International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Vitamin E Supplementation and Circulating Adiponectin Concentrations: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ARTICLE INFO

Keywords:
Vitamin E
Tocopherols
Adipokine
Adiponectin

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Received: March 19, 2017
Revised: August 22, 2017
Accepted: September 10, 2017

ABSTRACT

Background: Current results from clinical trials about vitamin E effects on adiponectin are ambiguous. Therefore, we conducted a meta-analysis of available RCTs to resolve this inconsistency.

Methods: The systematic search was performed in several databases including SCOPUS, PubMed-Medline, and Google Scholar until October 1st, 2017. We used fixed-effects model in combination with mean difference (MD) and 95% confidence intervals (CI) for the analysis of data.

Results: Meta-analysis of 6 RCTs (9 treatment arms) showed a significant increase in circulating adiponectin levels (MD: 0.36 µg/mL, 95% CI: 0.16 to 0.56; $p<0.001$), following vitamin E supplementation. In sub-group analysis, a significant increasing effect was observed only in trials with ≥400 mg/day dosage (MD: 0.78 µg/mL, 95% CI: 0.31, 1.24, $p=0.001$) and those trials lasting ≥6 months (MD: 0.58 µg/mL, 95% CI: 0.29, 0.86, $p<0.001$). In meta-regression, there was association between changes in adiponectin concentrations and duration of supplementation.

Conclusion: Our findings showed the significant increase effect of vitamin E supplementation on circulating adiponectin levels; however, a significant increasing effect was observed at doses above 400 mg/day and when supplementation lasting over 6 months.

Please cite this article as: Mohammadi-Sartang M, Dashtabi A, Mazloom Z. Vitamin E Supplementation and Circulating Adiponectin Concentrations: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Nutr Sci 2017;2(3):118-125.

Introduction

The adipose tissue produces several cytokines and hormone-like proteins termed adipokines including adiponectin which has garnered more attention in obesity and metabolic disorder research (1). Changes in plasma levels of adiponectin and hypoadiponectinemia, result in metabolic disorder such as atherosclerosis, dyslipidemia and insulin resistance (2). Adiponectin can serve as an important insulin-sensitizing molecule (3), and exerts several

other actions mostly by reducing glucose production form liver, enhancing fatty acid oxidation and improving endothelial dysfunction (4).

In parallel, adiponectin has emerged as an anti-inflammatory cytokine and cardio-protective molecule, with pleiotropic effects on the cardiovascular system as it is negatively related to cardiovascular risk (5, 6), and other risk factor such as obesity, metabolic syndrome, hypertension and diabetes (3). This anti-atherosclerotic molecule, reduces foam cell formation and adhesion molecule expression (7) and also stimulate of nitric oxide formation in endothelium and reduce inflammatory markers (3). Vitamin E supplementation might have positive effects on adipokine metabolism through up-regulation of adipokines expression in visceral fat (8).

However, the evidence in humans is particularly limited and inconclusive. Several clinical trials evaluated vitamin E supplementation in different populations on circulating adipokines level. Finding published clinical studies are inconsistent. Some trials (9, 10), showed positive effects of vitamin E, whereas no changes or reduction of adiponetin levels after the administration of vitamin E were observed in others (11). Thus, the data regarding the effects of vitamin E on adiponectin are controversial. Since the exact effects of vitamin E supplementation on plasma adiponectin concentrations is still inconclusive, a systematic review and meta-analysis of available controlled trials seems appropriate to summarize the current data to assess the overall effect of vitamin E supplementation on plasma adiponectin concentrations. Therefore, we conducted a meta-analysis of available RCTs to resolve this inconsistency.

Materials and Methods

Our meta-analysis was designed on the guidelines of the PRISMA statement (12). PubMed, Medline via Ovid, EMBASE, and ISI Web of Sciences databases were searched using the following search terms in titles and abstracts and also in combination with MESH terms: (vitamin E OR alpha tocopherol OR tocopherols OR tocotrienols) AND (adipokines OR adipocytokines OR adiponectin). The literature was searched up to 1st October 2017 and the search was confined to studies published in English. Two reviewers separately evaluated each article. Discrepancies were resolved by discussion with each other.

Original studies were selected to be included in this meta-analysis according to the following inclusion criteria: (i) being a RCTs with either parallel or cross-over design in adults (age≥18 years old), (ii) having an intervention duration at least 4 weeks; (iii) having an appropriate controlled design, and (iv) presenting sufficient information on adiponectin concentrations. The following data were abstracted using a standardized electronic form: first author's name, publication year, study location, study design, duration of the intervention, number of participants in the vitamin E and control group, form and administered dose of vitamin E, content of placebo, age, gender and body mass index (BMI) of the study participants.

We also extracted the mean concentration, and SDs of circulating adiponectin at study baseline, post-intervention, and/or change between baseline and post-intervention. We converted adiponectin into the same unit (μg/mL) for all studies. If concentrations of adiponectin were reported at the different intervals, only the final values were included in the meta-analysis. If studies used several doses of vitamin E, each dose was separately included in the analysis. The quality of eligible studies was using the Jadad scale (13), which assigned 0 or 1 point for each of the following 5 criteria: (i) report randomization, (ii) describe suitable method of randomization, (iii) report double-blinding, (iv) describe suitable method of double-blinding, and (v) report explanation and reason of withdrawals and dropouts. The scores with ≥3 and ≤2 were considered as high and low quality respectively (14).

The primary outcome measures were changes in adiponectin levels. Intervention effects were defined as mean differences (MD) and 95% CIs calculated for net changes in adiponectin concentrations. Net changes were calculated as follows: measure at the end of trial - measure at baseline of trial (15). When the standard error of the mean (SEM) was reported in place of SD, we converted it to SD for analyses using the following formula: SD=SEM×square root (n), where n is the number of participants in each group. If our interested outcomes were reported in median and range or 95% confidence interval [CI], mean and SD values were estimated using the method described by Hozo *et al.* (16).

Heterogeneity was assessed by Cochran's Q-test, and also I^2 test for calculating the percentage of heterogeneity (I^2 value>50% was assumed to indicate substantial heterogeneity among the studies. The pooled effect size was calculated using a random effects model in the presence of heterogeneity; otherwise, we applied a fixed-effects model. Pre-defined subgroup analyses based on dose of supplementation and trial duration were conducted. Sensitivity analysis was done with leave-one-out method (i.e. removing a single trial each time and repeating the analysis), to assess the impact of each study on the overall effect size.

Meta-regression was performed using unrestricted maximum likelihood method to explore the association between the net effect size, vitamin E dose, duration of supplementation, and baseline BMI of subjects. The potential publication bias was detected using the funnel plot, Begg's rank correlation, and Egger's weighted regression tests. For adjusting the analysis in the effects of publication bias, we used the Duval and Tweedie "trim and fill" and "fail-safe N" methods (17).

Results

The detailed process of the study selection was shown in Figure 1. In total, 217 articles were found in database search, and 189 articles were excluded, either because of duplication (n=65) or because they were not relevant to our present meta-analysis after the careful review of the titles and abstracts (n=137). Therefore, 15 potentially relevant articles were selected for full-text evaluation. After a careful evaluation, 9 articles were excluded for several reasons: not randomized placebo-controlled studies (n=2), adiponectin measurements were not performed (n=4), used vitamin E in combination with other supplement/drug without an appropriate control group (n=2) and not adequate data (n=1). Thus, 6 RCTS with 9 treatment arms were ultimately selected for inclusion in the meta-analysis.

A summary of the study characteristics included in the meta-analysis is presented in Table 1. Data were pooled from 6 eligible studies comprising 9 treatment arms, which included 452 subjects, with 230 participants in the vitamin E arm and 222 in the control arm. The number of participants in these trials ranged from 20 to 75 subjects. The studies included were published between 2007 and 2014, and conducted in Iran (three studies), New Zealand (two studies) and Switzerland. Vitamin E dose ranged from 100 to 800 mg per day and the duration of vitamin E supplementation varied from 8 weeks to 2 years. Two trials selected subjects with type 2 diabetics; of the remaining 4 trials, one focused on nonalcoholic steatohepatitis, one included patients with metabolic syndrome, one trial was conducted on patients with cardiovascular diseases and one study was performed on overweight subjects. All the studies used a parallel design. Demographic and baseline parameters of the studies that were included are shown in Table 1.

The quality of these 6 studies ranged from 2 to 5 (maximum score), and 5 of these 6 included had higher quality, as assessed by the Jadad scale (Table 1). All of the studies had a parallel design and were randomized, double-blind, and placebo-controlled trials. All studies reported randomization; however, one study (10) did not adequately explain the randomization procedure. Three (10, 18, 19) of six included trials did not describe the blinding procedure. Only one study (10) did not report the details of dropouts and reasons for withdrawal.

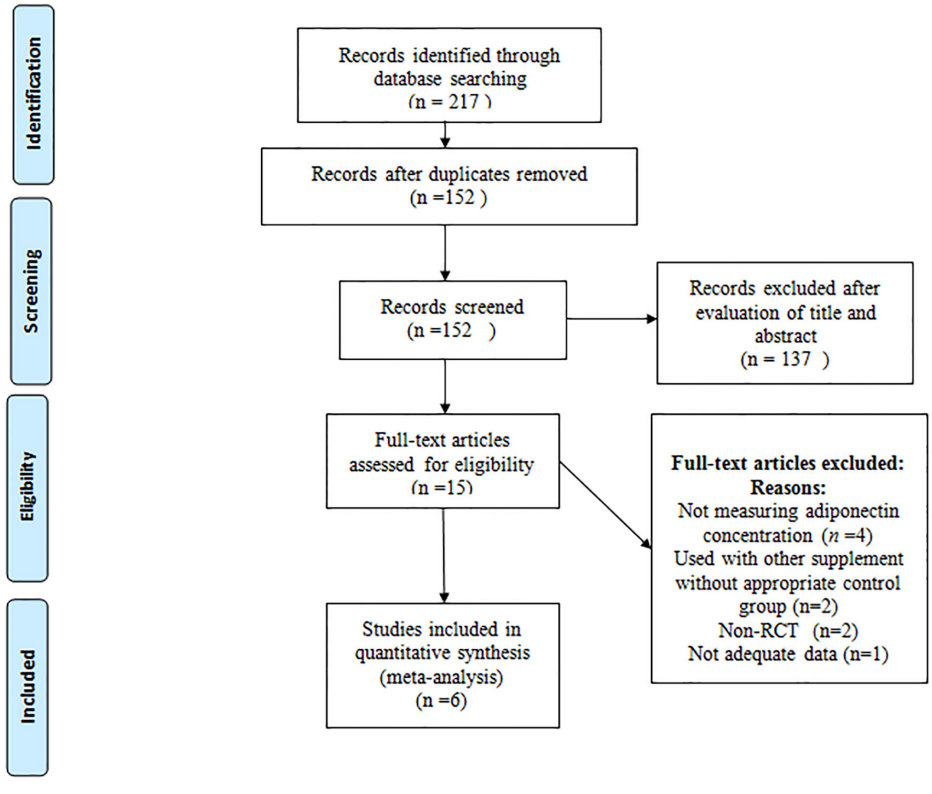

Figure 1: Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the effect of vitamin E supplementation on adiponectin

Table 1: Demographic characteristics of the included studies

Author, Year	Location	Population	Sample size (n)	Age (years)	BMI (kg/m^2)	Duration (weeks)	Intervention	Control	Vitamin E dose (mg/day)	Jadad score
Balmer *et al*., 2009	Switzerland	Nonalcoholic steatohepatitis	28	47.0	31.0	96	UDCA+ Vitamin E	UDCA+ placebo	800	2
Hashemi *et al*., 2014	Iran	Type 2 diabetics	68	44.0	27.7	12	Vitamin E	Corn oil	400	5
Hashemi *et al*., 2014	Iran	Type 2 diabetics	68	45.0	28.0	12	EPA+ Vitamin E	EPA	400	5
Manning *et al*., 2013	New Zealand	Metabolic syndrome	75	62.9	31.5	48	vitamin E	Placebo	100	5
Manning *et al*., 2013	New Zealand	Metabolic syndrome	74	62.9	31.7	48	ALA+ Vitamin E	ALA	100	5
Ramezani *et al*., 2015	Iran	Patients with CAD	42	56.3	26.8	8	Omega-3+ vitamin E	Omega-3+ Vitamin E placebo	400	5
Shadman *et al*., 2013	Iran	Type 2 diabetics	38	47.6	28.1	8	CLA+ Vitamin E,	CLA+ VitE placebo	100	4
Sutherland *et al*., 2007	New Zealand	Overweight subjects	20	47	34.7	24	Vitamin E	Placebo	800	3
Sutherland *et al*., 2007	New Zealand	Overweight subjects	39	47	34.7	24	Vitamin E	Placebo	800	3

ALA: Alpha lipoic acid; CLA: Conjugated linoleic acid; EPA: Ecosapantanoic acid; UDSA: Ursodeoxycholic acid

Meta-analysis of data from 9 treatment arms suggested a significant elevation in circulating adiponectin levels following vitamin E supplementation (MD: 0.36 µg/mL, 95% CI: 0.16 to 0.56; p<0.001); with no significant heterogeneity among the studies (I^2=37.36%, p=0.157) (Figure 2 upper plot). However, vitamin E's effect on plasma adiponectin concentrations was sensitive to the study performed by Manning *et al*. (a). Removing the mentioned study from the analysis resulted in non-significant effect (MD: 0.13 µg/mL, 95% CI: -0.07, 1.23, p=0.218). (Figure 2 lower plot). Because no significant heterogeneity was found, the results were reported based on fixed-effect models.

When the studies were categorized according to administered vitamin E dose, there was a significant greater adiponectin-increasing effect in trials with ≥400 mg/day (MD: 0.78 µg/mL, 95% CI: 0.31, 1.24, p=0.001) versus those with <400 mg/day dosage (MD: 0.38 µg/mL, 95% CI: -0.37, 1.15, p=0.317) (Figure 3). We also stratified the trials according to their duration and found a significant elevation of circulating adiponectin levels in those trials lasting ≥6 months (MD: 0.58 µg/mL, 95% CI: 0.29, 0.86, p<0.001), but not in lower duration (MD: 0.17 µg/mL, 95% CI: -0.09, 0.44, p=0.201) (Figure 4).

Potential associations between the adiponectin-increasing effects of vitamin E supplementation with regard to dose of supplementation, duration of intervention and baseline adiponectin levels were evaluated using unrestricted maximum likelihood meta-regression analysis. In meta-regression, changes in plasma adiponectin concentrations following vitamin E supplementation were found to be independent of dose of supplementation (slope: 0.0004; 95% CI: −0.003, 0.001; p=0.281), and baseline BMI (slope: 0.501; 95% CI: −0.02, 0.12; p=0.190), but it is associated with treatment duration (slope: 0.010; 95% CI: 0.001, 0.018; p=0.018) (Figure 5).

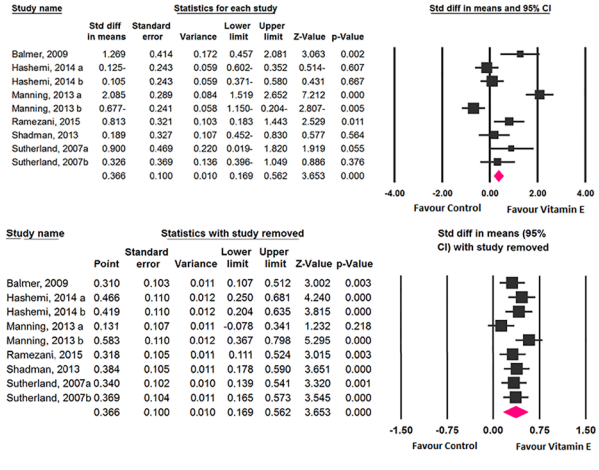

Figure 2: Forest plot displaying weight mean difference and 95% confidence intervals for the impact of vitamin E supplementation on circulating adiponectin concentrations (upper plot). Lower plot shows leave-one-out sensitivity analysis (lower plot).

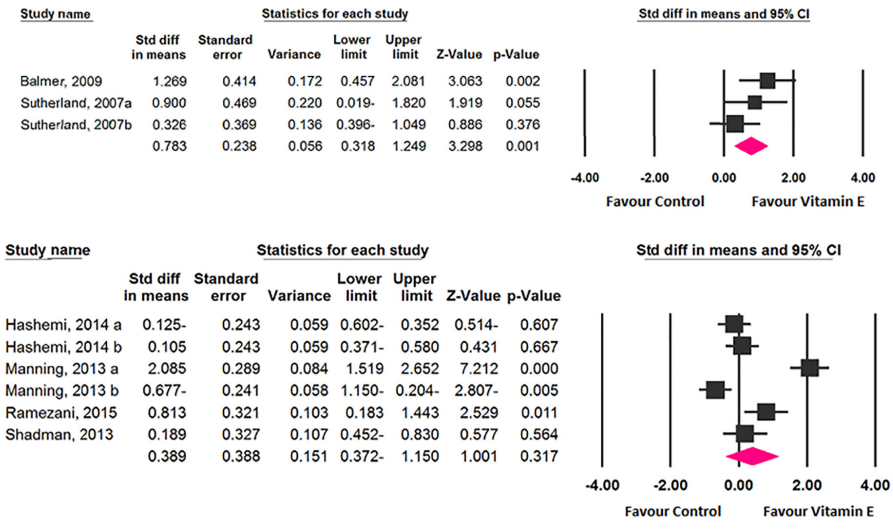

Figure 3: Forest plot displaying weight mean difference and 95% confidence intervals for the impact of vitamin E supplementation on circulating adiponectin concentrations in trials with supplemental doses ≥400 mg/day (upper plot) and <400 mg/day (lower plot).

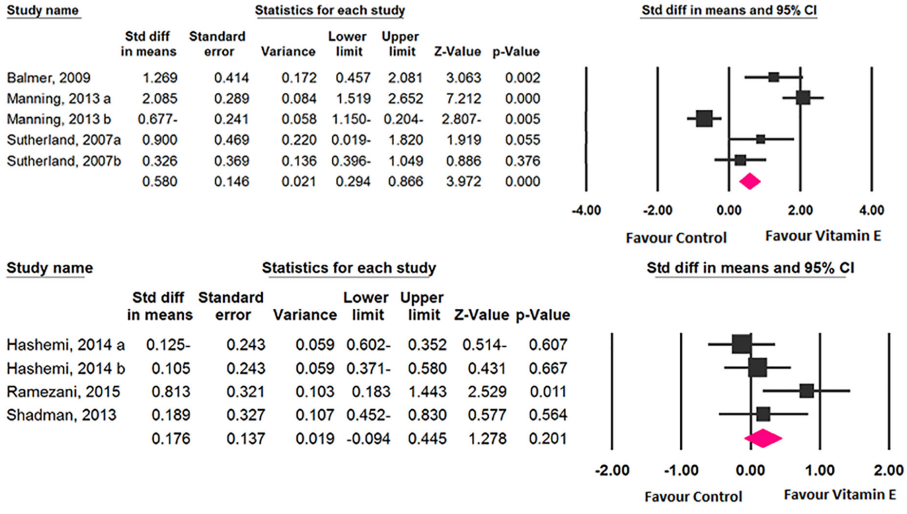

Figure 4: Forest plot displaying weight mean difference and 95% confidence intervals for the impact of vitamin E supplementation on circulating adiponectin concentrations in trials with supplemental duration ≥6 months (upper plot) and <6 months (lower plot).

The Funnel plot did not show a significant potential publication bias in the meta-analysis of vitamin E and adiponectin that was addressed by imputing no potentially missing studies using 'trim and fill' method (Figure 6). The results of Begg's rank correlation (Kendall's Tau with continuity correction=0.41, z=1.56, two-tailed p=0.117) and Egger's linear regression (intercept=6.20, standard error=4.19; 95% CI: −3.71, 16.11, t=1.47, df=7, two-tailed p=0.182) tests also did not show any sign of publication bias. The 'fail-safe N' test demonstrated that 9 studies would be needed to bring the effect size down to a non-significant (p>0.05) value.

Discussion

To the best of our knowledge, the current systematic review and meta-analysis are the first study to analyse available evidence from RCTs regarding the effects of vitamin E supplementation on circulating adiponectin concentrations. The findings of this meta-analysis showed a significant increasing effects of vitamin E on circulating adiponectin concentrations. However, in the sup-group analysis this significant increasing effect was observed only in those trials ≥6 months and with daily dose of vitamin E≥400 mg/d. Furthermore, the influence of vitamin E on circulating adiponectin levels was found to be dependent of duration of supplementation.

Since, adiponectin has a protecting role in cardiovascular diseases (CVDs); evaluation of its circulating levels is important. Actually, it seems that low levels of adiponectin have deleterious effects on cardiovascular system (20). The mechanisms by which vitamin E exerts its effect on adiponectin expression and secretion are not clear. Therefore, to

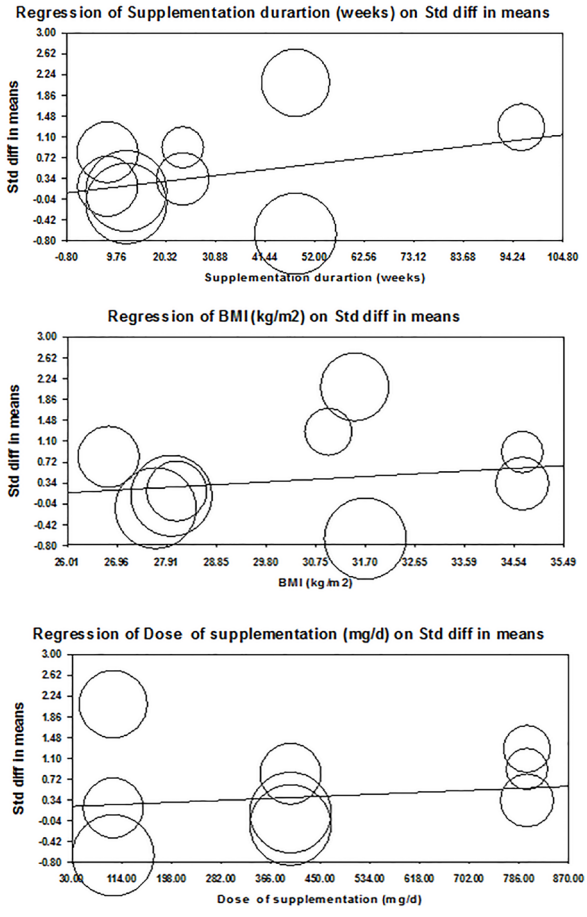

Figure 5: Meta-regression plots of the association between mean changes in plasma adiponectin concentrations with treatment duration, dose of supplementation and changes in baseline serum adiponectin concentrations.

answer to this question, Landrier *et al.* (8), tested the effect of vitamin E on adiponectin expression *in vivo* and observed that supplementation with 4 mg α -tocopherol after four-day, significantly increase serum adiponectin levels and also adipose adiponectin mRNA transcript.

Landrier *et al.* (8) have shown that tocopherol modulate adiponectin expression via direct regulation of PPARγ gene expression but not through its antioxidant capacity. After this study, one year later the study performed by Shen *et al.* (21), confirmed the Landrier results. In this study when 350 mg/kg of DL-α-tocopherol acetate was administered to obese rats, adiponectin levels were significantly increased in both circulation and adipocytes (mRNA and protein) compared with control group. These findings, and also those suggesting a PPARγ as inductor of adiponectin expression (22, 23), indicated a possible association between vitamin E, PPARγ, and adiponectin levels, and confirmed the hypothesis that vitamin E's activity in increasing adiponectin expression may be through PPARγ upregulation. Indeed, PPARγ can bind to PPRE, the functional region in the adiponectin promoter, and increased

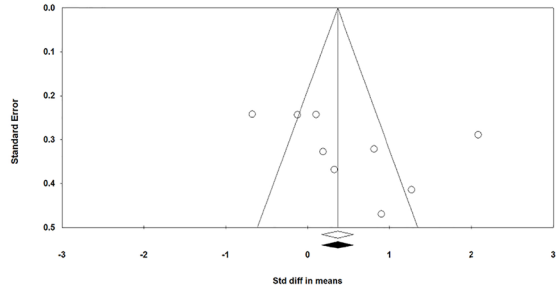

Figure 6: Funnel plot displaying publication bias in the studies reporting the effect of vitamin E supplementation on circulating adiponectin concentrations.

transcription of adiponectin in adipocytes (22). Therefore, vitamin E via induction of PPARγ can increase PPARγ affinity for binding to PPRE and subsequently upregulation of adiponectin (24, 25).

In human studies however, there have been conflicting findings on whether adiponectin augment occurs after vitamin E supplementation, with some RCTs suggest slight reduction or no change (11, 18), while others (9, 10), reporting increasing effect as our finding. It must be kept in mind that our sensitivity analysis showed that removing a treatment arm performed by Manning *et al.* (a), changed the effect of vitamin E on circulating adiponectin levels to non-significance. In this study, vitamin E plus α-lipoic acid was supplemented in subjects with metabolic syndrome. Without this study, we could not see any effect of vitamin E on circulating adiponectin; therefore, our findings should be interpreted with caution.

In our finding, a significant effect of vitamin E was observed only in the trials administered doses ≥400 mg/day and in those lasting ≥6 months. This finding seems to be consistent with other studies (10), which vitamin E was supplemented 400 IU twice per day (b.i.d) for a long term follow up (2 years) in nonalcoholic steatohepatitis patients. Thus, it is possible that vitamin E supplementation over 6 months with doses higher than 400 IU/d might be sufficient to increase adiponectin levels. This meta-analysis had several strengths. All the trials were double-blind, which strengthens the inference for a cause-and-effect relationship. The qualified RCTs generally had a high quality, as assessed by the Jadad scale. However, the present meta-analysis had several limitations that must be considered while interpreting our results. Most importantly, there were few eligible studies, and most of them had small populations (<60 subjects).

Conclusion

In this meta-analysis, a sufficient evidence was found regarding the significant effect of vitamin

E on circulating adiponectin levels, which is more evident in doses higher than 400 mg per day and in trials lasting over 6 months. Additional high-quality well-designed studies should be performed to approve our findings.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None declared.

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