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Alpha-Lipoic Acid (ALA) as a supplementation for weight loss: Results from a Meta-Analysis of Randomized Controlled Trials

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Abstract

Objectives—Obesity is associated with significant morbidity and mortality rates. Even modest weight loss may be associated with health benefits. Alpha-lipoic acid (ALA) is a naturally occurring antioxidant. Studies have suggested anti-obesity properties of ALA; however, results are inconsistent. The purpose of this study is to conduct a meta-analysis of the effect of ALA on weight and body mass index (BMI).

Methods—A comprehensive, systematic literature search identified 10 articles on randomized, double-blind, placebo-controlled studies involving ALA. We conducted a meta-analysis of mean weight and BMI change differences between ALA and placebo treatment groups.

Results—ALA treatment coincided with a statistically significant 1.27 kg (CI=0.25 to 2.29) greater mean weight loss compared to the placebo group. A significant overall mean BMI difference of -0.43 kg/m^2 (CI=-0.82 to -0.03) was found between the ALA and placebo groups. Meta-regression analysis showed no significance in ALA dose on BMI and weight changes. Study duration significantly affected BMI change, but not weight change.

Conclusions—ALA treatment showed small, yet significant short-term weight loss compared to placebo. Further research is needed to examine the effect of different doses and the long-term benefits of ALA on weight management.

Keywords

thioctic acid; weight; body mass; diabetes; alpha lipoic acid

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Introduction

Obesity is a growing worldwide epidemic with an estimated 1.9 billion overweight and 600 million obese adults (1). Obesity is associated with significant morbidity and mortality through its close association with ailments such as cardiovascular disease and diabetes (2). Even modest weight loss may be associated with prevention of diabetes, reduction in blood pressure, lower cholesterol and triglyceride levels, and other health benefits (3-5).

Alpha lipoic acid (ALA), also known as thioctic acid, is a naturally occurring short chain fatty acid which contains a thiol bond (6). It is an essential cofactor for energy production in the mitochondria (7). ALA is also a powerful antioxidant and a free radical scavenger (6, 8, 9). ALA is marketed in the US as an over-the-counter nutritional antioxidant supplement, alone or in combination with other antioxidants. In medicine, ALA has been shown to reduce symptoms of diabetic polyneuropathy, and several clinical trials established some efficacy and an excellent safety profile in this patient population (10-15).

Previous studies have suggested anti-obesity properties of ALA (16-18). In animal studies, it has showed that ALA supplementation promotes the reduction of body weight and fat mass by decreasing food intake and enhancing energy expenditure, possibly by suppressing hypothalamic AMP-activated protein kinase (AMPK) activity (19-22). However, studies in humans with ALA supplementation are limited, and the results have been inconsistent. Some clinical trials have shown that ALA supplementation may help overweight or obese individuals lose weight (17, 18), while other studies have observed no effects of ALA on weight (23, 24). Nevertheless, ALA appears to have a wide range of beneficial effects on obesity related conditions such as insulin resistance, metabolic syndrome, and type II diabetes, including their complications such as vascular damage (7, 13).

We performed a systematic review and comprehensive meta-analysis to assess the effects of ALA as a weight-loss supplement. On the basis of the results from single studies, we hypothesized that ALA is more effective than placebo for reducing body weight.

Methods

Studies were identified using Pubmed, PsychINFO, and Web of Science. Additionally, a manual search was used among references cited in retrieved articles, related review articles, and meta-analyses. Two reviewers (EZ and KL) independently conducted the literature search using the following terms: (α-Lipoic OR alpha-lipoic OR “lipoic acid” OR thioctic OR “α-LA”) AND (weight OR obesity OR overweight OR BMI OR “body mass” OR diabete* OR diabeti* OR diabeto* OR “diabetes mellitus” OR “body fat” OR “fat mass”) AND ((clinical [Title/Abstract] AND trial [Title/Abstract]).

Selection Criteria

The following inclusion criteria were used: (i) studies were randomized and placebo-controlled, (ii) subjects were human with a mean age of ≥18 years old (iii) studies were ≥3 weeks in length, and (iv) studies reported weight and/or BMI before and after intervention regardless if the stated aim was weight reduction or else. The present meta-analysis was

conducted and reported according to the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analysis) guidelines (25).

Data Extraction

Two reviewers (EZ and KL) independently reviewed each article and extracted all data. After study selection and data extraction, a third reviewer (SK) checked all extracted data to clarify any missing data. To obtain missing information, we contacted the authors to request relevant data. Correlation coefficients were used to calculate and impute the missing standard deviation of change from baseline applying the methods described in Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. (26, 27). The following data were extracted: study design, sample size, medication dose, duration of follow-up, demographical variables (age, gender), body weight, and body mass index (BMI). Outcomes of overlapping samples from the same investigators were extracted from the more detailed report.

Statistical Analyses

To avoid publication bias, we conducted a comprehensive search among published studies. Publication bias was also assessed visually with funnel plots and statistically with Egger's regression test (28). Statistical heterogeneity was assessed using Q and I^2 test (in which $I^2 \geq 50\%$ was considered to indicate heterogeneity). We examined the difference between ALA treatment and placebo by calculating the mean difference using the software Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ, USA). To combine studies, the random-effects model was used with the results for a fixed-effects model presented on figures.

Results

Our study selection process is presented in Figure 1. A total of 728 articles excluding duplicates were identified. After screening the title and abstract, 112 articles were selected for further evaluation. After full-text review, 101 articles not fulfilling the selection criteria were excluded. Of the excluded articles, 33 were not placebo controlled, 59 provided no weight data, 4 were not randomized, and 4 included patients under 18 years of age.

Overall, we identified 11 eligible studies with 12 appropriate treatment arms for inclusion in this review. Of these studies, eight of them reported weight outcomes and seven of them reported BMI outcomes. Studies in this meta-analysis were carried out in various populations, including patients with diabetes mellitus (11, 23, 29), metabolic syndrome (30), rheumatoid arthritis (31), and non-alcoholic fatty liver disease (32). Three studies were designed as weight loss interventions, and conducted with overweight and obese individuals (18, 33, 34). Three studies employed dietary interventions with ALA or placebo (16, 18, 32). Details of the studies are summarized in Table 1.

The total number of participants in these studies was 534 for the ALA group and 413 for the placebo group. The study durations were between 8 weeks to 52 weeks. ALA doses were between 300 mg/day to 1800 mg/day.

Meta-analyses

Weight Change—Overall weight loss was 1.27 kg (CI=-2.29 to -0.25) greater in ALA treatment compared to that in placebo group (Figure 2). We found no evidence of publication bias in the body weight change analysis (Egger's test intercept = -1.659, CI = -5.10 to 1.78). There was a significant heterogeneity across interventions (I^2=68.12, d.f.=8, p<0.001).

Meta-regression analysis showed that neither intervention duration (P.E.=-2.00, CI=-4.02 to 0.01, p = 0.051) nor ALA dose had a significant effect on weight change (P.E.=-0.956, CI=-3.08 to 1.16, p=0.377).

BMI Change—Meta-analysis of BMI changes between ALA and placebo groups is shown in Figure 3. A significant overall mean BMI difference was found -0.40 kg/m^2 (CI=-0.76 to -0.03) between the ALA and placebo groups. We found no evidence of publication bias in the body weight change analysis (Egger's test intercept = -0.04, CI = -4.87 to 4.77). There was a significant heterogeneity across interventions (I^2=73.24, d.f.=8, p<0.001).

Meta-regression analysis showed no significant effect of ALA dose (P.E.=-0.16, CI=-0.48 to 0.14, p=0.29) on BMI change. Intervention duration significantly affects BMI change (P.E.=-0.50, CI=-0.76 to -0.25, p<0.001).

Sub-group analyses—We employed two separate sub-group analyses to test the effectiveness of ALA in weight loss interventions (16, 18, 33) and in studies with diet intervention (16, 18, 32). In the first analysis, we found no significant difference on effectiveness of ALA in weight loss interventions (-1.27, CI=-2.04 to -0.53) compared to those non-weight loss interventions (-1.14 CI=-2.99 to 0.69) (Q=0.01, d.f.=1, p=0.90). Cumulative analysis of BMI reduction in weight loss interventions (-0.48 kg/m^2 CI=-0.88 to -0.08) was similar to those non-weight loss interventions (-0.30 kg/m^2 CI=-0.80 to 0.28) (Q=0.23, d.f.=1, p=0.63). There was no significant heterogeneity in body weight (Q=2.95, d.f.=3, p=0.399) and BMI (Q=2.47, d.f.=2, p=0.291) analyses in weight loss interventions.

In the second sub-group analysis, we found no significant difference between body weight changes in ALA with diet intervention studies (-1.26 kg, CI=-2.14 to -0.37) compared to those only ALA intervention studies (-1.29kg, CI=-3.03 to 0.44)(Q=0.001, d.f.=1, p=0.97). Cumulative analysis of BMI reduction in ALA with diet interventions (-0.50 kg/m^2 CI=-0.83 to -0.17) were similar to those ALA without diet interventions (-0.26 kg/m^2 CI=-0.97 to -0.43)(Q=0.35, d.f.=1, p=0.55). There was no significant heterogeneity in body weight (Q=2.47, d.f.=2, p=0.290) and BMI (Q=4.09, d.f.=2, p=0.129) analyses in diet interventions.

Safety—Only three studies in this meta-analysis reported intervention related side effects and related withdrawal rates (11, 18, 33). Two of these studies specifically described the types of side effects (18, 33). The most commonly reported side effects that were related with ALA in these two studies were gastrointestinal symptoms, such as abdominal pain and nausea, and dermatological symptoms, such as urticaria and itching sensation. No severe side effects were reported in any of the studies. Cumulative analysis of the percentage of subjects who experienced side effects (O.R.=1.25, CI=0.84 to 1.85) and withdrawal rates

due to the side effects (O.R.= 0.43, CI=0.19 to 0.98) did not differ among the ALA and placebo groups.

Discussion

Cumulative results in this meta-analysis showed significant reduction of body weight and BMI with ALA treatment compared to placebo, regardless if it was used for weight loss or other purposes. Meta-regression analyses showed that shorter duration of ALA intervention achieved greater BMI reduction than longer interventions. Incidences of side effects and all-cause discontinuation was similar between ALA and placebo.

Small but significant reduction of body weight with ALA intervention is in line with previous open label (17, 35) and randomized studies (16, 18, 33, 36). Although there was no indication of publication bias for all outcome measures in our analysis, significant heterogeneity across studies was detected. Possible explanations of this heterogeneity can be the diversity of study samples, as well as study aims. Of these 10 studies, only three were designed as a weight management intervention, which specifically recruited overweight and obese individuals (16, 18, 33). Furthermore, most of the studies included in our analysis were conducted in various samples, including patients with diabetes mellitus, metabolic syndrome, and Takotsubo syndrome (11, 23, 29, 37). These studies focused on various effects of ALA intervention, such as anti-inflammatory or anti-diabetic effects (11, 23, 29, 37). On the other hand, previous open label studies have well documented the effectiveness of ALA on weight loss in overweight and obese individuals (17, 35). Although, our sub-group analyses revealed no significant differences on body weight and BMI changes with ALA treatment in weight loss and non-weight loss interventions, as well as in diet and non-diet interventions, ALA yielded more robust effects when it is used in weight loss interventions or when it is used in addition to a diet intervention. These results conclude that ALA supplementation with diet intervention may provide more beneficial effects on body weight management in overweight and obese individuals.

Previous studies have suggested that weight reduction from ALA can be time and dose dependent (18, 33). In our analyses, we found that intervention duration, but not ALA dose, significantly related with the reduction of BMI. Studies in our meta-analysis explored various doses of ALA intervention (300 mg/day to 1800 mg/day) on different intervention durations (8 weeks to 52 weeks). Only one placebo controlled study compared the effectiveness of different doses of ALA on body weight (18). Koh et al. (18) explored the effects of 1200 mg/day and 1800 mg/day ALA intervention on body weight loss. They found that the higher dose of ALA resulted in significant weight loss and BMI reduction throughout the study compared to placebo. The lower dose of ALA led to significant weight loss in the first weeks of this study, however this effect was not sustainable through the entire duration of the study. From these findings, we can argue that the effect of ALA on body weight is limited to the short term, especially when it is used at lower doses with an adaptation mechanism taking over later. This may have implications for future study designs, for example phasic use of the medication may be tried.

In our meta-analysis, the incidences of side effects were similar between the ALA and placebo treatment arms. Withdrawal rates due to side effects were lower in ALA treated patients than those in the placebo group. ALA has been reported as a well-tolerated supplementation with no serious side effects (14, 18, 33). Although the maximum dose of ALA has not been defined, previous studies have shown that ALA can be used safely up to as high as 1800 mg/day (18). Only a small number of studies in our meta-analysis reported the side effect details. Therefore, we were not able to compare the incidences of specific side effects between the ALA and placebo groups.

Given our findings, it is important to note some limitations of this meta-analysis. The number of studies and included patients were small. Furthermore, studies, study populations, and main results in cumulative analyses were heterogeneous. Due to the relatively small number of studies, our meta-regression analyses had limited power. Although there was no evidence of publication bias for all outcome measures on funnel plots and Egger's Tests, the relatively small number of studies also limits the assessment of publication bias.

Finally, in our meta-analysis we were not able to evaluate the effects of ALA on specific compositions of body weight, such as lean mass, fat mass or body water composition. The reason of this limitation is that only one study (18) in our meta-analysis reported body fat mass changes measured by impedance meter. In this study treatment with 1800 mg/day ALA resulted more body fat loss compared to the other arms, however this difference was not significant. On the other hand, previous ALA studies in animals demonstrated significant reductions in body fat mass measured by weighing removed fat mass (38, 39). Measurement methods of body compositions may explain this discrepancy between human and animal studies. Future studies are needed to evaluate the effects of ALA on specific body weight compositions.

In summary, findings from this meta-analysis suggest that ALA may be a useful supplementation for weight loss in overweight and obese individuals. The benefits of ALA compared to placebo appear smaller than that of available prescription weight loss medications (40-42). However, ALA can be considered in clinical practice due to its benign side-effect profile, other beneficial effects such as in diabetic neuropathy, and low cost comparing to the available weight loss medications. Further research is needed to examine the effect of different doses and the long-term benefits of ALA on weight management.

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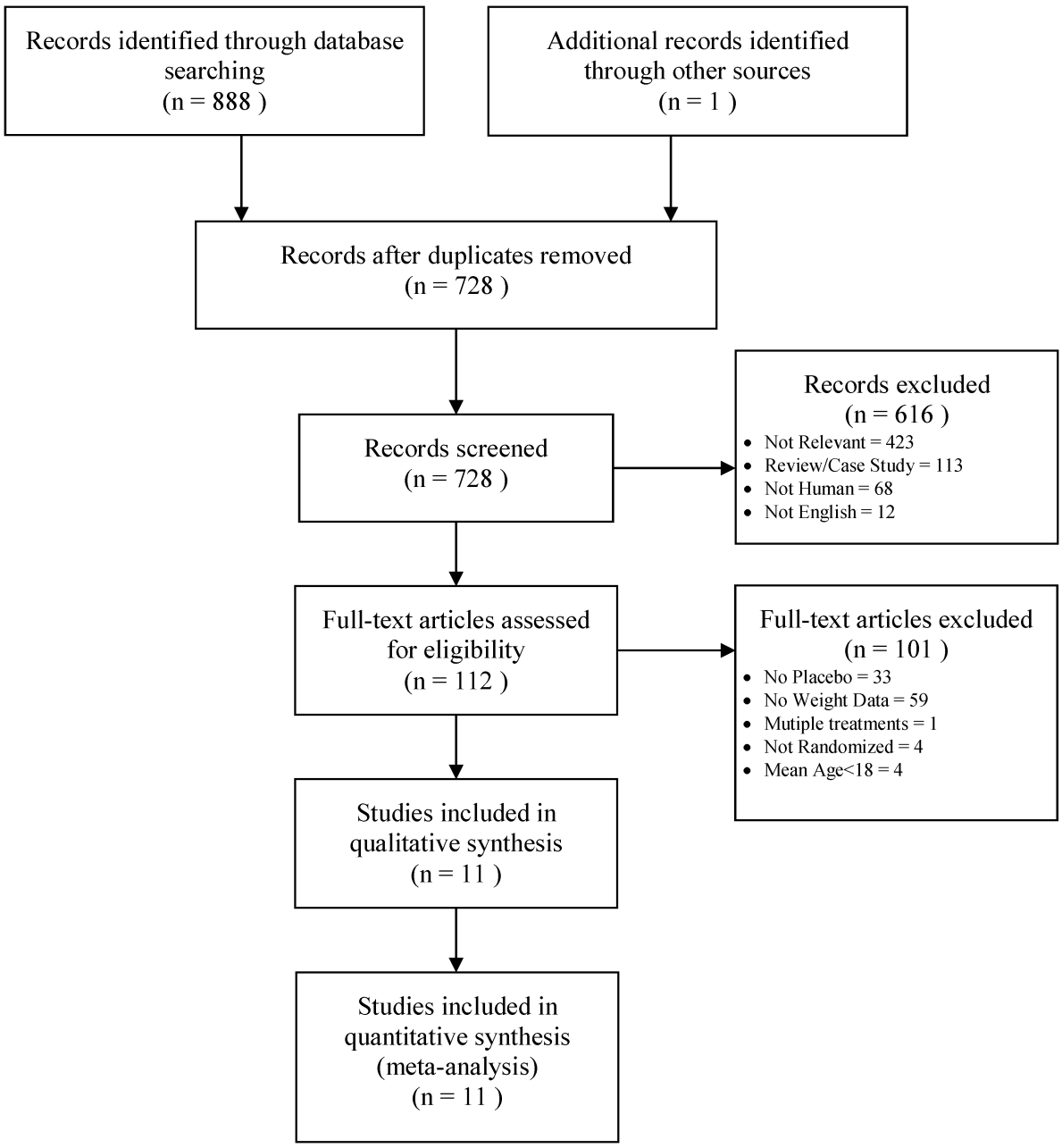

Figure 1. Flow Chart Depicting Selection of Studies

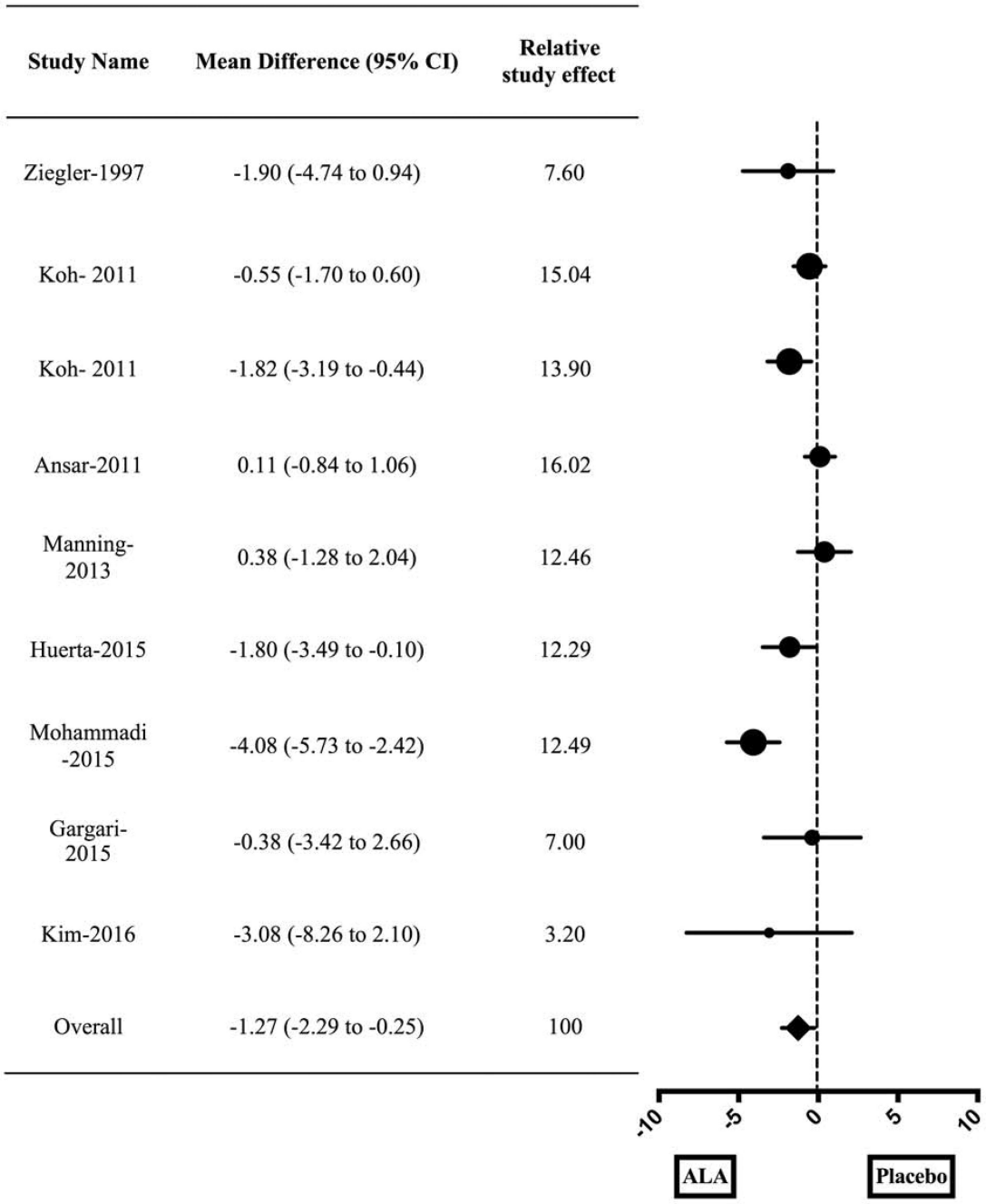

Figure 2. Mean body weight differences between ALA treatment and placebo

Heterogeneity: Tau^2=1.45; I^2=68.12%; Q=25.98, d.f=8, p<0.001

Overall effect: Z=-2.442, p=0.015

Study Name	Mean Difference (95% CI)	Relative study effect
Koh- 2011	-0.24 (-0.56 to 0.08)	16.48
Koh- 2011	-0.73 (-1.09 to -0.36)	15.90
Udupa-2012	0.36 (-2.42 to 3.14)	1.59
Gianturco-2013	-0.60 (-1.14 to –0.05)	13.28
Manning-2013	0.14 (-0.43 to 0.73)	12.75
Mohammadi -2015	-1.09 (-1.39 to -0.78)	16.66
Gargari-2015	-0.15 (-1.37 to 1.07)	6.07
Marfella-2016	0.20 (-0.33 to 0.73)	12.43
Kim-2016	-0.66 (-2.32 to 1.00)	3.85
Overall	-0.40 (-0.76 to -0.03)	100

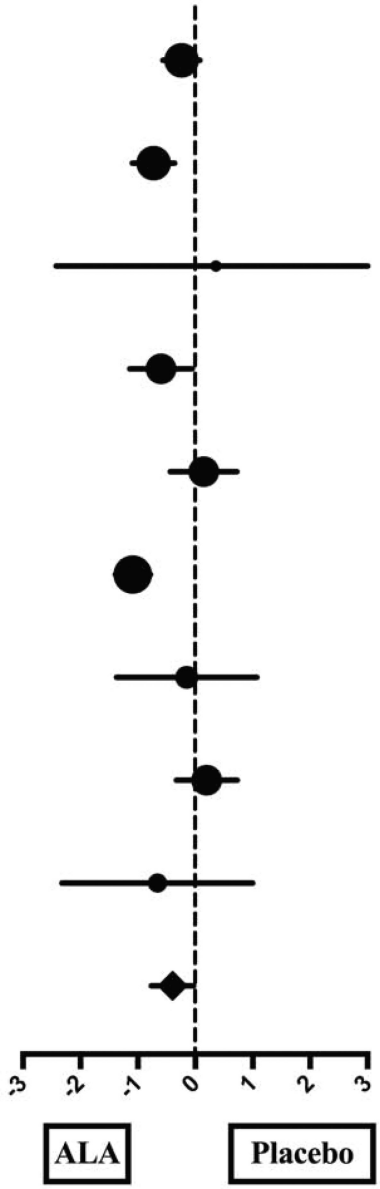

Figure 3. Mean BMI differences between ALA treatment and placebo

Heterogeneity: Tau^2=0.18; I^2=73.24%; Q=29.90, d.f=8, p<0.001

Overall effect: Z=-2.139, p=0.033

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Table 1

Included ALA Studies

	Study Sample	Diet	Study Duration	Study Size (ALA/Control)	Dose (mg PO QD)	ALA Weight Change (mean ± SD)	Control Weight Change (mean ± SD)	ALA BMI Change (mean ± SD)	Control BMI Change (mean ± SD)
Ansar et al., 2011 (23)	Patients with Diabetes Mellitus		8 weeks	29/28	300	-2.08 ± 5.15	-1.12 ± 5.87		
Gargari et al., 2015 (31)	Women with Rheumatoid Arthritis		8 weeks	33/32	1200	-0.06 ± 6.85	0.32 ± 5.59	-0.01 ± 2.89	0.14 ± 2.08
Gianturco et al., 2013 (32)	Patients with nonalcoholic fatty liver disease	Energy restricted diet	52 weeks	52/46	400			-0.3 ± 1.69	0.3 ± 0.92
Huerta et al., 2015 (16)	BMI 27.5 to 40 women individuals	Energy restricted diet	10 weeks	20/22	300	-7 ± 3.1	-5.2 ± 2.5		
Kim et al., 2016 (33)	Patients with schizophrenia who gained ≥ 10% body weight with antipsychotic treatment		12 weeks	10/12	600-1800 as tolerated; mean 1620.0	-1.34 ± 6.48	1.74 ± 5.93	-0.52 ± 1.99	0.14 ± 1.99
Koh et al., 2011 (18)	BMI ≥ 27	Calorie-restricted diet	20 weeks	120/120	1200	-1.49 ± 3.24	-0.94 ± 3.84	-0.57 ± 1.19	-0.33 ± 1.36
Koh et al., 2011 (18)	BMI ≥ 27	Calorie-restricted diet	20 weeks	120/120	1800	-2.76 ± 4.79	-0.94 ± 3.84	-1.06 ± 1.53	-0.33 ± 1.36
Manning et al., 2013 (30)	Patients with metabolic syndrome		12 months	34/40	600	0.33 ± 3.76	-0.05 ± 3.53	0.15 ± 1.27	-0.01 ± 1.29
Marfella et al., 2016 (37)	Patients with Takotsubo syndrome		12 months	24/24	600			-0.13 ± 0.89	-0.33 ± 0.91
Mohammadi et al., 2015 (36)	Male patients with chronic spinal cord injury		12 weeks	28/30	600	-3.7 ± 4.4	0.38 ± 1.4	-1 ± 0.6	0.09 ± 0.6
Udupa et al., 2012 (29)	Patients with Diabetes Mellitus		90 days	25/25	300			-0.8 ± 7.02	-1.16 ± 1.12
Ziegler et al., 1997 (11)	Patients with Diabetes Mellitus		4 months	39/34	800	-1.2 ± 5.28	0.7 ± 7.11		