Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2525–2531

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Effect of Omega-3 and vitamin E co-supplementation on serum lipids concentrations in overweight patients with metabolic disorders: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 3 June 2019
Accepted 8 July 2019

Keywords:
Omega-3
Fatty acids
Vitamin E
Lipid profile
Dyslipidemia

ABSTRACT

Background: Results of the studies assessed the effect of omega-3 and vitamin E co-supplementation on lipid profile in patients with metabolic syndrome (MS) are contradictory. Therefore, we carried out a systematic review and meta-analysis of randomized controlled trials (RCTs), to assess the effect of omega-3 and vitamin E co-supplementation on total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in patients with MS.

Methods: A systematic search was performed to find the related articles, up to April, 2019. There was no language and time limitation. Meta-analyses were carried out using both the random and fixed effects model where appropriate, and I2 index was used to evaluate the heterogeneity.

Results: Search yielded 1236 publications. Five RCTs with 254 patients were eligible. Results of the meta-analysis indicated that omega-3 and vitamin E co-supplementation significantly reduced the serum concentrations of TG and LDL, whereas, it had no significant effect on the serum levels of TC and HDL in overweight patients with MS.

Conclusion: Present systematic review and meta-analysis revealed that omega-3 and vitamin E co-supplementation have beneficial effects on lipid profile of overweight patients with MS. It significantly reduced the serum levels of TG and LDL in such patients.

1. Introduction

Metabolic syndrome (MS), as defined by the National Cholesterol Education Program–Adult Treatment Panel III, is the present of at least three out of five cardiovascular risk factors including abdominal obesity, impaired fasting glucose, elevated fasting triglycerides (TG), decreased high-density lipoprotein (HDL) cholesterol, and high blood pressure [1]. Over the past decade, the prevalence of MS has considerably increased [2]. This increase is directly associated with the prevalence of obesity and diabetes [3]. Epidemiological studies have shown that about 10%–20% of adults worldwide, and in some countries and age groups, up to 60% have MS [4]. It has been shown that MS enhances the risk of diabetes and cardiovascular diseases by 5 and 2 folds, respectively [5]. Several studies have shown that modifications in dietary fat composition can affect the risk of cardiovascular disease and MS. Evidence suggests that hypercaloric and hyperlipidic diets, especially rich in saturated fatty acids, promote obesity, insulin resistance, and dyslipidemia [6,7]. It has also been shown that MS and obesity are closely linked to the increase in inflammation and oxidative stress [8,9].

Cardioprotective effects of very long chain omega-3 polyunsaturated fatty acids have been reported previously [10]. It can reduce blood pressure, improved insulin sensitivity, improve vascular endothelial function and modulate inflammation [11]. Vitamin E has long been known as a strong lipid-soluble antioxidant [12]. It inhibits the oxidation of polyunsaturated fatty acids (PUFAs) such as omega-3 fatty acids [13]. Therefore, numerous studies have examined the synergistic effects of these two compounds. Results of the studies assessed the effect of omega-3 and vitamin E co-supplementation on lipid profile in patients with MS were contradictory. In 2016, a study reported that omega-3 and

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https://doi.org/10.1016/j.dsx.2019.07.001
1871-4021/

vitamin E co-supplementation in gestational diabetes women had beneficial effects on serum levels of TG, very-low-density lipoprotein (VLDL), and HDL, whereas, it did not influence total cholesterol (TC) and low-density lipoprotein (LDL) [14]. Another study indicated that this co-supplementation had no significant effect on lipid profile in patients with coronary artery disease [15]. Due to the discrepancy found in the results of the studies assessed the effect of omega-3 and vitamin E co-supplementation on lipid profile in patients with MS, we carried out a systematic review and meta-analysis of RCTs, to assess the effect of omega-3 and vitamin E co-supplementation on TC, TG, LDL and HDL in such patients.

2. Materials and methods

This systematic review was designed according to guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [16].

2.1. Data sources and search strategies

The search terms and strategies were constructed based on PICOS model, that the P stands for patient (overweight patients with metabolic disorders), the I stands for intervention (omega-3 and vitamin E co-supplementation), the C stands for comparator (placebo), the O stands for outcome (TG, TC, LDL-C, HDL-C and VLDL) and the S stands for study design (parallel clinical trial). We searched five international databases includes PubMed, Scopus, ISI web of science, Embase, Cochrane library up to April, 2019. The search strategies were combination of the following keywords: (omega-3 OR "Omega 3" OR ω-3 OR n-3 OR "alpha linolenic acid" OR "alpha-linolenic acid" OR "α-linolenic acid" OR linolenic OR ALA OR "fish oil" OR "Eicosapentanoic acid" OR "docosahexanoic acid" OR DHA OR EPA) AND ("Vitamin E" OR "Alpha-Tocopherol" OR "Vit E" OR Tocopherol) AND (Triglyceride OR Triacylglycerol OR TG OR cholesterol OR Lipoprotein OR "very low density lipoprotein" OR VLDL OR "low density lipoprotein" OR LDL OR LDL-C OR "high density lipoprotein" OR HDL OR HDL-C OR "lipid profile") AND (Intervention OR "controlled trial" OR randomized OR randomized OR random OR randomly OR placebo OR "clinical trial" OR Trial OR RCT) (Supplementary file 1, search strategy).

2.2. Inclusion and exclusion criteria

We included all the related Randomized Controlled Trials (RCTs) without limitation for language. The inclusion criteria is as follows: 1) RCTs with duration of more than 1 week, 2) RCTs which included adults (mean ages $\geq$18 years), overweight patients (body mass index (BMI) > 25), patients with MS and studies that co-supplemented vitamin E and omega-3, 3) RCTs with placebo or control group, 4) reported mean or median values of TG, TC, LDL, VLDL and HDL concentrations in baseline and at the end of the supplementation in control and intervention groups with SD, SEM or 95% CI. Exclusion criteria is as follows: 1) RCTs lacking adequate data for analyzing variables of interest, 2) animal studies, reviews, conference abstracts without original data, posters, letters to the editors, 3) studies included healthy subjects or patients with normal BMI.

2.3. Data extraction and quality assessment

Extraction of data was done independently by 2 authors (OA and RC) with using an excel form, and checked by the third author (AA). At first, titles and abstracts were screened for detection of eligible studies, then, the full text of each article was reviewed to determine whether the article is qualified for inclusion. Finally, following data was extracted: first author, publication year, study location, study population, study design, sample size, mean age of patients, body mass index (BMI) of patients, sources and dosage of vitamin E and omega-3, study duration and study outcomes. Jaded score [17] was used for evaluating the quality of the included studies. This scale assesses the randomization, blinding and the numbers and reasons of dropouts.

2.4. Quantitative data synthesis and statistical analysis

Effect sizes for all the variables of interest were reported as weighted mean differences (WMDs) and 95% CI. The effect sizes were pooled using a random effects model with DerSimonian and Laird method [18]. Wherever within-group changes did not report, mean value at the end of the study was subtracted from the mean at the baseline in each group. To calculate the SD, the following formula was used: SD = square root [(SD pre-treatment) ^{2} + (SD post-treatment) ^{2} − (2R × SD pre-treatment × SD post-treatment)], Correlation coefficient (R-value) was considered 0.8 [19]. When an SEM or SE was reported instead of SD, the SD was calculated based on the following formula: SD= SEM × square root of n (n = sample size in each group). Heterogeneity assessed by I^2 index (I2 value > 50%) [20]. The forest plot was used to present the pooled WMD and its 95% confidence interval (CI) schematically. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study characteristics

Our initial search retrieved 1236 articles. We removed 372 duplicate articles. After evaluating the titles and abstracts of articles, 855 studies were excluded, and 9 articles were selected for full text review. After considering inclusion and exclusion criteria, four articles were excluded (Fig. 1). Finally, this meta-analysis was performed on five trials [14,15,21–23] (Table 1), with 254 participants in which 127 patients were in control group and 127 patients were in intervention group, whose age ranged from 24 to 65 years old. All studies were conducted on patients with MS including type 2 diabetes mellitus [21], gestational diabetes [14], poly cystic ovarian syndrome [22] and Coronary artery disease [15,23]. Their treatment duration was 6 [14], 8 [15,23] and 12 [21,22] weeks. Dosage of omega-3 ranged from 400 mg/day to 1800 mg/day. All of the five studies were conducted in Iran [14,15,21–23]. A total of 5 publications with 5 effect sizes were included in the analysis of total cholesterol and LDL-C, and 4 effect sizes were included in the analysis of TG and HDL-C.

3.2. Meta-analysis

Results of the meta-analysis indicated that omega-3 and vitamin E co-supplementation significantly reduced the serum concentration of TG (WMD: −28.34 mg/dl (95% CI: −37.44, −19.22), I2 = 59.6%) (Fig. 2). In addition, we found that omega-3 and vitamin E co-supplementation statistically reduced the serum levels of LDL (WMD: −8.07 mg/dl, (95% CI: −15.10, −1.05), I2 = 90.9%) (Fig. 3). Whereas, omega-3 and vitamin E co-supplementation did not significantly affect the serum levels of TC and HDL (WMD: −11.48 mg/dl, (95% CI: −24.15, 1.20), I2 = 92.8%; WMD: −0.52 mg/dl, (95%CI: −4/70, 3.66), I2 = 95.5%; respectively) (Figs. 4 and 5).

3.3. Publication bias and sensitivity analysis

Egger's test revealed no evidence for publication bias

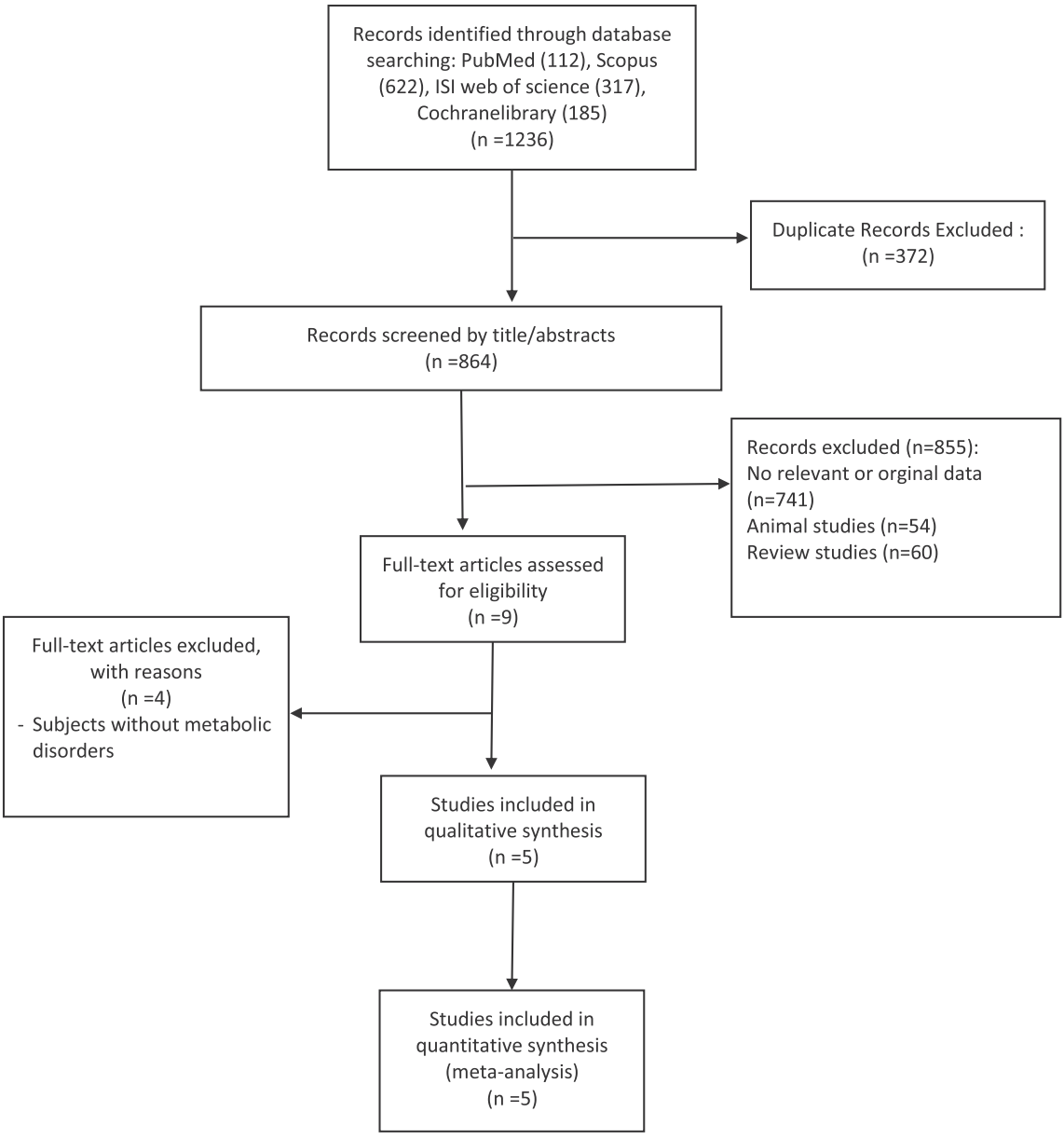

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Table 1
Characteristic of included studies in meta-analysis.

Author	year	country	Study design	participants	sex	Mean age (intervention/ control)	Mean BMI (intervention/ control)	Trial duration (week)	Daily dose of vitamin E (IU)	Type of Omega-3	Daily dose of Omega-3 (mg)	Sample size (intervention/ control)	Jaded score
M.R.Mahmoodi	2014	Iran	R/DB/ PL	Patients with type 2 diabetes	F	28/30.9	54/53.9	12	400	DHA/EPA	1800	22/24	4
M Taghizadeh	2016	Iran	R/DB/ PL	Patients with gestational diabetes	F	28.6/29.4	27.4/28.1	6	400	α-Linolenic acid	400	30/30	5
E Rahmani	2016	Iran	R/DB/ PL	Patients with polycystic ovary syndrome	F	24.9/26.6	28.4/29	12	400	α-Linolenic acid	400	34/34	5
S Saboori	2016	Iran	R/DB/ PL	Patients with Coronary Artery Disease	M	NR/NR	27.08/26.85	8	400	DHA/EPA	300	21/19	3
A Ramezani	2018	Iran	R/DB/ PL	Patients with Coronary Artery Disease	M	45–65	<30/<30	8	400	DHA/EPA	1200	20/20	5

Abbreviations: DB, double-blinded; PC, placebo-controlled; R, randomized; NR, not reported; F, Female; M, Male; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic acid.

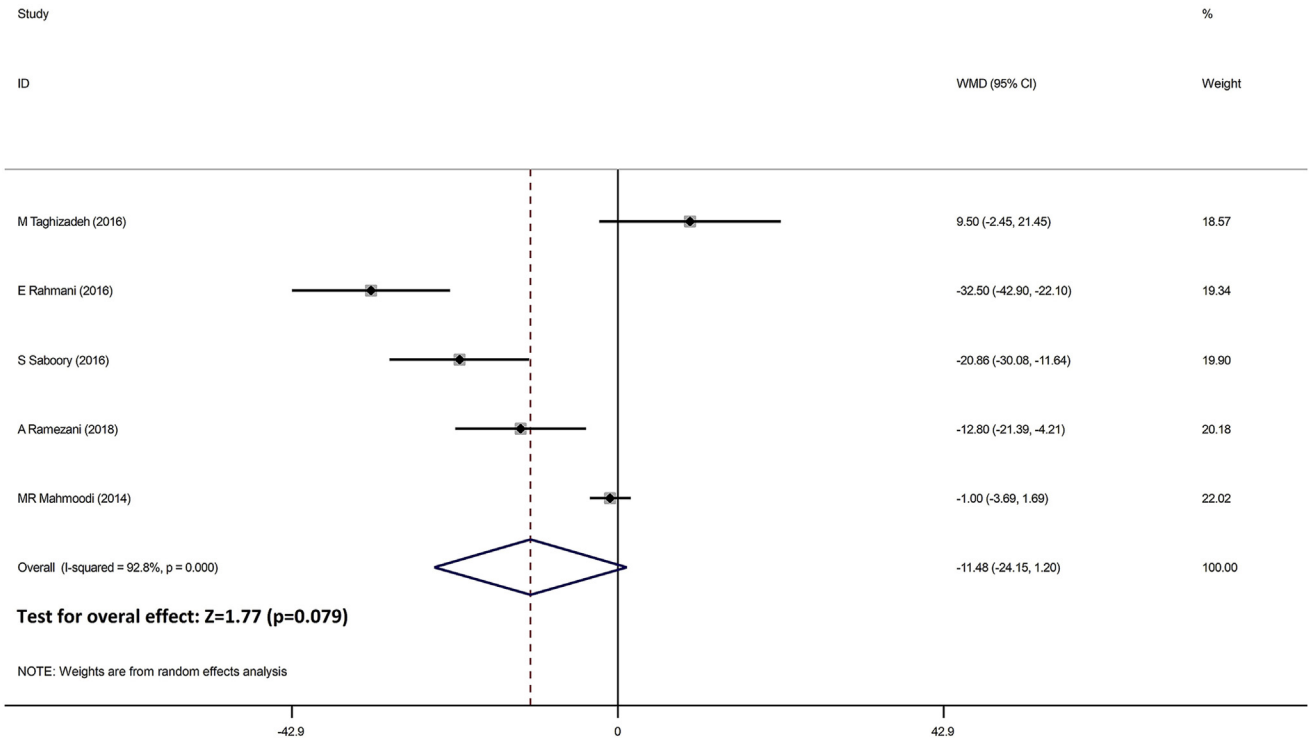

Fig. 2. Forest plot of the effect of combined omega-3 and vitamin E supplementation on total cholesterol.

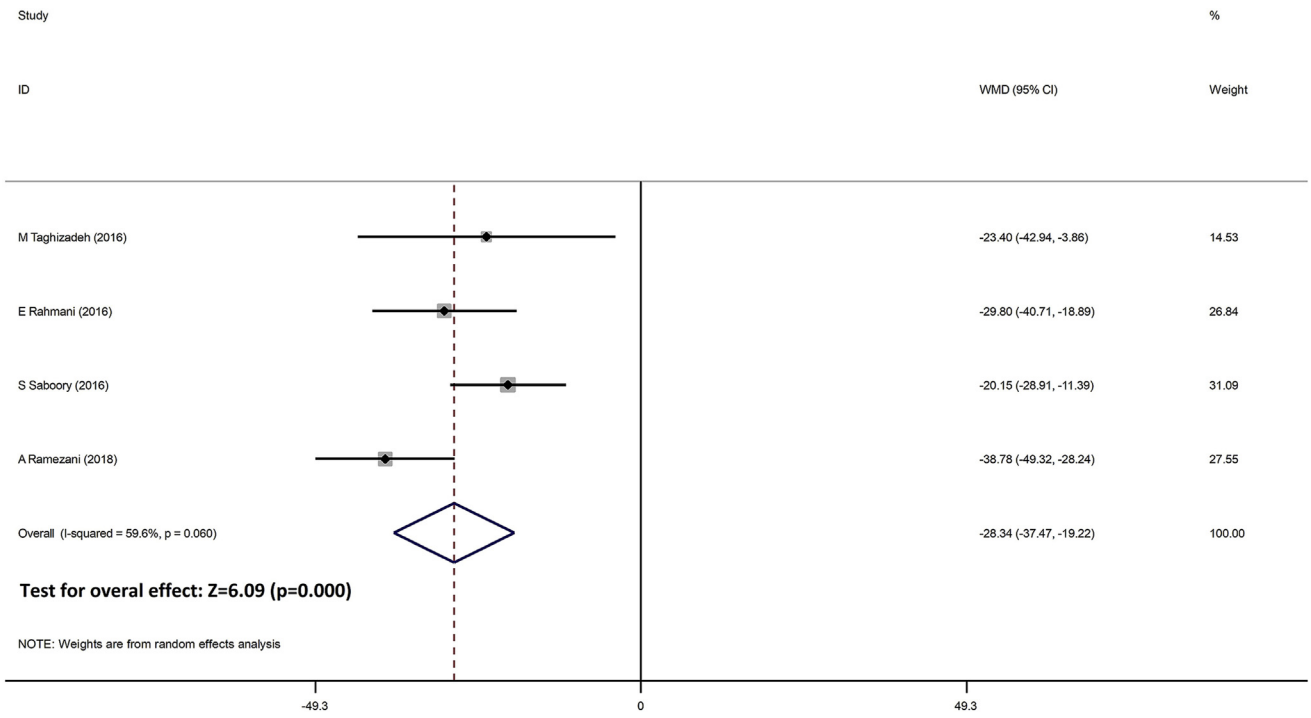

Fig. 3. Forest plot of the effect of combined omega-3 and vitamin E supplementation on triglyceride.

(triglyceride: $p = 0.368$; total cholesterol: $p = 0.647$; LDL: $p = 0.694$ and HDL: $p = 0.491$). To evaluate the strength of our results, we made a sensitivity analysis. However, removing each individual study by sensitivity analysis did not change the pooled effect size.

4. Discussion

Results of the present systematic review and meta-analysis revealed that omega-3 and vitamin E co-supplementation significantly reduced the serum levels of TG and LDL, whereas, it had no

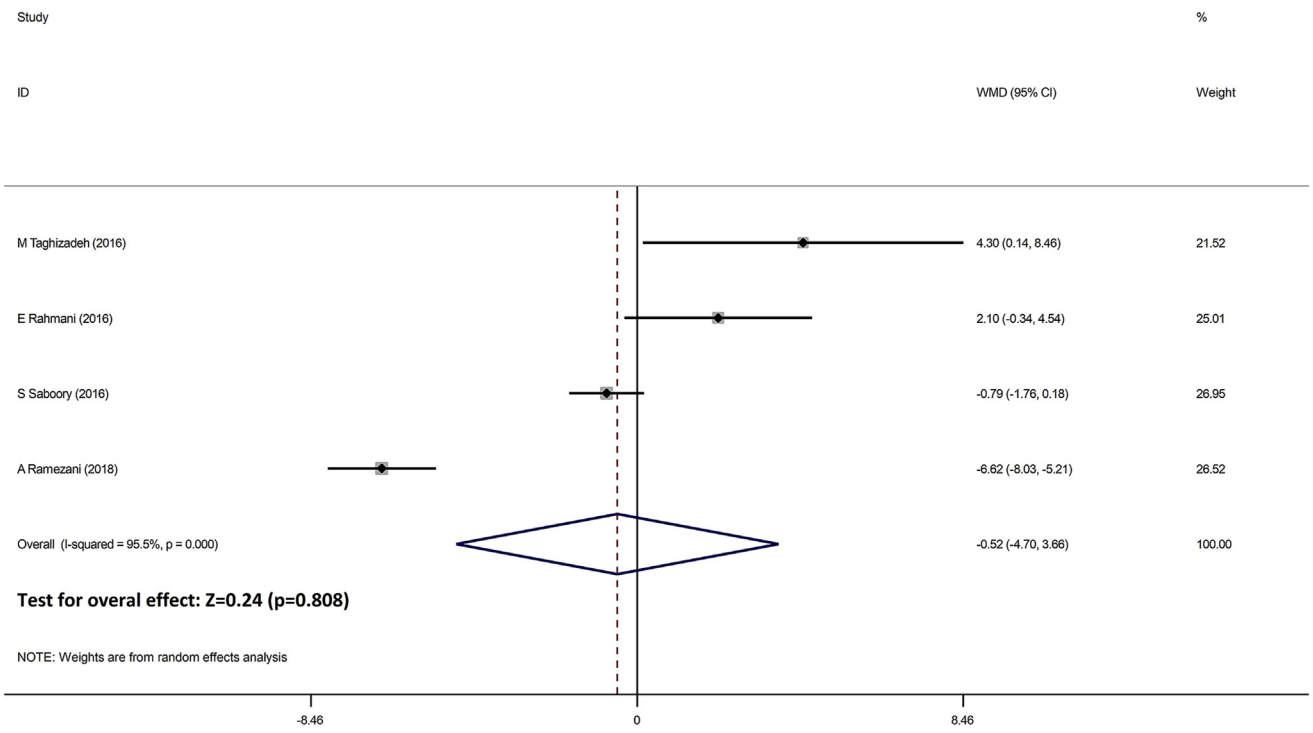

Fig. 4. Forest plot of the effect of combined omega-3 and vitamin E supplementation on high-density lipoprotein.

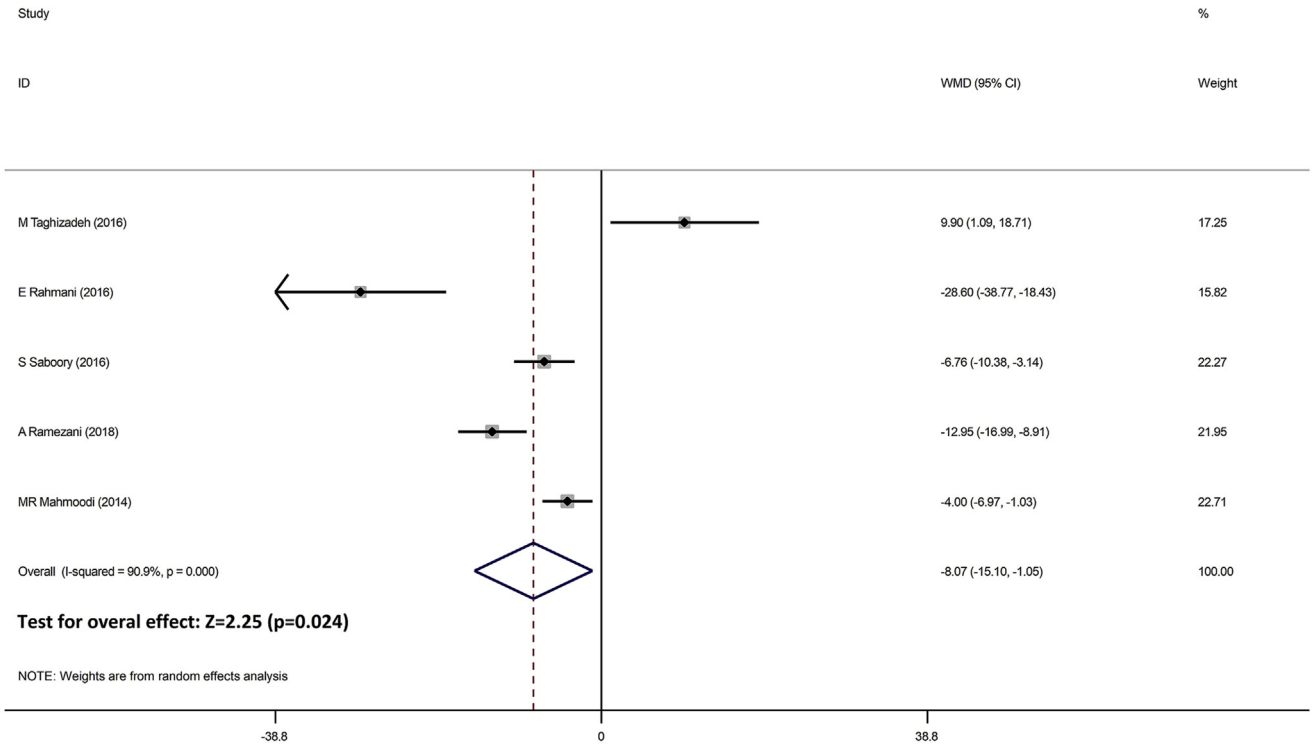

Fig. 5. Forest plot of the effect of combined omega-3 and vitamin E supplementation on low-density lipoprotein.

significant effect on the serum levels of TC and HDL in overweight patients with MS.

The three main components of dyslipidemia related to the MS are the increased levels of both TG and LDL, and the decreased levels of HDL [24]. It has been shown that the insulin resistance and the increased blood levels of insulin which occur in patients with MS, enhance the production of very low-density lipoprotein particles. In addition, the deficiency in insulin-dependent lipoprotein lipase leads to an increase in triglyceride-rich lipoproteins levels in the blood and a decrease in HDL levels [24]. All these abnormalities,

ultimately increase the risk of cardiovascular disease in patients with MS [24]. As a result of the high prevalence of cardiovascular diseases in patients with MS, substantial studies have investigated the clinical management and treatment of dyslipidemia in such patients. Both the American Heart Association and the Institute of Medicine recommend the consumption of omega-3 poly-unsaturated fatty acids to decrease serum TG levels in dyslipidemic patients [25]. The mechanisms in which omega-3 improves the lipid metabolism have been partially clarified. Omega-3 increases the activity of lipoprotein lipase and reduces the secretion of apoB-48, which consequently reduces atherogenic chylomicron remnant [26]. Moreover, it reduces VLDL levels by increasing the activity of lipoprotein lipase and decreasing the hepatic secretion of apoB-100 [26].

Vitamin E is a potent fat-soluble antioxidant compound whose deficiency is associated with many diseases. Lower serum levels of vitamin E in patients with MS has been reported in numerous studies [27,28]. It has been shown that an increase in the reactive oxygen species (ROSs) levels, is implicated in the pathogenesis of the MS [8]. Therefore, an adequate amount of vitamin E levels seems to be essential in such patients. On the other hand, increase in ROSs causes an excessive lipid peroxidation and a damage to proteins and DNA [29]. Vitamin E, as an important part of the non-enzymatic antioxidative barrier, reduces damages of poly-unsaturated fatty acids such as omega-3 fatty acids. Therefore, numerous studies have assessed the synergistic effect of these compounds.

Evidence suggest the beneficial effects of omega-3 supplementation on lipid profile [30]. A recent systematic review and meta-analysis indicated that omega-3 alone could significantly improve TC, LDL, HDL, and TG levels in patients with nonalcoholic fatty liver disease [31]. However, a systematic review and meta-analysis indicated that vitamin E alone has no significant effect on serum lipids including TC, HDL and LDL [32]. Studies that assessed the effect of omega-3 and vitamin E co-supplementation on lipid profile, have found contradictory results [14,15]. Recently, a systematic review and meta-analysis revealed that co-supplementation of omega-3 and vitamin E had no significant effect on HDL, LDL, TC and TG levels [33]. This finding is not in line with our findings. We found that omega-3 plus vitamin E supplementation significantly reduced the serum levels of TG and LDL, whereas, it had no effect on the serum levels of TC and HDL. The reason for this discrepancy between the results might partly, be due to the difference in subjects included in the studies. In the meta-analysis by Sepidarkish et al., [33] there was no limitation on the subjects' health status, and they included both the healthy participants and patients with various types of diseases in the meta-analysis. Whereas, to better understand the effect of this co-supplementation, we only included studies conducted on patients with MS. Therefore, it can be assumed that co-supplementation of omega-3 and vitamin E, may have different effects in different health status.

Our systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of omega-3 and vitamin E co-supplementation on lipid profile in patients with MS. Second, we included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. Third, this review is based on an up to date literature search from a large number of databases. An important limitation of this meta-analysis is the low number of the trials that limits the strength of the conclusion of the present meta-analysis; however, we hope this study will be helpful for future studies.

In conclusion, the present systematic review and meta-analysis indicated that omega-3 and vitamin E co-supplementation had beneficial effects on the lipid profile of the patients with MS. Results of the meta-analysis indicated that this co-supplementation can reduce the blood levels of the LDL and TG. However, further well-designed studies are needed to confirm the results of the present meta-analysis.

Conflicts of interest

All authors declare that they have no competing interests.

Contributions

AA and OA designed the study. RC and OA reviewed and selected the articles. OA and RC extracted needed data from articles. AA and OA performed data analysis and interpretation. AA drafted the manuscript.

Funding

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.001.

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