Vitamin E and cardiovascular diseases

Subjects: Nursing

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Cardiovascular diseases (CVD) cause about 1/3 of global deaths. Therefore, new strategies for the prevention and treatment of cardiovascular events are highly sought-after. Vitamin E is known for significant antioxidative and anti-inflammatory properties, and has been studied in the prevention of CVD, supported by findings that vitamin E deficiency is associated with increased risk of cardiovascular events. However, randomized controlled trials in humans reveal conflicting and ultimately disappointing results regarding the reduction of cardiovascular events with vitamin E supplementation. As we discuss in detail, this outcome is strongly affected by study design, cohort selection, co-morbidities, genetic variations, age, and gender. For effective chronic primary and secondary prevention by vitamin E, oxidative and inflammatory status might not have been sufficiently antagonized. In contrast, acute administration of vitamin E may be more translatable into positive clinical outcomes. In patients with myocardial infarction (MI), which is associated with severe oxidative and inflammatory reactions, decreased plasma levels of vitamin E have been found. The offsetting of this acute vitamin E deficiency via short-term treatment in MI has shown promising results, and, thus, acute medication, rather than chronic supplementation, with vitamin E might revitalize vitamin E therapy and even provide positive clinical outcomes.

Keywords: vitamin E ; cardiovascular disease ; myocardial infarction ; risk factors ; treatment strategy

1. Introduction

Cardiovascular diseases (CVD) such as atherosclerosis are a major cause of mortality and morbidity worldwide. Vitamin E is a very potent antioxidant, and shows anti-inflammatory properties . Therefore, vitamin E, particularly the α-tocopherol (α-TOH) form, has been suggested as a promising candidate in the prevention of CVD. However, enthusiastic research on vitamin E in large clinical trials has only resulted in controversial and mostly discouraging outcomes, and ultimately has not provided evidence for overall beneficial effects of vitamin E in CVD, with a few exceptions, as discussed below. The aim of the present review is to critically summarize the data available on vitamin E supplementation in CVD in general and systematically investigate potential reasons for the observed conflicting results, and we also provide a perspective on what we have learned from the past trials for future trials. We ultimately redirect the focus from chronic vitamin E supplementation to short-term vitamin E medication in acute clinical settings caused by high inflammatory and oxidative stress, such as MI.

2. Vitamin E and Risk Factors for Cardiovascular Events

The association between vitamin E and risk factors for cardiovascular events will be discussed in detail in the review “Cardiovascular and Metabolic Protection by Vitamin E: A Matter of Treatment Strategy?” by Melanie Ziegler, Maria Wallert, Stefan Lorkowski and Karlheinz Peter and is summarized in Table 1.

Table 1. Vitamin E and Risk Factors for Cardiovascular Events.

Risk Factor	Type of Study	Author	Participants	Endpoints	Vitamin E Dosage
Hypertension					

SBP (systolic blood pressure) DPB (diastolic blood pressure)	Observational	Kuwabara et al. [1]	*n* = 3507	Higher vitamin E intake is associated with a lower percentage of subjects with hypertension	
	Interventional	Boshtam et al. [2]	*n* = 70 mild hypertensive patients	Significant decrease in SBP and DBP (mainly in SBP)	134 mg per day (200 IU) for 27 weeks
	Interventional	Tmj et al. [3]	*n* = 60 mild hypertensive subjects	Decrease in blood pressure	134 mg (200 IU) per day for 12 weeks
	Interventional	Palumbo et al. [4]	*n* = 142 treated hypertensive patients	No clinically relevant effect on blood pressure	300 mg per day for 12 weeks
	Interventional	Mihalj et al. [5]	*n* = 57 treated hypertensive patients	No further effect of vitamin E/C supplementation	720 mg vitamin E and 25 mg vitamin C per day for 8 weeks
	Interventional	Barbagallo et al. [6]	*n* = 12 hypertensive patients	No effect of vitamin E treatment on SBP or DBP	600 mg vitamin E per day for 4 weeks
Hyperlipidemia					
Hypercholesterolemic (HC)	Observational Interventional	Cangemi et al. [7]	*n* = 30 HC patients *n* = 20 healthy subjects *n* = 30 HC patients	Lower vitamin E plasma level in HC patients vs. healthy subjects Administration of atorvastatin restored vitamin E/TC plasma level	10 mg atorvastatin per day for 30 days
	Observational	Shin et al. [8]	*n* = 76 HC patients	Increased α-TOH/lipid plasma level in HC patients	20–40 mg simvastatin per day for 8 weeks

	Observational	Blom et al. [9]	*n* = 738 HC patients	Increased vitamin E/TC plasma level in evolocumab (anti-PCSK9 antibody)-treated patients from baseline to week 52,	10 or 80 mg atorvastatin per day or 80 mg atorvastatin plus 10 mg ezetimibe per day for 52 weeks, 420 mg Evolocumab or placebo for 8 weeks
	Interventional	Liu et al. [10]	*n* = 19 HC patients	Increased vitamin E/LDL-C plasma level in atorvastatin-treated HC patients	10 mg atorvastatin per day for 5 months
	Interventional	Leonard et al. [11]	*n* = 44 HC patients	Vitamin E supplementation did not alter cholesterol levels under statin therapy	268 mg (400 IU) vitamin E per day or placebo for 12 weeks
Thrombosis					
	Interventional	Glynn et al. [12]	*n* = 39,876 women aged 45 and older	Women taking vitamin E were 21% less likely to suffer a venous thromboembolism	Vitamin E (540 mg) or a placebo on alternate days over a 10-year period.
	Interventional	Vuckovic et al. [13]	2506 patients with venous thrombosis, 2506 partner controls, and 2684 random-digit-dialing (RDD) controls *n* = 96 patients supplemented with vitamin E	No association of vitamin E supplementation with a reduced venous thrombosis risk	No information was obtained on the dosage of vitamin E intake
Age					
	Observational	Ortega et al. [14]	*n*= 120 aged subjects (65–91 years)	Lower vitamin E intake and α-TOH/TC plasma level correlates with cognitive impairment in elderly	-

	Observational	Vatassery et al. [15]	48 healthy male volunteers aged 24–91 years	α-TOH plasma level remained unchanged, decreased α-TOH level in platelets of elderly subjects	-
	Observational	Capuron et al. [16]	*n* = 69 aged subjects (73–86 years)	Lower α-TOH plasma level in subjects with poor physical and mental health status	-
	Observational	Requejo et al. [17]	*n* = 120 aged subjects (65–91 years)	95.2% are below recommendations of a-TOH intake	-
	Observational	Rudman et al. [18]	*n* = 34 eating-dependent nursing home residents	The vast majority did not receive micronutrient supplements	-
	Interventional	De la Fuente et al. [19]	*n* = 33 aged subjects (65–75 years) *n*= 30 controls (25–35 years)	α-TOH improves immune functions and therefore health in aged people	200 mg α-TOH per day for 3 months
Obesity					
	Observational	Silva et al. [20]	*n* = 33 overweight adolescents *n* = 42 obese adolescents *n* = 75 healthy adolescents (10–15 years)	Crude and energy-adjusted intake of vitamin E positively correlate with BMI, but not with plasma level of vitamin E; α-TOH/LDL-C and α-TOH/TC decrease in obese and overweight adolescents	-
	Observational	Mehmetoglu et al. [21]	*n* = 98 obese patients *n* = 78 healthy subjects (18–65 years)	Decreased α-TOH/TC + TG plasma level in obese subjects	-
	Observational	Kljno et al. [22]	*n* = 17 obese girls *n* = 7 healthy girls (8–15 years)	α-TOH/total lipids decreased in plasma and in LDL in obese subjects	-

	Observational	Strauss et al. [23]	*n* = 6139 children (6–19 years) enrolled in the NHANES III	Decreased α-TOH/TC + TG plasma level in obese subjects	-
	Observational	Molnar et al. [24]	*n* = 15 obese adolescents *n* = 16 healthy adolescents (13–16 years)	α-TOH/TC + TG plasma level remained unchanged in obese subjects	-
	Observational	Gunanti et al. [25]	6139 children (8–15 years) enrolled in the 2001–2004 NHANES	Adequate plasma level of α-TOH/TC are associated with reduced probability of overweight	-
Diabetes mellitus type 2 (DMT2)					
	Observational	Schneider et al. [26]	*n* = 31 DMT2 patients (46–79 years) *n* = 31 control subjects (38–63 years)	VLDLs and LDLs of DMT2 patients contained fewer vitamin E molecules compared to controls due to PLPT	-
	Observational	Galvan et al. [27]	*n* = 12 male DMT2 patients (49–54 years) *n* = 19 control subjects (29–34 years)	Insulin infusion decreased α-TOH/LDL-C plasma level	-
	Observational (meta-analysis)	Kollerits et al. [28]	*n* = 20,136 subjects	Vitamin E-binding protein afamin is an independent predictor for DMT2 incidence, increase in afamin is associated with prevalence DMT2	-
	Observational/ Interventional	Mayer-Davis et al. [29]	*n* = 895 non-diabetic adults (45–65 years) (*n* = 318 non-supplement users and *n* = 577 supplement users)	α-TOH plasma level is decreased in DMT2 patients and correlates with diabetes incidence, but not the nutritional intake/use of supplements	-/not defined

Observational	[30] et al.	*n* = 62 DMT2 patients (49–64 years) *n* = 20 controls subjects	Decreased α-TOH/TC, TG serum level in diabetic patients with macroangiopathy versus without vascular changes	-
Observational	Salonen et al. [31]	*n* = 944 male healthy subjects (42–60 years)	Decreased α-TOH plasma levels associated with increase diabetes risk	-
Observational	Eljaoudi et al. [32]	*n* = 60 DMT2 patients *n* = 40 healthy subjects (31–76 years)	Decreased α-TOH plasma level in DMT2	-
Observational	Nourooz-Zadeh et al. [33]	*n* = 87 DMT2 patients *n* = 41 healthy subjects (17–86 years)	Decreased α-TOH/TC plasma level in DMT2	-
Observational	Mehmetoglu et al. [21]	*n*= 98 obese subjects *n* = 78 healthy subjects (18–65 years)	no correlation of α-TOH/TC + TG plasma level and insulin resistance in obese subjects	-
Interventional	Rafighi et al. [34]	*n* = 170 DMT2 patients (30–60 years)	Vitamin E supplementation decreased blood glucose level, antioxidative capacity, (increased SOD and GSH enzyme activity), oxidative stress and insulin resistance	200 mg (300 IU) vitamin E (/day) and 267 mg vitamin C per day for 3 months
Interventional	Manning et al. [35]	*n* = 80 healthy subjects (38–57 years)	Vitamin E supplementation decreased inflammatory processes, fasting plasma glucose and improved insulin sensitivity in overweight subjects	537 mg (800 IU) vitamin E per day or placebo for 3 months

	Interventional (Meta-analysis)	Xu et al. [36]	*n* = 714 subjects	vitamin E supplementation did not change glycemic control (HbA1c, fasting glucose, fasting insulin)	134–1074 mg (200–1600 IU) per day for 6–27 weeks
Fatty Liver Disease					
	Observational	Erhardt et al. [37]	*n* = 50 NASH patients *n* = 40 healthy controls (35–67 years)	Decreased α-TOH plasma levels in NASH patients	-
	Observational	Machado et al. [38]	*n* = 43 NASH patients *n* = 33 healthy controls (27–68 years)	Increased α-TOH plasma levels in NASH patients	-
	Interventional	Violet et al. [39]	*n* = 6 female NASH patients (33–53 years) *n* = 10 female healthy controls (19–35 years)	Alteration of α-TOH kinetics in women with obesity-associated hepatosteatosis compared to healthy controls, decreased release of α-TOH from the liver, lower α-TOH plasma level	2 mg α-TOH once
	Interventional	Sanyal et al. [40]	*n* = 167 NASH patients (*n* = 83 placebo, *n* = 84 α-TOH, 34–59 years)	α-TOH supplementation improves ALT, AST, lobular inflammation and NASH compared to placebo treated group	537 mg (800 IU) α-TOH per day or placebo for 2 years
	Interventional	Lavine et al. [41]	*n* = 11 NASH patients (<16 years)	α-TOH supplementation decreased ALT, AST, ALP	268–805 mg (400–1200 IU) α-TOH for 4–10 months
Metabolic syndrome (MetS)					
	Observational	Ford et al. [42]	MetS patients and healthy controls from NHANES III (≥20 years)	Lower α-TOH plasma level in MetS patients	-

	Observational	Beydoun et al. [43]	*n* = 3008–9099 participants from NHANES 2001–2006 (20–85 years)	Higher α-TOH plasma level in MetS patients	-
	Observational	Yen et al. [44]	*n* = 72 MetS patients *n* = 105 healthy controls	α-TOH/TG plasma level remained unchanged	-
	Interventional	Mah et al. [45]	*n* = 10 MetS patients *n* = 10 healthy controls	MetS patients have lower α-TOH /lipid plasma level and lower α-TOH absorption and impaired hepatic trafficking compared to healthy subjects	15 mg α-TOH once

3. **Cardiovascular Events, particularly MI**

An early study by Gey et al. [46] found a strong inverse association between plasma vitamin E level and mortality of ischemic heart disease. Furthermore, the risk of angina pectoris was inversely associated with the plasma concentration of vitamin E in a case-controlled population study of 110 cases of angina, even after adjustment for age, smoking habit, blood pressure, lipids, and relative weight [47].

Recently, Huang et al. reported in a long-term prospective cohort study, including biochemical analysis of 29,092 participants, that higher baseline serum α-TOH was associated with lower risk of overall mortality and mortality from all major causes. This study supports the long-term health benefits of higher serum α-TOH for overall and disease-specific mortality such as CVD [48]. Several observational studies [49][50][51][52][53][54][55][56] have consistently shown that vitamin E supplementation and/or high vitamin E intake is associated with a decreased risk of CVD. To our knowledge, only one Mendelian randomization study in China showed that high vitamin E levels were associated with an increased risk of CVD [57]. Despite this study, the overall consistency in the other studies has led many to suggest that vitamin E supplements may reduce the risk of CVD and several interventional trials have begun to study the cardioprotective effect of vitamin E.

Most studies have focused on vitamin E and the risk of CVD in general, while only a few have looked at the risk of major single causes of CVD like MI. A recent study from China stated that high vitamin E levels could increase the risk of MI [57]. A prospective study by Hak et al. [58] also reported that men without a history of CVD and with higher plasma vitamin E tended to have an increased MI risk. Hense and colleagues [59] found no association between serum vitamin E concentration and MI risk in their study population; however, they suggested that this might have been due to the high average levels of vitamin E in their study population.

A high plasma level may not be associated with a lower risk of MI; nevertheless, an interesting observation is a decrease in vitamin E plasma level in MI patients [60]. Within the first 48 h after MI, the plasma level of vitamin E declines significantly by 26% [61], and remains low until the third day after the start of the catabolic response [62]. Following an infarct, Sood et al. [63] showed that reperfusion was associated with excessive oxidative stress and increased consumption of this antioxidant not only in the ischemic but also in the reperfused myocardium. Vitamin E can be suggested as a valid marker for reperfusion and supplementation of vitamin E could be a therapeutic option for antioxidative protection of the myocardium in the acute setting.

Overall, numerous observational studies have consistently reported that high vitamin E intake or supplementation is associated with a decreased risk of CVD and overall mortality. However, no interventional trials in humans has shown, so far, the benefit of a supplementation of vitamin E to prevent any cardiovascular event. In contrast, promising preclinical data [64], the decrease in vitamin E plasma level within the first 48 h after MI and the high demand for vitamin E during reperfusion justify further investigations of a short-term vitamin E supplementation in patients presenting with acute MI.

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