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Systematic review and meta-analyses of vitamin E (alpha-tocopherol) supplementation and blood lipid parameters in patients with diabetes mellitus

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ABSTRACT

Background and aims: The studies have shown that α-tocopherol supplementation could improve lipid profile in diabetes mellitus (DM) patients. Nonetheless, the result remains inconsistent. Therefore, this meta-analysis was performed to evaluate the efficacy of α-tocopherol supplement on lipid parameters in DM patients.
Methods: We conducted an extensive search via Cochrane Library, PubMed, Scopus, and Web of Science databases to acquire the reported RCTs up to October 2020.
Results: The results showed no effects of α-tocopherol supplementation on lipid profile in DM patients except when used ≥12 weeks.
Conclusions: α-tocopherol supplementation in DM patients had no significant effect on lipid profiles.

1. Introduction

Diabetes mellitus (DM) is manifested by chronic and persistent hyperglycemia over time because of impaired in the secretion or action of insulin [1]. DM has been increasing greatly in recent years, affecting almost 8.5% of the world population [2]. The rapid increase seems unstoppable, leading to the global public health burden [1]. The primary causes of morbidity and mortality in DM are cardiovascular diseases (CVD) [3–7]. Dyslipidemia is defined as increased levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC), and reduced high-density lipoprotein cholesterol (HDL-C) levels [8]. In situations that dyslipidemia uncontrolled, this could lead to chronic inflammation [9]. Chronic inflammation leads to some diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases [10,11]. In comparison to other types of DM, patients with T2DM were mostly observed present with low levels of HDL-C and with high triglyceride (TG), VLDL-C, and LDL-C levels [12–15]. Furthermore, epidemiological data have

Abbreviations: WMD, weighted mean difference; DM, diabetes mellitus; T2DM, Diabetes mellitus type 2; T1DM, Diabetes mellitus type 1; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; α-tocopherol, alpha-tocopherol.

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shown that high LDL-C and low HDL-C levels in patients with DM increase the risk of CVD development [4,6,16,17]. Therefore, control of dyslipidemia could be an appropriate strategy in prevention and treatment of T2DM and other chronic diseases.

Vitamin E is one of the critical fat-soluble dietary antioxidants which naturally exist in two forms, i.e., tocopherols and tocotrienols. Each of them has four subgroups including (R,R,R)-α, -β, -γ, -δ forms. However, the essential form is α-tocopherol, which is mainly obtained from foods rich in vitamin E such as vegetable oils, nuts, seeds and green leafy vegetables [18]. Although obtaining sufficient amounts of vitamin E from foods is a crucial strategy, the majority of the patients with DM did not consume enough of these foods. Sufficient vitamin E is pertinent in the present context because vitamin E plays a critical role to preserve cell membranes of, low-density lipoproteins and polyunsaturated fatty acids, from oxidation with free radicals [19]. The anti-inflammatory and antioxidant effects of vitamin E have been proven. In vivo and in vitro studies have shown that vitamin E can reduce lipid peroxidation by breakdown chain propagation [20]. Furthermore, oxidation of LDL decreases by vitamin E supplementation [21].The documents suggested that vitamin E suppresses the development of atherogenesis by affecting blood vessels smooth muscle and endothelial cells [22,23].

The randomised controlled trials (RCTs) have demonstrated the beneficial effects of vitamin E (α-tocopherol) supplementation in the improvement of blood lipid parameters [24–26]. Nonetheless, the result remains inconsistent, which could be related to the design of the study, the dose of the supplement, method of supplementation, and the subjects' characteristics in the different studies. A meta-analysis of RCTs has demonstrated that tocotrienols supplementation, another form of vitamin E, would significantly increase HDL-C with no considerable effects on LDL-C, total cholesterol (TC), and TG [27]. Both forms of vitamin E supplements (α-tocopherol and tocotrienols) improved glycemic control in patients type 2 DM but only among those with inadequate glycemic control and their serum vitamin E was below the normal ranges at baseline [28]. The beneficial effects of vitamin E among patients with type 1 DM are not known. Systematic review and meta-analysis of RCTs on the effects of vitamin E in the form of α-tocopherol supplementation on blood lipid parameters in patients with DM is scared. Therefore, this systematic review and meta-analysis were conducted to identify the effect of vitamin E (α-tocopherol) supplementation on blood lipid parameters (TC, TG, HDL-C, and LDL-C) in patients with DM.

2. Methods

2.1. Selections process

The inclusion of the RCTs included those that have evaluated the effects of vitamin E in the form of α-tocopherol supplementation on blood lipid parameters (TC, TG, HDL-C, and LDL-C) among patients with a confirmed diagnosis of DM. The literature searched was conducted up to October 2020 and published in English languages. These articles must be published as research papers and randomised, parallel, controlled studies, conducted in humans, and the intervention group received only either α-tocopherol supplement or α-tocopherol supplement with other intervention with duration of more than 4 weeks. The included articles presented their data based on mean changes in blood lipid parameters in both groups. Studies were excluded if included pregnant or lactating women, they had incomplete data or incomplete full-texts, and studies without control or placebo group and they were crossover cases.

2.2. Literature search

The selection procedures were based on the PRISMA guidelines [29]. An extensive search was performed via Cochrane Library, PubMed, Scopus, and Web of Science databases and Google Scholar engine to acquire the reported randomised clinical trials (RCTs) up to October 2020 based on the articles published in English language using the following terms on the abstract, title, keywords, and text. These included diabetes mellitus OR type 2 diabetes OR type 1 diabetes AND vitamin E OR alpha-tocopherol AND plasma lipids OR lipid profile OR serum lipids OR lipoproteins. The details of search could be available in Appendix 1. The references of these included articles were manually searched to identify any articles which did not found via systematic search.

2.3. Data extraction

The two authors (AM, FR) checked all the relevant articles. Then, the duplicate articles based on the title and abstract were excluded. We assessed the quality assessments of the articles using the Jadad's score [30] (Table 1). The cross-check of all information was accomplished two times to diminish potential error. When the two authors disagreed about the subject matters, the third author was consulted to solve the issue (BMY). The details of the studies were extracted and categorised according to the name of first author's, the date of publication, country of research, type of diabetes, sample size, study design, sex, vitamin E supplements and placebo (dosage and type), study duration and study quality. All blood lipid parameters (TC, TG, HDL-C, and LDL-C) amounts were analyzed as mg/dL. To change the units from mmol/L to mg/dL for blood lipid parameters we multiplied mmol/L by 38.67 for HDL-C, LDL-C, and TC and for TG multiplied by 88.57 [31].

2.4. Subgroup analysis

A subgroup analysis was done to determine the heterogeneity of the studies by analysing using (i) study duration (<12 weeks vs $\geq$ 12 weeks), (ii) the dosage of vitamin E (α-tocopherol) supplement (<700 IU/day, 700–900 IU/day, and >900 IU/day)), (iii) the quality of studies according to Jadad's score (<3 vs $\geq$ 3), (iv) method of supplementation (α-tocopherol supplementation alone vs vitamin α-tocopherol supplementation with other treatment).

2.5. Data analysis and quality assessment

The effects of the α-tocopherol supplementation on blood lipid parameters (TC, TG, HDL-C, and LDL-C) in patients with DM were estimated. Data analyses were performed using STATA software version 14.0 (Stata Corporation, College Station, TX, USA) and $p < 0.05$ was considered statistically significant. The mean with standard deviation (SD) and 95% CIs were extracted to evaluate the effects of the α-tocopherol supplementation on blood lipid parameters in patients with DM. Any statistical data provided in the form of standard error (SE) or interquartile range (IQR) was changed into mean and standard deviation (SD) using the appropriate adjustment formulae [32]. To illustrate the existence and the percentage of heterogeneity among the included studies, I-squared statistics (I^2) test and Cochran's Q test were used respectively. The I-squared statistics that was more than 50% and Q test at $p < 0.05$ demonstrated significant heterogeneity. To determine the pooled effect size based on weighted mean difference (WMD) with 95% confidence interval, fixed or random effects models were performed. Subgroup analysis was performed according to the study

Table 1
Specifications of the included studies.

Authors, year	Country	Type of Diabetes	Study design	Sample size (Intervention/ Control)	Sex (M/ F)	Supplement and placebo name (type and dosage)	Duration of study	Blood Lipid parameters	Lifetime (intervention/ control) (Years)	BMI (intervention/ control)	Main outcome	Quality of studies (Jaded score)
Aghadavod et al., 2018 [24]	Iran	Patients with diabetic nephropathy	R/PC/DB randomised, double-blind, placebo-controlled cli	27/27	M/F	vitamin E (800 IUday)/placebo	12 weeks	TC TG HDL-C LDL-C	62.2/64.5	30.9/31.1	Reduced TC and LDL-C and increased HDL-C	4
Hejazi et al., 2015 [38]	Iran	Patients with Type 2 Diabetes Mellitus	R/PC/SB	14/13	M/F	vitamin E (400IU)/placebo (acetate cellulose)	6 weeks	TC TG HDL-C LDL-C	48/46.61	29.22/28.81	No efficacy on TC,TG, HDL-C, LDL-C	2
Fuller et al., 1996 [36]	USA	Patients with type 1 and 2 diabetes	R/PC	15/13	M/F	RRR-α-tocopheryl acetate ((1632 mg (1200 IU))/placebo	8 weeks	TC TG HDL-C LDL-C	47/47	26.4/27.7	No efficacy on TC,TG, HDL-C, LDL-C	2
Ble-Castillo et al., 2005 [37]	Mexico	Patients with Type 2 Diabetes Mellitus	R/PC	13/21	F	D-a tocopherol acetate (800IU/day)/ placebo (corn starch)	6 weeks	TG HDL-C LDL-C TC	51.31/55.33	27.83/27.29	No efficacy on TG, LDL-C and HDL-C and increased TC	1
Boshtam et al., 2005 [39]	Iran	Patients with Type 2 Diabetes Mellitus	R/PC/TB Randomised, triple-blind, placebo-controlled trial	50/50	M/F	vitamin E (200 IU/day)/placebo	27 weeks	TC TG	52.8/54.5	25.0/24.2	No efficacy on TC and TG	3
Shadman et al. (a) 2013 [40]	Iran	Patients with Type 2 Diabetes Mellitus	R/PC/DB	17/19	MF	VitE (100 IU/d) + CLA (3.0 g/d)/CLA (3.0 g/ d) + VitE placebo	8 weeks	TC TG LDL-C	47.6/45.1	28.1/27.4	No efficacy on TC, TG, LDL-C	3
Shadman et al. (b) 2013 [40]	Iran	Patients with Type 2 Diabetes Mellitus	R/PC/DB	9/10	F	VitE (100 IU/d) + CLA (3.0 g/d)/CLA (3.0 g/ d) + VitE placebo	8 weeks	HDL-C	47.6/45.1	28.1/27.4	No efficacy on HDL-C	3
Shadman et al. (c) 2013 [40]	Iran	Patients with Type 2 Diabetes Mellitus	R/PC/DB	8/9	M	VitE (100 IU/d) + CLA (3.0 g/d)/CLA (3.0 g/ d) + VitE placebo	8 weeks	HDL-C	47.6/45.1	28.1/27.4	No efficacy on HDL-C	3
Authors, year	Country	Type of Diabetes	Study design	Sample size (Intervention/ Control)	Sex	Supplement and placebo name (type and dosage)	Duration of study	Blood Lipid parameters	Lifetime (intervention/ control) (Years)	BMI (intervention/ control)	Main outcome	Quality of studies (Jaded score)
de Oliveira et al. (a) 2011 [41]	Brazil	Patients with Type 2 Diabetes Mellitus	R/PC/DB	25/26	M/F	α-tocopherol (800 mg)/placebo	16 Weeks	TC TG HDL-C LDL-C	≥39 38−75 years))	<25 25−30 >30	No efficacy on TC, TG, HDL-C, LDL-C	3
de Oliveira et al. (b) 2011 [41]	Brazil	Patients with Type 2 Diabetes Mellitus	R/PC/DB	25/26	M/F	α-tocopherol (800 mg) + Lipoic acid (LA) (600 mg)/Lipoic acid (LA) (600 mg)	16 Weeks	TC TG HDL-C LDL-C	≥39 38−75 years))	<25 25−30 >30	No efficacy on TC, TG, HDL-C, LDL-C	3
Dass et al., 2018 [25]	India	Patients with Type 2 Diabetes Mellitus	R/PC/OL	31/27	MF	Vitamin E (400 mg) + Metformin (500 mg) + Glimepiride (1 mg)/Metformin (500 mg) + Glimepiride (1 mg)	12 weeks	TC LDL-C TG	51.38/52.7	24.94/25.79	Reduced TC and TG	3
El-Aal et al. (a) 2018 [26]	Palestine	Patients with Type 2	R/PC/SB	10/10	M	Vitamin E (400 mg) + Metformin (500 mg)/ Metformin (500 mg) + placebo	12.8 weeks	TC HDL-C	51.02 (40−60 years)	29.82/29.43	Improvement of TC and TG	2

(*continued on next page*)

Table 1 (*continued*)

Authors, year	Country	Type of Diabetes	Study design	Sample size (Intervention/ Control)	Sex (M/ F)	Supplement and placebo name (type and dosage)	Duration of study	Blood Lipid parameters	Lifetime (intervention/ control) (Years)	BMI (intervention/ control)	Main outcome	Quality of studies (Jaded score)
		Diabetes Mellitus						LDL				
								TG				
El-Aal et al. (b) 2018 [26]	Palestine	Patients with Type 2 Diabetes Mellitus	R/PC/SB	10/10	M	Vitamin E (400 mg) + Metformin (500 mg) + Vitamin C (500 mg)/Metformin (500 mg) + Vitamin C (500 mg)	12.8 weeks	TC	51.02 (40–60 years)	30.74/33.86	Improvement of TC and TG	2
								TG				
								HDL-C				
								LDL-C				
Park and Choi 2002 [42]	Korea	Patients with Type 2 Diabetes Mellitus	R/PC	48/50	MF	α-tocopherol (200 mg) + CSII/placebo (CSII)	8.6 weeks	TC	49.4/49.5	23.0/23.4	No efficacy on TC, TG, HDL-C, LDL-C	1
								TG				
								HDL-C				
								LDL-C				

R/PC/DB: Randomised, double-blind, placebo-controlled trial; R/PC: Randomised, placebo-controlled trial; R/PC/TB: Randomised, triple-blind, placebo-controlled trial; R/PC/SB: Randomised, single-blind, placebo-controlled trial; R/PC/OL: Randomised, placebo open-label trial; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CLA: conjugated linoleic acid; LA: lipoic acid; CSII: Continuous subcutaneous insulin infusion; M: male; F: female.

duration, the dosages of vitamin E (α-tocopherol) supplementation, quality of articles according to Jaded's score, and method of supplementation to characterize the source of heterogeneity. Egger's test [33], Begg's test [34], and funnel plots [35] were used to distinguish the possible publication bias. The sensitivity analysis was performed to explore the contribution of a particular study to the absolute mean difference.

3. Results

3.1. Initial study assessments

A total of 2808 papers were assessed by the two independent authors through a systematic search of four databases which 949 articles were excluded because of duplicate articles. Of 1859 articles, a further evaluation identified that seven articles matched the study criteria and were included in the analyses. Another three studies were identified after further checking the list of references to these included studies. Finally, 10 studies with 14 effect-sizes were included for the meta-analysis study (Fig. 1).

3.2. Study characteristics

Of the total 613 patients included in the study, 302 of them were in the intervention group, and the rest of them (n = 311) were in the control group. The 10 studies were conducted in several countries including USA [36], Mexico [37], Iran [24,38–40], Brazil [41], India [25], Palestine [26], and Korea [42] between the years of 1996 and 2018 (Table 1). All of these RCTs utilizes triple-blind control study (n = 1), double-blind, placebo-controlled study (n = 3); single-blind placebo-controlled study (n = 2), randomised, placebo-controlled trial (n = 3) and placebo open-label controlled study (n = 1). The 10 studies had 12, 12, 11, and 11 arms for assessment of the impacts of α-tocopherol supplement on level of TC, TG, HDL-C, and LDL-C, respectively. The studies (n = 10) were carried out among patients with diabetic nephropathy (n = 1) [24], involved patients with both type 1 and 2 DM (n = 1) [36] and patients with type 2 DM (n = 8) [25,26,37–42]. The study duration ranged between 6 and 27 weeks with the dose of vitamin E supplementations ranged from 100 to 1770 IU per day. The Jadad's score indicated that the one of these studies scored 4 [24], four studies scored 3 [25,39–41], three studies scored 2 [26,36,38], and two studies scored 1 [37,42].

3.3. The impacts of vitamin E supplement on lipid blood tests (TC, TG, HDL-C, and LDL-C)

The assessment of 12 effect sizes through fixed or random effect models showed no effects of vitamin E (α-tocopherol) supplementation on TC levels (WMD: −0.69 mg/dl; 95% CI: −15.03, 13.65; p = 0.93) (Fig. 2). The results of the subgroup analysis remained the same except for the studies with duration ≥12 weeks (WMD: −12.93 mg/dl; 95% CI: −18.25, −7.61) and Jaded score ≥ 3 (WMD: −12.23 mg/dl; 95% CI: −17.34, −7.12) (Table 3).

The WMD of the 12 effect sizes with random effect models demonstrated no significant effects of vitamin E (α-tocopherol) supplementation on TG levels (WMD: 1.33 mg/dl; 95% CI: −9.19, 11.85; p = 0.80) (Fig. 3). The findings remain similar in subgroup analysis. (Table 3).

Pooled effect sizes of 11 effect sizes showed no effects of vitamin E (α-tocopherol) supplementation on HDL-C levels (WMD: 0.68 mg/dl; 95% CI: −1.25, 2.61; p = 0.51) (Fig. 4). In the subgroup analysis, no significant changes after vitamin E (α-tocopherol) supplementation was seen except for the studies with duration ≥ 12 week (WMD: 2.57 mg/dl; 95% CI: 1.49, 3.64), and vitamin E (α-tocopherol)

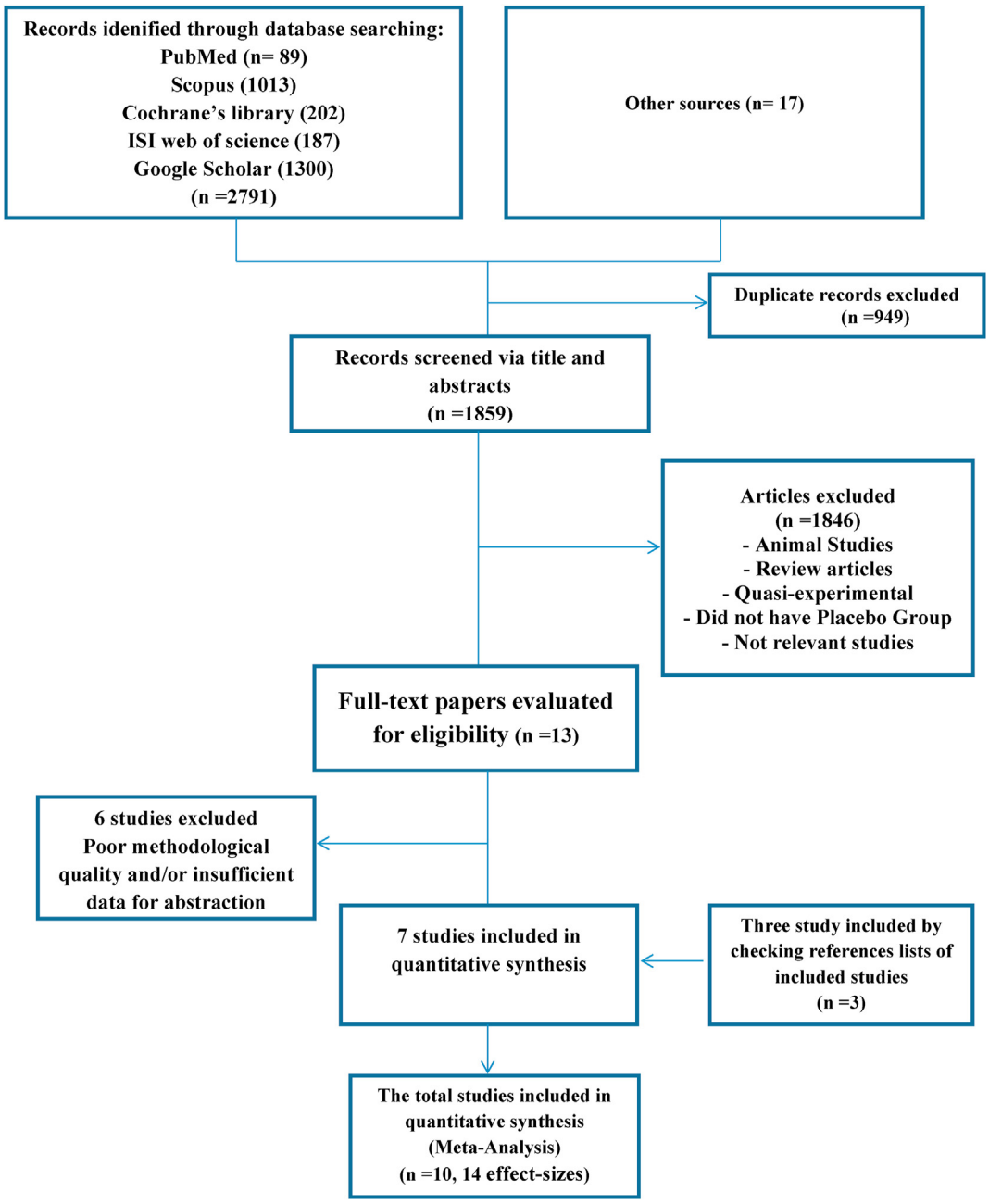

Fig. 1. Flowchart for the process of the study selection.

supplementation combined with other treatment (WMD: 1.80; mg/dl 95% CI: 0.47, 3.13) (Table 3).

Using random effect models in 11 effect sizes indicated no effects of vitamin E (α-tocopherol) supplementation on LDL-C levels (WMD: −0.52 mg/dl; 95% CI: −8.30, 7.25; p = 0.90) (Fig. 5). The results did not change in the subgroup analysis (Table 3).

3.4. Sensitivity analyses

No significant changes were seen in results with the calculated pooled effect size for the effect of vitamin E (α-tocopherol) supplementation on TG, and, LDL-C levels. However, the Sensitivity analyses showed that the pooled WMD for TC was a significant change between the pre- (- 0.69; 95% CI, −15.03, 13.65) and post-sensitivity pooled WMD (−6.35; 95% CI, −12.65, −0.06) excluding the study by Ble-Castillo et al.; and for HDL-C showed the same results before-(0.68; 95% CI, −1.25, 2.61) and after-sensitivity pooled WMD (1.61; 95% CI, 0.37, 2.86) excluding the study by Ble-Castillo et al. (Table 2).

3.5. Publication bias

Although the funnel plots show an asymmetry in this meta-analysis (Fig. 6), no publication bias was reported for the effect of the vitamin E (α-tocopherol) supplementation on TC (Begg's test: p = 0.45 and Egger's test: p = 0.59), TG (Begg's test: p = 0.84 and Egger's test: p = 0.25), HDL-C (Begg's test: p = 0.43 and Egger's test: p = 0.96), and LDL-C (Begg's test: p = 0.76 and Egger's test: p = 0.95) levels.

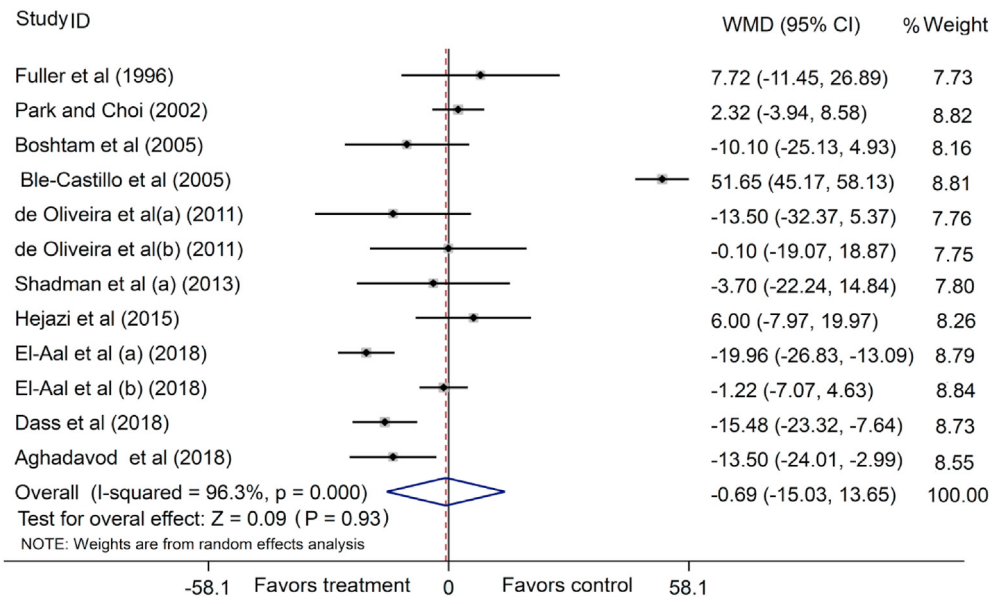

Fig. 2. The impact of vitamin E (α-tocopherol) supplement on TC (mg/dl) in patients with diabetes mellitus. A fixed-effect model was used to determine the pooled effect size. WMD, the weighted mean difference.

Table 2
The outcomes of the pooled effect size utilising leave-one-out sensitivity analysis.

Outcomes	Before conducting sensitivity analysis			Upper & lower of effect size	After conducting sensitivity analysis		
	Number of effect sizes	Pooled WMD (random effect)	95% CI		Pooled WMD (random effect)	95% CI	Excluded Studies
TC	12	- 0.69	−15.03, 13.65	Upper	1.16	−13.84, 16.17	El-Aal et al. (a)
				Lower	−6.35	−12.65, −0.06	Ble-Castillo et al.
TG	12	1.33	−9.19, 11.85	Upper	4.30	−5.51, 14.11	El-Aal et al. (a)
				Lower	−4.38	−11.10, 2.33	Ble-Castillo et al.
HDL-C	11	0.68	−1.25, 2.61	Upper	1.62	0.37, 2.86	Ble-Castillo et al.
				Lower	0.31	−1.76, 2.38	Aghadavod et al.
LDL-C	11	−0.52	−8.30, 7.25	Upper	1.39	−6.07, 8.85	El-Aal et al. (a)
				Lower	−3.40	−10.32, 3.52	Ble-Castillo et al.

TG, triglycerides; TC, total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; WMD, the weighted mean difference.

Table 3
The effects of vitamin E supplement on lipid profile (TC, TG, HDL-C, and LDL-C) in patients with diabetes mellitus according to subgroup analysis.

Outcomes	Subgroups analyses		Number of effect sizes	WMD	(95% CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
TC	Trial duration (week)	≥12 week	5	−12.93	−18.25, −7.61	<0.001	0.68	0.0%	<0.001
		<12 week	7	6.24	−14.36, 26.82	0.56	<0.001	97.6%	
	Vitamin E dose	>900 IU/day	3	−2.05	−14.20, 10.09	0.74	0.29	18.5%	
		700–900 IU/day	5	0.37	−27.14, 27.88	0.98	<0.001	98.6%	
		<700 IU/day	4	0.90	−4.24, 6.05	0.73	0.39	0.1%	
	Jaded score	≥3	6	−12.23	−17.34, −7.12	<0.001	0.67	0.0%	
		<3	6	7.77	−14.77, 30.31	0.50	<0.001	98.0%	
	type of intervention	Vitamin E alone	6	5.00	−23.77, 33.77	0.73	<0.001	96.9%	
		Vitamin E + other treatment	6	−6.99	−15.73, 1.76	0.12	<0.001	83.9%	
TG	Trial duration (week)	≥12 week	5	−2.07	−7.88, 3.73	0.48	0.88	0.0%	<0.001
		<12 week	7	7.06	−11.10, 25.22	0.45	<0.001	86.8%	
	Vitamin E dose	>900 IU/day	3	1.47	−27.50, 30.45	0.92	0.78	0.0%	
		700–900 IU/day	5	5.42	−15.96, 26.79	0.62	<0.001	90.5%	
		<700 IU/day	4	0.33	−5.81, 6.48	0.92	0.71	0.0%	
	Jaded score	≥3	6	−1.39	−7.07, 4.29	0.63	0.78	0.0%	
		<3	6	6.24	−13.67, 26.15	0.54	<0.001	88.5%	
	type of intervention	Vitamin E alone	6	20.53	−8.46, 49.51	0.17	<0.001	80.4%	
		Vitamin E with other treatment	6	−6.64	−16.11, 2.83	0.17	0.006	69.4%	

Table 3 (*continued*)

Outcomes	Subgroups analyses		Number of effect sizes	WMD	(95% CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
Outcomes	Subgroups		Number of effect sizes	WMD	(95% CI)	P within group	P heterogeneity	I^2	P heterogeneity between sub-groups
HDL-C	Trial duration (week)	≥12 week	5	2.57	1.49, 3.64	<0.001	0.24	27.1%	<0.001
		<12 week	6	−1.28	−2.88, 0.31	0.12	0.21	29.5%	
	Vitamin E dose	>900 IU/day	3	−0.58	−5.43, 4.28	0.82	0.15	47.3%	
		700–900 IU/day	4	1.36	−1.68, 4.39	0.38	<0.001	95.2%	
		<700 IU/day	4	0.20	−1.82, 2.21	0.85	0.74	0.0%	
	Jaded score	≥3	5	1.60	−0.87, 4.06	0.20	0.16	40%	
		<3	6	0.17	−2.45, 2.79	0.90	<0.001	91.5%	
	type of intervention	Vitamin E alone	5	−0.49	−3.94, 2.97	0.78	<0.001	83.9%	
		Vitamin E + other treatment	6	1.80	0.47, 3.13	0.008	0.13	41.1%	
LDL-C	Trial duration (week)	≥12 week	6	−8.53	−18.13, 1.06	0.08	<0.001	88.5%	<0.001
		<12 week	5	9.87	−2.96, 22.70	0.13	<0.001	85.8%	
	Vitamin E dose	>900 IU/day	3	−4.75	−20.28, 10.77	0.55	0.09	59.3%	
		700–900 IU/day	5	−0.95	−14.08, 12.19	0.89	<0.001	94.8%	
		<700 IU/day	3	3.54	−8.16, 15.24	0.55	0.03	71.0%	
	Jaded score	≥3	5	−7.31	−19.49, 4.86	0.24	<0.001	82.6%	
		<3	6	4.80	−6.84, 16.43	0.42	<0.001	92.6%	
	type of intervention	Vitamin E alone	5	5.83	−12.85, 24.50	0.54	<0.001	90.6%	
		Vitamin E with other treatment	6	−4.94	−12.89, 3.02	0.22	<0.001	87.1%	

TG, triglycerides; TC, total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; WMD, the weighted mean difference.

4. Discussion

The results of this systematic review and meta-analysis demonstrated that vitamin E (α-tocopherol) supplementation did not affect the levels of TC, TG, HDL-C, and LDL-C in patients with DM. However, the subgroup analysis showed that vitamin E (α-tocopherol) supplementation could significantly decrease TC and increased HDL-C levels when supplementation duration was ≥12 weeks. According to our research, this is the first meta-analysis of RCTs assessing the impacts of vitamin E (α-tocopherol) supplementations on blood lipid parameters in patients with DM. The previous study illustrated that vitamin E supplementation in patients with type 2 DM did not show any effect on TC, cholesterol fraction, TG and insulin resistant [41]. On the other hand, El-Aal et al. (2018) showed significant changes in the metabolic indicators, including improvement in glycemic control, HDL-C and insulin function [26]. The exact mechanisms on how vitamin E affects blood lipid parameters are not known, but it is hypothesized that the changes in oxidative stress are mediating these effects. In this case, prolonged exposure to oxidative stress has unfavorable impacts on lipid metabolism [43].

Vitamin E supplementation would inhibit inflammation and oxidation and improve obesity leading to the improvement in insulin resistance state [44]. Decrease of oxidative stress trough vitamin E supplementation leads to the improvement in lipid metabolism. Also, insulin resistance (IR) is a notable characteristic of various diseases, including type 2 DM, coronary disease, and arterial hypertension [45]. Insulin resistant affect TG metabolism

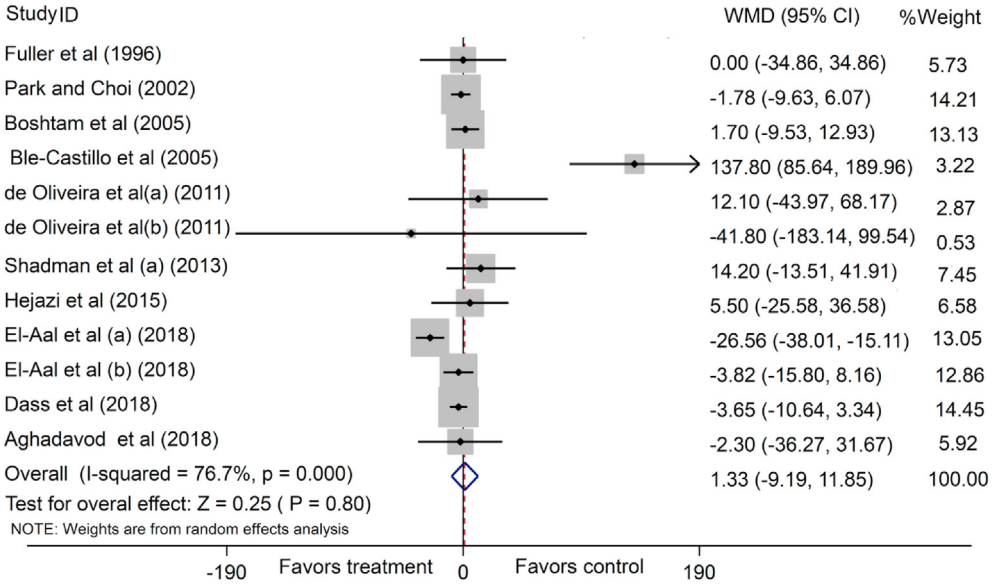

Fig. 3. The impact of vitamin E (α-tocopherol) supplement on TG (mg/dL) in patients with diabetes mellitus. A fixed-effect model was used to determine the pooled effect size. WMD, the weighted mean difference.

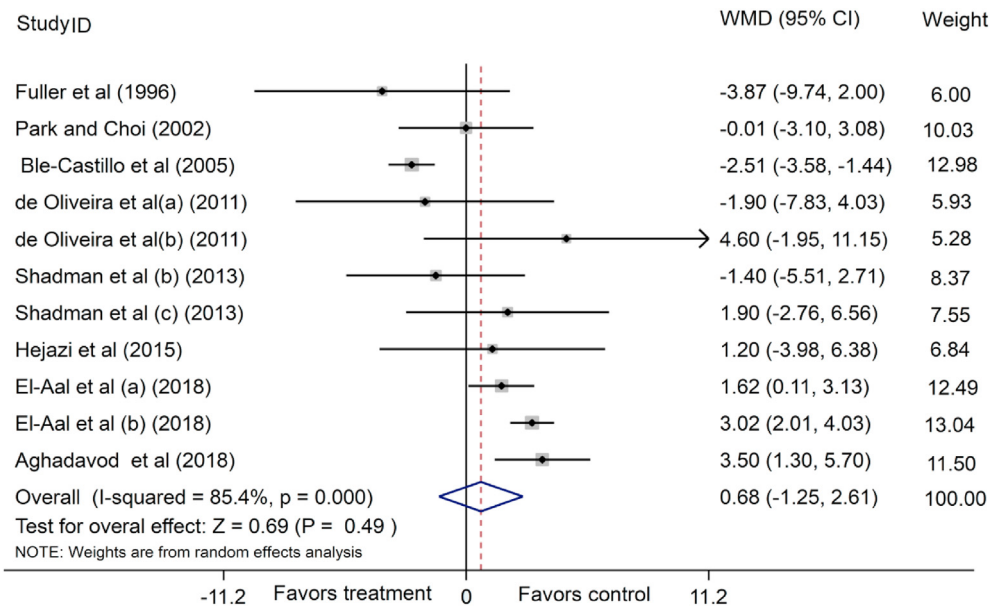

Fig. 4. The impact of vitamin E (α-tocopherol) supplement on HDL-C (mg/dL) in patients with diabetes mellitus. A fixed-effect model was used to determine the pooled effect size. WMD, the weighted mean difference.

producing the unfavorable effect. A significant relationship between serum lipoproteins and IR in patients with type 2 DM was demonstrated [46]. In another study, Upritchard et al. demonstrated that reducing cellular oxidative stress and ROS levels could improve insulin action [47]. Vitamin E improves the IR, and that was relevant to the suppression mechanism of the peroxisome proliferator-activated receptor-alpha expression [48]. D-α-tocopherol regulates the gene expression regarding lipid metabolism, causing a down-regulated the expressions of hepatic PPAR-α, PPAR-β, and PPAR-γ [49]. This is because vitamin E supplements may stimulate the proliferator-activated-receptor-γ (the activator of lipogenic genes and adipocyte differentiation) transduction pathway [50], reducing cholesterol levels. Vitamin E suppresses signal protein kinase C transduction pathways, which is correlated with the metabolism of lipid parameters [51].

4.1. Strengths and limitations

The strength of the meta-analysis should be considered. Although the heterogeneity between the included studies was evident, this study has confirmed the heterogeneity by analysing according to a sub-group analysis. Finally, by using a random-effect model in the meta-analysis, any heterogeneity between the included studies was detected.

There is some limitation for this study including the sample size of some included studies, shortage of high-quality studies as assessed using a Jaded score, and the baseline vitamin E deficiency was not assessed among all the studies which may influence the results of current analyses. The majority of the included studies did not have data about physical activity and energy intake that could be a potential confounder in the current study. Also our meta-

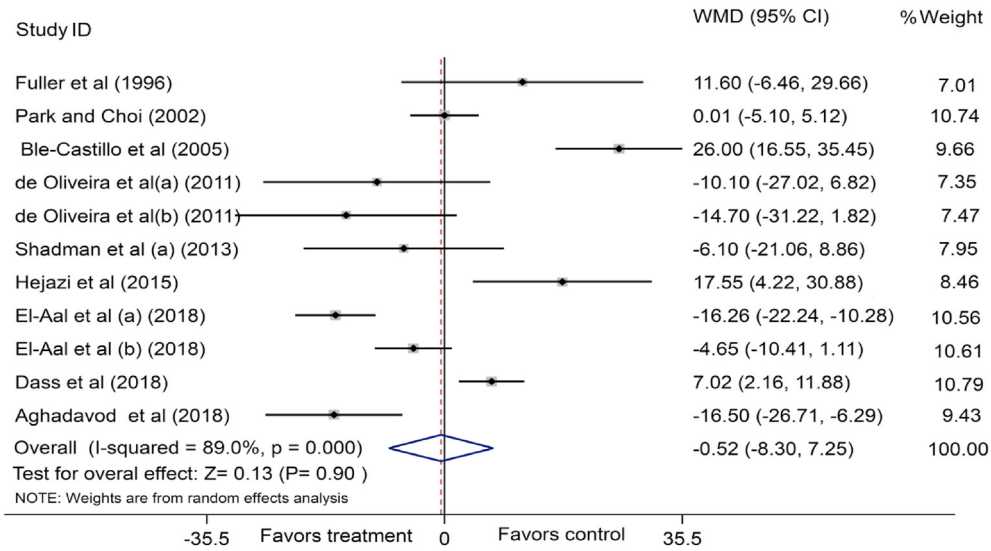

Fig. 5. The impact of vitamin E (α-tocopherol) supplement on LDL-C (mg/dL) in patients with diabetes mellitus. A fixed-effect model was used to determine the pooled effect size. WMD, weighted mean difference.

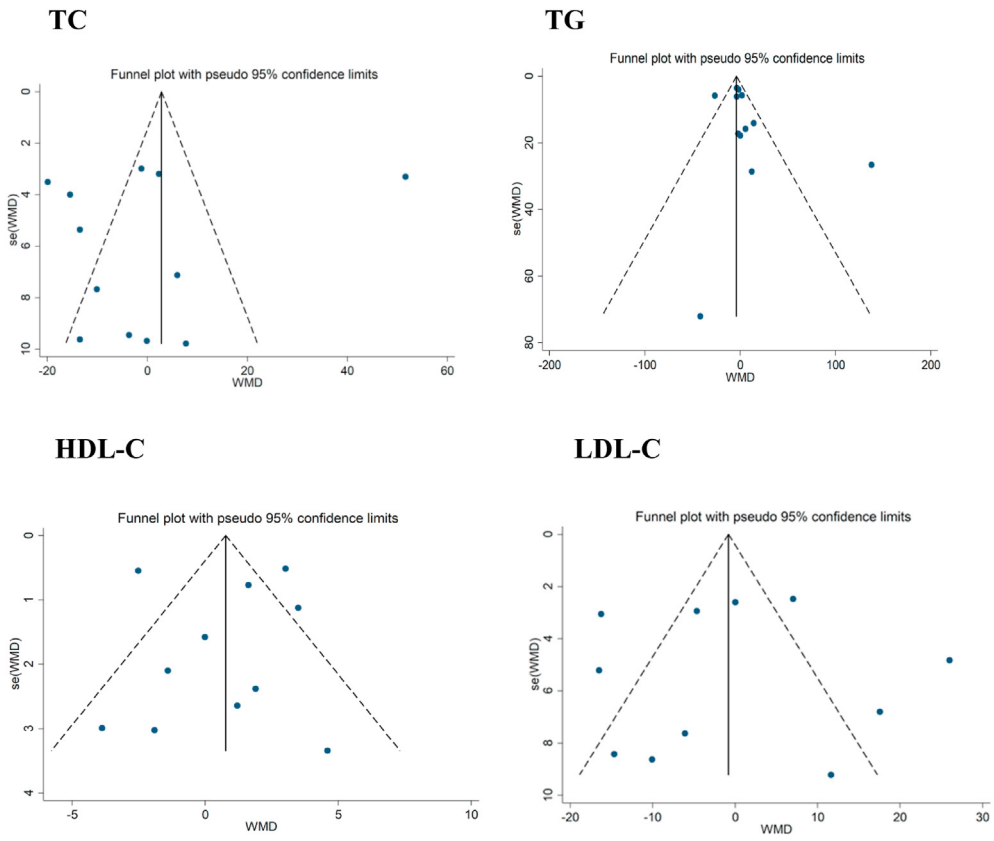

Fig. 6. Funnel plots of trials measured TC, TG, HDL-C, and LDL-C level.

analysis did not register in the PROSPRO. The other sources of potential included articles were not searched which can influence the results of vitamin E (alpha-tocopherol) supplementation. The vast majority of studies originated from Eastern countries; thus, extrapolation of these results to Western populations is questionable. Significant heterogeneity was encountered perhaps due to various regimens, doses, duration, center settings, populations enrolled etc. may significantly undermine the validity of the results. Due to very few studies carried out in many occasions the evidence to support of the result is low and should be interpreted by caution. Many of the studies suffer from significant sources of bias and this could effect on generalization of results. Finally, we included only trials published in English language which this could increase missing chance of some studies.

5. Conclusions

The results of this meta-analysis showed that the vitamin E (α-tocopherol) supplementation did not affect blood lipid parameters (TC, TG, HDL-C, and LDL-C) in patients with DM. However, a subgroup analysis demonstrated that the vitamin E (α-tocopherol) supplementation might have beneficial effects on TC and HDL-C levels when supplemented for ≥12 weeks duration.

Author contributions

AM, and FR responsible for the study design, literature search, data analyses and completed the manuscript. ZH, AM, SMR, MG, and LM reviewed, and extracted the study outcomes. All of the study process was supervised by BMY and EF.

Declaration of competing interest

None.

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Declaration of competing interest

No conflict of interest declared by the authors.

Appendix 1. Literature Search

Patients	Intervention	Outcomes
[diabetes mellitus OR type 2 diabetes OR diabetes mellitus, type 2 OR T2DM OR non-insulin-dependent diabetes mellitus OR NIDDM OR type 1 diabetes OR insulin-dependent diabetes mellitus OR IDDM OR diabetes mellitus, type 1 OR T1DM]	[vitamin E OR alpha-tocopherol OR Vit E OR tocopherol]	[plasma lipids OR lipid profile OR total cholesterol OR serum lipids OR triglycerides OR lipoproteins OR cholesterol OR triacylglycerol OR lipids OR low-density lipoprotein cholesterol OR very-low-density lipoprotein cholesterol OR high-density lipoprotein cholesterol OR HDL-C OR LDL-C OR VLDL-C OR TC OR LDL OR HDL OR VLDL OR TG]

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