC was reported in just 6 datasets of 12 included studies. It seems that missing WC value led to nonsignificant effect of ALA on WC while the effects of ALA on body weight and BMI were significant. The observed heterogeneity for WC was low. Nevertheless for finding the heterogeneity sources and attenuating their effects, we preferred meta regression due to low numbers of included paper and insufficient studies in each subgroup. Many factors could contribute to the observed heterogeneity. In the present systematic review, the influence of several known subgroups on pooled effect size was assessed. After considering the effect of health status, between-study heterogeneity for WC was attenuated. However, baseline BMI, mean age and



(a)



(b)

Fig. 5. Funnel plot for a) body weight and b) body mass index. The horizontal axis indicated the weighted mean difference. The vertical axis indicated the standard error of the mean. Results of each study are represented by black circles. The vertical line in each plot represents the overall effect size.

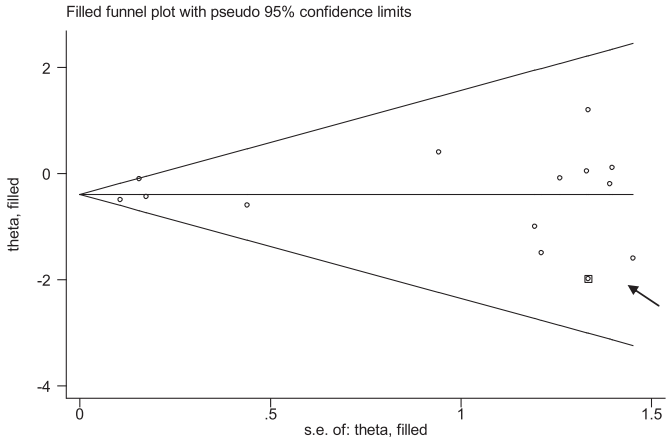


Fig. 6. Trim and fill funnel plot. Circles represent the weight of the included clinical trials and a box stand for an added publication.

dosage, duration and study quality did not reduce the heterogeneity as the same value for health status. In unhealthy subjects, WC decreased (−2.0 cm) more compared to the unhealthy (0.3 cm) individuals. However, this reduction was not considerable in a clinical practice.

Lifestyle can play a major role in obesity treatment [51,52]. However, some clinical trials did not point to the maintenance of usual dietary intake and physical activity level through the treatment, and most studies did not adjust results for these parameters. Therefore, the effects of life style and other confounding factors are not clear. In the present study, meta regression for confounding adjustment did not alter the pooled effect size. However, in the clinical practice this issue should be considered because changes in these parameters might blunt the effects of ALA supplement.

Precise mechanisms for anti-obesity effects of ALA have not been identified yet. However, multiple potential mechanisms have been suggested. ALA is a nutraceutical supplement that affects several gene expression and cellular targets involved in feeding behavior control, energy expenditure, lipogenesis, and fat oxidation [21,47]. It has been proposed that ALA has main impacts on AMPK. AMPK incorporates signals in the appetite regulation center and affects food intake as well as energy expenditure [47]. It was reported that ALA can reduce appetite and energy intake via reducing hypothalamic AMPK activity pathway [53].

The results of the current systematic review in safety of ALA are in line with earlier narrative reviews [47,54]. Our study indicated that up to 1200 mg/day ALA had no serious side effects and was well tolerated as this issue had been confirmed by previous short- and long-term studies. Skin sensation and fever were two main adverse effects that were reported in participants taking daily dosage of 1800 mg/day.

The present meta-analysis had several limitations. The effects of disease background and gender on the efficacy of ALA supplement remained unclear. Due to insufficient studies we could not examine the effects of ALA on other anthropometric indices. Furthermore in most included studies, anthropometric indices were secondary endpoints, and details about the measurements that can affect the results were not explained. The strength of the current study was the existence of low heterogeneity for body weight, BMI and WC values as showed by the I^2 index. Moreover, subgroup analysis and assessment of the study quality and its effect on the overall effect sizes were evaluated.

5. Conclusion

The present meta-analysis on clinical trials revealed that supplementation with ALA slightly but significantly decreased body weight and BMI, whereas it had no effect on WC. Up to 1200 mg/day of ALA did not show adverse effects, however for clinical practice; it seems that ALA cannot be a cost-effective complementary therapy for obesity management. Due to its antioxidant properties, it might have beneficial effects in subjects with disease background. Further studies are needed to clarify the effects of ALA on metabolic parameter to reveal the efficacy of this nutraceutical supplement in unhealthy overweight and obese individuals.

Conflict of interest

All authors declared no conflict of interest.

References

[1] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and

adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–81.
[2] Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. Environ Health 2012;11:42–51.
[3] McCormick B, Stone I. Economic costs of obesity and the case for government intervention. Obes Rev 2007;8:161–4.
[4] de Zwaan M, Petersen I, Kaerber M, Burgmer R, Nolting B, Legenbauer T, et al. Obesity and quality of life: a controlled study of normal-weight and obese individuals. Psychosomatics 2009;50:474–82.
[5] Kitahara CM, Flint AJ, de Gonzalez AB, Bernstein L, Brotzman M, MacInnis RJ, et al. Association between class III obesity (BMI of 40–59 kg/m^2) and mortality: a pooled analysis of 20 prospective studies. PLoS Med 2014;11:e1001673.
[6] Fazelian S, Namazi N, Heshmati J. Self-treatment with anti-obesity medications in overweight and obese women in Tehran-Iran. Res J Rec Sci 2014;3:23–7.
[7] Dulloo AG. The search for compounds that stimulate thermogenesis in obesity management: from pharmaceuticals to functional food ingredients. Obes Rev 2011;12:866–83.
[8] Soeliman FA, Azadbakht L. Weight loss maintenance: a review on dietary related strategies. J Res Med Sci 2014;19:268–75.
[9] Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Better dietary adherence and weight maintenance achieved by a long-term moderate-fat diet. Br J Nutr 2007;97:399–404.
[10] Keshavarz SA, Nourieh Z, Attar MJH, Azadbakht L. Effect of soymilk consumption on waist circumference and cardiovascular risks among overweight and obese female adults. Int J Prev Med 2012;3:798–805.
[11] Azizi, Mirmiran, Azadbakht. Predictors of cardiovascular risk factors in Tehranian adolescents: Tehran lipid and glucose study. Int J Vitam Nutr Res 2004;74:307–12.
[12] Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007;335:1194–9.
[13] Kang JG, Park C-Y. Anti-obesity drugs: a review about their effects and safety. Diabetes Metab J 2012;36:13–25.
[14] Valdecantos MP, Perez-Matute P, Martinez JA. Obesity and oxidative stress: role of antioxidant supplementation. Rev Invest Clin 2009;61:127–39.
[15] Setorki M, Nazari B, Asgary S, Azadbakht L, Rafieian-Kopaei M. Anti atherosclerotic effects of verjuice on hypocholesterolemic rabbits. Afr J Pharm Pharmacol 2011;5:1038–45.
[16] Baboota RK, Bishnoi M, Ambalam P, Kondepudi KK, Sarma SM, Boparai RK, et al. Functional food ingredients for the management of obesity and associated co-morbidities – a review. J Funct Foods 2013;5:997–1012.
[17] Nabavi SF, Russo GL, Daglia M, Nabavi SM. Role of quercetin as an alternative for obesity treatment: you are what you eat! Food Chem 2015;179:305–10.
[18] Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr 2010;91:73–81.
[19] Hashemipour M, Kelishadi R, Shapouri J, Sarrafzadegan N, Amini M, Tavakoli N, et al. Effect of zinc supplementation on insulin resistance and components of the metabolic syndrome in prepubertal obese children. Hormones 2009;8:279–85.
[20] Amiot M, Riva C, Vinet A. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. Obes Rev 2016;17:573–86.
[21] Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim Biophys Acta 2009;1790:1149–60.
[22] Mohammadi V, Khalili M, Eghtesadi S, Dehghani S, Jazayeri S, Aghababaee SK, et al. The effect of alpha-lipoic acid (ALA) supplementation on cardiovascular risk factors in men with chronic spinal cord injury: a clinical trial. Spinal Cord 2015;53:621–4.
[23] Vidovic B, Milovanovic S, Dordevic B, Kotur-Stevuljevic J, Stefanovic A, Ivanisevic J, et al. Effect of alpha-lipoic acid supplementation on oxidative stress markers and antioxidative defense in patients with schizophrenia. Psychiatr Danub 2014;26:205–13.
[24] Bilska A, Dubiel M, Sokolowska-Jezewicz M, Lorenc-Koci E, Wlodek L. Alpha-lipoic acid differently affects the reserpine-induced oxidative stress in the striatum and prefrontal cortex of rat brain. Neuroscience 2007;146:1758–71.
[25] Kim WJ, Kang JY, Kwon DK, Song YJ, Lee KH. Effects of alpha-lipoic acid supplementation on malondialdehyde contents and superoxide dismutase in rat skeletal muscles. Food Sci Biotechnol 2011;20:1133–6.
[26] Prieto-Hontoria PL, Pérez-Matute P, Fernández-Galilea M, Martínez JA, Moreno-Aliaga MJ. Lipoic acid inhibits leptin secretion and Sp1 activity in adipocytes. Mol Nutr Food Res 2011;55:1059–69.
[27] Wang Y, Li X, Guo Y, Chan L, Guan X. α-Lipoic acid increases energy expenditure by enhancing adenosine monophosphate-activated protein kinase–peroxisome proliferator-activated receptor-γ coactivator-1α signaling in the skeletal muscle of aged mice. Metabolism 2010;59:967–76.
[28] Huerta AE, Navas-Carretero S, Prieto-Hontoria PL, Martínez JA, Moreno-Aliaga MJ. Effects of α-lipoic acid and eicosapentaenoic acid in overweight and obese women during weight loss. Obesity 2015;23:313–21.
[29] Zhang Y, Han P, Wu N, He B, Lu Y, Li S, et al. Amelioration of lipid abnormalities by alpha-lipoic acid through antioxidative and anti-inflammatory effects. Obesity 2011;19:1647–53.
[30] Kim NW, Song YM, Kim E, Cho HS, Cheon KA, Kim SJ, et al. Adjunctive alpha-lipoic acid reduces weight gain compared with placebo at 12 weeks in schizophrenic patients treated with atypical antipsychotics: a double-blind randomized placebo-controlled study. Int Clin Psychopharmacol 2016;31:265–74.
[31] Bilska A, Wlodek L. Lipoic acid – the drug of the future. Pharmacol Rep 2005;57:570–7.
[32] Koh EH, Lee WJ, Lee SA, Kim EH, Cho EH, Jeong E, et al. Effects of alpha-lipoic acid on body weight in obese subjects. Am J Med 2011;124:85.e1–8.
[33] Gargari BP, Kolahi S, Dehghan P, Khabbazi A, Mirtaheri E. Effects of alpha-lipoic acid supplementation on clinical status and anthropometric indices in women with rheumatoid arthritis. Curr Top Nutraceut Res 2015;13:33–40.
[34] Ansar H, Mazloom Z, Kazemi F, Hejazi N. Effect of alpha-lipoic acid on blood glucose, insulin resistance, and glutathione peroxidase of type 2 diabetic patients. Saudi Med J 2011;32:584–8.
[35] Vidovic BB, Milasinovic NZ, Kotur-Stevuljevic JM, Dilber SP, Krusic MTK, Dordevic BI, et al. Encapsulation of alpha-lipoic acid into chitosan and alginate/gelatin hydrogel microparticles and its in vitro antioxidant activity. Chem Ind 2016;70:49–58.
[36] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[37] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
[38] Kerkhoffs GM, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The influence of obesity on the complication rate and outcome of total knee arthroplasty. J Bone Joint Surg Am 2012;94:1839–44.
[39] Okanovic A, Prnjavorac B, Jusufovic E, Sejdinovic R. Alpha-lipoic acid reduces body weight and regulates triglycerides in obese patients with diabetes mellitus. Med Glas 2015;12:122–7.
[40] 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;22:244–50.
[41] Xiang GD, Pu JH, Yue L, Hou J, Sun HL. alpha-Lipoic acid can improve endothelial dysfunction in subjects with impaired fasting glucose. Metab Clin Exp 2011;60:480–5.
[42] Manning PJ, Sutherland WH, Williams SM, Walker RJ, Berry EA, De Jong SA, et al. The effect of lipoic acid and vitamin E therapies in individuals with the metabolic syndrome. Nutr Metab Cardiovas 2013;23:543–9.
[43] Ziegler D, Gries FA. alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. Diabetes 1997;46:S62–6.
[44] Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients – a 4-month randomized controlled multicenter trial (DEKAN study). Diabetes Care 1997;20:369–73.
[45] Huerta AE, Prieto-Hontoria PL, Fernandez-Galilea M, Sainz N, Cuervo M, Martínez JA, et al. Circulating irisin and glucose metabolism in overweight/obese women: effects of alpha-lipoic acid and eicosapentaenoic acid. J Physiol Biochem 2015;71:547–58.
[46] 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 (Oxf) 2008;68:716–23.
[47] Carrier B, Rideout TC. Anti-obesity and lipid-lowering properties of alpha-lipoic acid. J Hum Nutr Food Sci 2013;1:1008–114.
[48] Brufani M. alpha-lipoic acid: drug or dietary supplement? An overview on the pharmacokinetics, available formulations and clinical evidence in the diabetes complications. Progr Nutr Clin Endocrinol 2014;16:62–74.
[49] Moura FA, de Andrade KQ, dos Santos JC, Goulart MO. Lipoic acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem 2015;15:458–83.
[50] Azadbakht L, Zaribaf F, Haghighatdoost F, Surkan P, Esmaillzadeh A. Determinants of central adiposity among Iranian population. Zahedan J Res Med Sci 2013;15:7–13.
[51] Azadbakht, Mirmiran, Shiva, Azizi. General obesity and central adiposity in a representative sample of Tehranian adults: prevalence and determinants. Int J Vitam Nutr Res 2005;75:297–304.
[52] Mirmiran P, Azadbakht L, Azizi F. Dietary behaviour of Tehranian adolescents does not accord with their nutritional knowledge. Public Health Nutr 2007;10:897–901.
[53] Lee WJ, Eun HK, Jong CW, Kim MS, Park JY, Lee KU. Obesity: the role of hypothalamic AMP-activated protein kinase in body weight regulation. Int J Biochem Cell Biol 2005;37:2254–9.
[54] Cremer DR, Rabeler R, Roberts A, Lynch B. Long-term safety of alpha-lipoic acid (ALA) consumption: a 2-year study. Regul Toxicol Pharmacol 2006;46:193–201.