Critical Review

Vitamin E: Regulatory Role in the Cardiovascular System

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Abstract

Cardiovascular disease (CVD) is one of the major causes of morbidity and mortality, all around the world. Vitamin E is an important nutrient influencing key cellular and molecular mechanisms as well as gene expression regulation centrally involved in the prevention of CVD. Cell culture and animal studies have focused on the identification of vitamin E regulated signaling pathways and involvement on inflammation, lipid homeostasis, and atherosclerotic plaque stability. While some of these vitamin E functions were verified in clinical trials, some of the positive effects were not translated into beneficial outcomes in epidemiological studies. In recent years, the physiological metabolites of vitamin E, including the liver derived (long- and short-chain) metabolites and phosphorylated (α-, γ-tocopheryl phosphate) forms, have also provided novel mechanistic insight into CVD regulation that expands beyond the vitamin E precursor. It is certain that this emerging insight into the molecular and cellular action of vitamin E will help to design further studies, either in animal models or clinical trials, on the reduction of risk for CVDs. This review focuses on vitamin E-mediated preventive cardiovascular effects and discusses novel insights into the biology and mechanism of action of vitamin E metabolites in CVD. © 2019 IUBMB Life, 71(4):507–515, 2019

Keywords: vitamin E; α-tocopherol; long-chain metabolites; tocopheryl phosphate; cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) is a group of disorders united with vascular and cardiac functions such as myocardial infarction, heart failure, and atherosclerosis. With the highest mortality and morbidity rates, CVD is also the major cause of death all around the world. According to the World Health Organization report, an estimated 17.5 million people died from CVD in 2012 that represents 31% of all global deaths (1). Nearly 4 million people per year die from CVD in European countries. CVD-related deaths are expected to reach more than 23.6 million, globally, by 2030 due to increased incidence of the disease (2).

Various risk factors in the progression of cardiovascular disorders have been well documented by epidemiological studies (3). Studies identifying the major risk factors for developing CVD focus on serum cholesterol, hypertension, diet, and smoking. While high blood cholesterol levels (defined as 240 mg/dL or higher) are expected to lead to 18% of strokes and to 56% of ischemic heart disease, which equals to 4.4 million deaths per year (4), antecedent hypertension was observed in 75% of patients with heart failure (5). With regard to attributable deaths, tobacco use causes about 1.6 million CVD-related deaths (9% of all CVD), followed by high blood glucose (6%), physical inactivity (6%), and obesity (5%) (6). An inverse association between Vitamin E supplementation and risk of CVD has been also demonstrated in several studies (7–9).

Tocopherols and tocotrienols are two forms of vitamin E and each compound has four analogs: α, β, γ, and δ (10). Despite the proposed beneficial role of vitamin E in preventing free radical damage, non-antioxidant cellular effects have been determined as major pathways for disease protection. Non-antioxidant

Abbreviations: *α-CEHCs, α-carboxyethyl hydroxychromans; CVD, Cardiovascular disease; CPS-II, Cancer Prevention Study II; FS, Finnish Cohort Study; IWHS, Iowa Women's Health Study; JNK, C-Jun N terminal kinase; LDL, Low density lipoprotein; NFκB, Nuclear factor-kappa B; Nrf2, Nuclear factor erythroid 2–related factor 2; NHS, Nurses' Health Study; oxLDL, oxidized LDL; PKC, Protein kinase C; PPAR, Peroxisome proliferator-activated receptor; SHHS, Scottish Heart Health Study; TNF-α, Tumor necrosis factor α; TP, Tocopheryl phosphate*

Volume 71, Number 4, April 2019, Pages 507–515

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Received 30 October 2018; Accepted 24 January 2019

DOI 10.1002/iub.2020

Published online 18 February 2019 in Wiley Online Library (wileyonlinelibrary.com)

cellular effects of vitamin E and some of its metabolites include the regulation of signaling pathways that specifically modulate transcription factors as well as signal transduction proteins/enzymes (11). During the past two decades, vitamin E has been shown to modulate cellular responses including survival, inflammation, migration, secretion, and immunity either by modulating enzymes in signal transduction pathways such as protein kinase B, protein kinase C (PKC), protein phosphatase 2A, protein tyrosine phosphatase, phosphoinositide 3-kinase, phospholipase A2, 5-, 12-, and 15-lipoxygenases, and MAPK or regulating activities of specific transcription factors such as nuclear factor-kappa B (NFκB), nuclear factor erythroid 2–related factor 2 (Nrf2), and peroxisome proliferator-activated receptor gamma (PPARγ) (12). However, conflicting findings, obtained from a large number of clinical trials, failed to translate beneficial outcomes in humans. Recent literature has discovered novel and even unexpected mechanistic insights of vitamin E metabolites derived by hepatic metabolism in CVD regulation (13). In this review, the role of vitamin E and its metabolites against CVD, which have been demonstrated by *in vitro/in vivo* experiments, together with clinical studies, has been summarized and cellular and molecular outcomes regarding its beneficial role have been highlighted.

VITAMIN E AGAINST CVD

Vitamin E is a fat-soluble vitamin that has critical roles in various diseases. Many *in vitro/in vivo* and clinical studies have been performed with α-tocopherol, the biologically most active form of vitamin E. The results obtained from those studies showed us that vitamin E regulates a number of cell properties such as signal transduction, cell proliferation, and gene expression. In this section, we summarize the role of vitamin E on CVD including atherosclerosis, ischemia/reperfusion, and heart failure.

In Vitro and In Vivo Experiments

A number of cell culture and animal studies reported the preventive role of α-tocopherol in CVD due to its important effects in modulating signaling pathways and gene expression (Table 1). The first evidence on the effect of α-tocopherol comes from Azzi's group which is related to its inhibitory capacity on PKC activity followed by a downregulation of smooth muscle cell (SMC) proliferation in rat aorta smooth muscle (A7r5) and human smooth muscle (HAI) cell lines (14–16). Alpha-tocopherol has also shown to be an inhibitor of superoxide production in human adherent monocytes by impairing assembly of NADPH-oxidase and attenuating of p47 membrane translocation and phosphorylation which results from its PKC inhibitory capacity (17). Upston et al (31) showed that α-tocopherol does not reduce lipid peroxidation in CVD lesions. Another important data, reported also by Azzi's group have shown that treatment of human SMCs, HL-60 macrophages, and THP-1 monocytes by α-tocopherol inhibited the uptake of oxidized low-density lipoprotein (oxLDL) by reducing CD36 expression (18, 19). Later on, it has been reported that α-tocopherol decreases oxLDL-mediated foam cell formation via preventing NFkB induction and P-selectin expression in U937 macrophage cell line (20). In parallel, vitamin E containing HDL was shown to reduce oxLDL-stimulated foam cell formation, oxidative stress, and apoptosis in mouse macrophage RAW264.7 cell line (32).

Atheroprotective effects of vitamin E have also been tested in animal models. Dietary intake of vitamin E, by using palm, olive, or sunflower oil supplemented diets, was found to be related to

TABLE 1 *Regulatory effects of vitamin E against cardiovascular diseases tested by in vitro/in vivo experiments*

Mechanism of Action	*Cell Type or Animal Model*	*References*
Inhibition of cell proliferation and LDL oxidation by modulating PKC activity together with p47 phosphorylation	Rat aorta smooth muscle (A7r5), human smooth muscle (HAI), and primary human monocyte cells	(14), (15), (16), (17)
Inhibition of oxLDL uptake through the downregulation of CD36	Human aortic smooth muscle, HL-60 differentiated macrophage, THP-1 monocyte, and macrophage cells	(18, 19)
Decrease in lipid accumulation and inflammatory response by inhibiting NFkB signaling pathway	U937 macrophage	(20)
Protection against atherosclerotic lesion development and aorta damage	$LDLR^{-/-}$ mice and Wistar rats	(21), (22)
Reduction of cholesterol-induced atherosclerotic lesions through inhibition of CD36, PKC signaling, MMP-1 and -9, c-jun phosphorylation as well as the induction of Nrf2, PPARγ, LXRα, and ABCA-1 levels	$ApoE^{-/-}$ mice and hypercholesterolemic rabbits	(23), (24), (25), (26), (27), (28)
Reduction of mortality following acute myocardial infarction or heart failure	Rat	(29), (30)

reduced atherosclerotic lesion size in the aorta of mice (33). Additionally, mice receiving vitamin E, together with Coenzyme Q10, showed attenuation in the progression of atherosclerosis at the aortic root, arch, and descending thoracic aorta (34). Another group reported vitamin E supplementation was effective to decrease atherosclerotic lesions in LDL receptor-deficient ($LDLR^{-/-}$) mice (21). The effect of vitamin E was also observed in the reduction of aorta damage, which was proven morphologically by measuring collagen accumulation and elastic fiber dissociation in a homocysteine- and cholesterol-induced atherosclerosis model using rats (35).

Development of macrophage foam cells is a well-defined early and unique feature of atherosclerosis progression. Scavenger receptors are a group of "membrane-bound receptors," which are localized abundantly in the membrane of macrophages and identified in the recognition and binding of ligands, including oxidized phospholipids/lipoproteins and modified lipid particles (22). *in vivo* studies suggest that CD36, which is considered the most important scavenger receptor in the context of CVD, plays an essential role in the atherogenic process (especially foam cell formation) and localizes in a number of cell types such as monocytes/macrophages, endothelial, and SMCs (36). It has been shown that α-tocopherol supplementation reduces CD36 mRNA expression while increasing mRNA expressions of PPARγ, LXRα, and ABCA1 in $ApoE^{-/-}$ mice (23).

Hypercholesterolemia is one of the main risk factor of atherosclerosis and ischemic diseases such as myocardial and cerebral infarction. Beneficial effects of vitamin E in the progression of atherosclerosis have also been reported in a high cholesterol diet fed rabbit model from our laboratory. In our earlier *in vivo* studies, we have observed that α-tocopherol prevents formation of cholesterol-induced atherosclerotic lesions by decreasing PKC activity (24). Following studies from our laboratory showed that α-tocopherol prevents cholesterol-mediated atherosclerotic lesion development as well as decreasing CD36 mRNA expression (25). The inhibitory role of vitamin E against CD36 mRNA expression in aorta tissue was also found in correlation with peripheral blood mononuclear cells of this rabbit model (26).

During the progression of atherosclerosis, delivery of cholesterol as oxLDL, following recognition by CD36 receptor, activates a signaling cascade that include mitogen-activated protein kinase (MAPK), c-jun N-terminal kinase-1 (JNK1), and matrix metalloproteinase (MMP) which stimulates inflammation, with an invasion of monocytes. Our results have also shown that α-tocopherol decreases JNK1-mediated c-jun phosphorylation, in addition to the inhibition of proteasome activity and MMP-9 expression, in a hypercholesterolemia-induced atherosclerotic process (27). Vitamin E protected development of atherosclerosis also through induction of PPARγ and Nrf2 levels followed by the enhancement of their downstream target ABCA1 and GSTα, respectively, and reduction of MMP-1 in hypercholesterolemic rabbit model (28). In our laboratory, by using proteomic analysis, we have identified differentially expressed proteins in the aortic tissues of vitamin E supplemented hypercholesterolemic rabbits. Among 73 proteins that are differentially expressed: (i) apolipoprotein A-I and apolipoprotein E in lipid metabolism, (ii) peroxiredoxin 1, peroxiredoxin 2, and thioredoxin in antioxidant system, (iii) 14-3-3 protein beta alpha and 14-3-3 protein zeta delta in cell signaling, (iv) biglycan, smooth muscle α-actin, tropomyosin, and vimentin as structural and contractile proteins are the most important ones detected and related to crucial mechanisms occurring in atherosclerosis (37).

Inflammation is another area of interest in vitamin E research. Anti-inflammatory effects of α-tocopherol have been also reported in cell culture and animal studies. A major part of its anti-inflammatory role occurs through the inhibition of NFκB (38), reduction in PKC activity (17, 39) as well as the reduced synthesis of adhesion molecules, such as vascular cell adhesion molecule-1, intercellular adhesion molecule 1, and E-selectin (40). A modulatory effect of α-tocopherol during inflammation has also determined due to the decreased secretion of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-8, possibly by inhibiting 5-lipoxygenase, NF-κB activation, and PKC (41). These findings obtained so far indicate that vitamin E modulates atherosclerosis development via modulating gene expression and enzyme activity involved in inflammation, oxLDL uptake, and foam cell formation, both at a cellular level and in animal models.

In addition to atherosclerosis, a role of vitamin E in other cardiovascular disorders, including ischemic heart disease and heart failure, has been tested with a number of *in vitro* as well as *in vivo* models. Daily dosage of a nutrient mixture, consisting of vitamin E, vitamin C, docosahexaenoic acid, eicosapentaenoic acid, and L-arginine, was shown to reduce risk factors in CVD, which was induced by high fat diet in C57Bl/6 mice (42). Ischemic heart disease is a common form of CVD associated with several pathological disorders including myocardial infarction. Sethi et al. (29) evaluated the hypothesis that early supplementation of vitamin E reduces the mortality due to its protective outcome against acute myocardial infarction, which was induced by the ligation of the left anterior descending coronary artery. Another type of CVD, heart failure is characterized by a depleted metabolic energy reserve and the upregulation of several molecular mechanisms leading to cardiac hypertrophy, inflammation, fibrosis, angiogenesis, and apoptosis (43). In excessive stress conditions, due to loss of cardiomyocyte cell function that can induce apoptotic or necrotic death mechanisms can lead to heart failure. Related studies have defined the beneficial role of vitamin E through the reduction of apoptotic activity in cardiomyocytes (44). Hamblin et al. (30) reported diet enriched with 2000 IU of vitamin E/kg for 8 weeks showed cardioprotective effect against streptozotocin-induced diabetic heart failure in rats. Previous studies by our group have shown that, α-tocopherol supplementation prevented cholesterol-mediated cardiomyocyte damage via reducing LXRα and scavenger receptor expressions, while inducing 27-hydroxycholesterol and ABCA1 levels in a hypercholesterolemic rabbit model (45).

Other forms of vitamin E, such as tocotrienols, have also been found to reduce risk of CVD by lowering circulatory levels of cholesterol and triglyceride which are the major risk factors for CVD (46). In this scenario, tocotrienols might regulate cholesterol metabolism by reducing LDL oxidation and suppressing the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, a crucial enzyme of cholesterol synthesis (47). These findings, in addition to animal studies, support the preventive role of tocotrienols in the progression of atherosclerosis (48, 49). Apart from these data, several studies have pointed to tocotrienols as a cardioprotective compound due to their ability of activating proteasomes and improving myocardial health (50).

Clinical Studies

A number of *in vitro* and *in vivo* investigations have identified the regulatory effect of vitamin E on cholesterol metabolism, signal transduction, inflammation, and atherosclerotic plaque stability as mentioned above. According to these studies, vitamin E was considered to be protective against development of CVD and in a number of clinical studies which were followed up over years (51). In this part of our review, we summarize the role of vitamin E, particularly α-tocopherol, against CVD and enlighten the large-scaled human intervention trials in this goal.

Association between vitamin E intake from food and/or supplements and risk of CVD has been analyzed by cohort studies: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (52), Nurses' Health Study (NHS) (7), Health Professionals Follow-up Study (8, 53), The Zutphen Study (54), Cancer Prevention Study II (CPS-II), Finnish Cohort Study (FS) (55), Iowa Women's Health Study (IWHS) (56, 57), Scottish Heart Health Study (SHHS) (58), and Physician Health Study (59). These early major cohort studies reported promising findings on reducing the risk of coronary heart disease either from dietary or supplemental vitamin E intake such as (i) 5% reduction among men in SHHS study (58), (ii) a 40% reduction among men in HPFS study (8), (iii) 34% reduction among women in NHS study (7), (iv) 62% reduction among women in IWHS study (56), (v) 32% reduction among men in addition to 65% reduction among women in FS study (55).

Besides its beneficial effect in reducing coronary heart disease risk, vitamin E also showed protection against other cardiovascular complications. The CPS-II observed a 10–14% reduction in ischemic heart disease risk among women using vitamin E, vitamin C, and/or vitamin A without multivitamins or plus multivitamins (60). In another study, individuals who supplemented with vitamin E for more than 4 years have showed 59% reduction in coronary heart disease mortality (59). The Cambridge Heart Antioxidant Study demonstrated that treatment with α-tocopherol (400–800 mg/dL) reduced the risk of myocardial infarction in patients with coronary atherosclerosis (9). The secondary prevention with antioxidants of cardiovascular disease in end-stage renal disease study showed that α-tocopherol (800 mg/dL) administration significantly reduced the composite endpoint of myocardial infarction (fatal and nonfatal), ischemic stroke in patients with chronic kidney disease (61). The Multi-Ethnic Study of Atherosclerosis investigated risk factors associated with subclinical CVD and found beneficial effects of dietary vitamin E intake among individuals (62).

A number of clinical investigations were also focused on the effect of γ-tocopherol, which is inversely correlated with coronary heart disease (63, 64) either supplemented alone or in mixture with other analogs. Studies using γ-tocopherol supplementation alone and in combination with α-tocopherol revealed reduced biomarkers of oxidative stress in patients with metabolic syndrome (65) and attenuated exercise-increased coagulation as well as platelet aggregation (66) better than α-tocopherol alone. On the contrary, Stonehouse et al. (67) examined the effect of palm-tocotrienols in a randomized controlled trial and did not observe any significant change either in vascular function or CVD risk factors.

Further studies have also compared the effect of vitamin E supplementation to dietary intake. Ehab et al. (68) found that higher dietary intake of fat-soluble vitamins (K, E, and D) were associated with a reduced risk of mortality from heart failure among Japanese women but not men. In another study, women who supplemented vitamin E more than 2 years showed a 41% reduction in coronary disease compared to their counterparts (69). Loffredo et al. (70) reported that when supplemented alone, vitamin E reduces myocardial infarction in interventional trials while it appears to be ineffective when associated with other antioxidants.

Despite the promising findings against cardiovascular complications, some of the clinical trials reported controversial data that were not focused on positive effects of vitamin E supplementation. Hercberg et al. (71) tested the efficiency of supplementation with a combination of vitamins and minerals in reducing the incidence of cancer and ischemic CVD in the general population in Supplementation en Vitamines et Mineraux Antioxydants study. They did not confirm any significant correlation between vitamin E supplementation and ischemic CVD incidence between groups. Similarly, The Japan Collaborative Cohort Study found no significant association between vitamin A and E intake and mortality from total stroke, coronary heart disease, and CVD in Japanese men and women (72). In another study, Myung et al. (73) found no evidence to support the use of vitamin and antioxidant supplements for the prevention of CVD. However, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico investigated the effects of α-tocopherol and n-3 polyunsaturated fatty acids (PUFA) combination in patients with myocardial infarction. Despite the beneficial effect of dietary supplementation with n-3 PUFA against cardiovascular events, vitamin E supplemented group has showed no improvement (74). The Heart Outcomes Prevention Evaluation study showed that 400 IU of α-tocopherol administered daily for 4–6 years had no beneficial effects on cardiovascular outcomes in a high-risk elderly patient population (75). Recently published PREvención con DIeta MEDiterránea study also reported no significant relation between vitamin E and total mortality in high cardiovascular risk (76). Another study subjected long-term vitamin E supplementation to randomized trial of initially healthy women has also not identified any significant change in the overall risk of incident of heart failure (77).

TABLE 2 *Controversial effects of vitamin E against cardiovascular disease tested by clinical studies*

Beneficial effect		*Nonbeneficial effect*	
Associated disease	*References*	*Associated disease*	*References*
Reduction of coronary heart disease either by dietary or supplemental vitamin E intake	(7), (8), (55), (56), (58), (59), (69)	No change on the incidence of ischemic CVDs by the use of vitamin mix which include vitamin E	(71), (73)
Reduced risk of myocardial infarction following the treatment with α-tocopherol	(9), (61), (70)	No beneficial effect in patients with myocardial infarction and cardiovascular outcomes by α-tocopherol	(74), (75)
Prevention by γ-tocopherol against coronary heart disease	(63), (65)	No correlation between the overall risk of heart failure and long-term vitamin E supplementation	(77)
Reduced risk of mortality from heart failure following dietary intakes of fat-soluble vitamins (K, E, and D)	(68)		

A list of controversial findings obtained from clinical studies is highlighted in Table 2. Mixed outcome in clinical trials of vitamin E supplementation might be explained by several factors, including the selection of volunteers, the sizes of cohorts, dose and duration of supplementation, the presence of nutrients in the diet, supplemented form of vitamin E with respect to its levels already present at baseline, or pathophysiological conditions that effect vitamin E levels, such as inflammation, tobacco use, and infection (78). Additionally, polymorphisms in genes of individuals that modulate the uptake and transportation of vitamin E, such as human tocopherol-associated protein 1, α-tocopherol transfer protein, SR-BI, CD36, ABCA1, and ABCG1, have been hypothesized to important for the lack of any preventive effect via influencing vitamin E levels in plasma and tissues (79–81). These polymorphisms might also regulate vitamin E-mediated signaling pathways and gene expressions, which explain the responsiveness to vitamin E, followed by the translation into an increased risk for CVD, including atherosclerosis (82, 83). In parallel, polymorphisms involved in inflammatory genes or specific enzymes, such as cytokines and/or catechol-O-methyltransferase, might be the reason of different responses following vitamin E supplementation (84, 85). In view of these findings, gene polymorphisms, in addition to the other factors that affect uptake, distribution, and transportation as well as effector functions of vitamin E, might lead to difficulty in obtaining clear data in determining the effect against CVD.

Despite the answers mentioned above, the question still stands why *in vitro* and *in vivo* studies observe beneficial effect of vitamin E, while clinical studies reveal disappointing findings. Conflicting data among clinical trials are addressing the establishment of selection criteria such as the presence of specific biomarkers to anticipate who is likely to benefit from supplementation of vitamin E. We believe comparative pharmacokinetic and clinical trials to pinpoint side effects and adverse outcomes will increase scientific validity and clinical applicability. Furthermore, personalization of vitamin E supplementation, by using certain subpopulations of individuals with a specific genotype, such as patients with type-2 diabetes and haptoglobin 2-2 genotype (86) will be a good strategy in future studies.

VITAMIN E METABOLISM AND ITS FUNCTION IN CVD

Recent investigations have also highlighted the potential biological activities of α-tocopherol metabolites, such as long- and short-chain catabolism products and α-tocopheryl phosphate (α-TP), a phosphoric acid ester of α-tocopherol. These metabolites have been found to modulate pathophysiological processes including proliferation, apoptosis, lipid metabolism, and inflammatory processes (13, 87). Hepatic metabolism of α-tocopherol involves CYP3A4-mediated ω-hydroxylation and α-oxidation steps that take place in endoplasmic reticulum and lead the production of alpha long-chain metabolites, including the alpha-13′-hydroxychromanol and alpha-13′-carboxychromanol. Following steps of β-oxidation in mitochondria lead to the formation of short-chain metabolites, such as α-carboxyethyl hydroxychromans (α-CEHCs) (88). Beside the preventive features of α-tocopherol, its metabolites have also shown to influence CVD at lower concentrations and with different mechanisms than its precursor α-tocopherol. In this part of our review, we summarize findings that enlighten the contribution of long- and short-chain α-tocopherol metabolites, in addition to α-TP, as beneficial agents against CVD.

The α-tocopherol metabolite α-CEHC, together with γ- and δ-CEHCs as the corresponding end product of γ- and

δ-tocopherol metabolism, is excreted with urine and mostly used as a parameter of tocopherol supply (89). Besides that, CEHCs are reported to act as bioactive compounds by binding and modulating the activity of transcription factors, nuclear receptors, and enzymes (90). Studies also identified anti-inflammatory (91) and anti-oxidative (92) roles of α-CEHC as well as the inhibitory effect against oxLDL formation (93) and PKC signaling (94). Due to lack of purified α-13′-hydroxychromanol and α-13′-carboxychromanol compounds, only a few studies on the function of long-chain metabolites have been done so far. Limited studies showed alpha long-chain metabolites might act on different pathways in reducing atherosclerosis development, than its precursor, α-tocopherol. In *in vitro* cultures of human macrophages, Wallert et al. (95) reported that alpha long-chain metabolites reduced oxLDL-induced foam cell formation through the induction of CD36 expression, in contrast to the inhibitory effect of α-tocopherol. Recently published data also revealed beneficial effect of long-chain metabolites which might be coupled with the upregulation of PLIN2, a well-studied lipid droplet-associated protein, followed by a protection against stearic acid-induced lipotoxicity (96). In addition to the regulation of oxLDL uptake and lipotoxicity, alpha long-chain metabolites may be involved in modulating the inflammatory response via reducing LPS-mediated secretion of pro-inflammatory cytokines and nitric oxide production (97, 98). The emerging function of alpha long-chain metabolites, especially α-13′-carboxychromanol, was also observed in the suppression of acute inflammation as well as bronchial hyper-reactivity via accumulating at the sites of inflammation followed by the inhibition of 5-lipoxygenase and the production of 5-lipoxygenase-derived lipid mediators (99).

Beside side chain oxidation, the phosphorylated form of α-tocopherol, known as α-TP, might be more active and unique than α-tocopherol in regulating cellular events, including proliferation, survival/apoptosis, enzyme translocation, and lipid transport, due to its similarity to phosphorylated messenger lipids and ability to modulate protein-membrane interactions (100, 101). THP-1 monocytes that are deficient in hydrolyzing α-TP have been widely used in earlier studies. In this system, α-TP was shown to reduce the proliferation of THP-1 monocytes while α-tocopherol had no significant effect (102). Wu et al. (103) showed α-TP, more effectively than α-tocopherol, inhibits apoptosis and enhances migration and capillary tube structure formation in endothelial progenitor cells under high glucose/hypoxic conditions. In another study, α-TP enhanced the promoter activity of human vascular endothelial growth factor, more effectively than α-tocopherol (104) which suggests α-TP might be involved in vasculogenesis and angiogenesis (105). Additionally, *in vivo* studies using hypercholesterolemic rabbits and apoE knockout mice, either by our group or others, have determined the preventive role of α-TP against atherosclerotic lesion development as a result of reduction in proinflammatory cytokines (IL-1β, IL-6, IL-8, CRP, PAI1, and TNF-α) and CD36 scavenger receptor levels (106–109). In a rat ischemia/reperfusion model, α-TP supplementation led to downregulation of apoptosis and upregulation of survival via increasing anti-apoptotic p42/44 ERK kinase and p38 MAPKβ signaling as well as DNA binding of NFκB and reducing proapoptotic proteins p38 MAPKα, JNK, and phosphorylation of c-Src (110).

CONCLUSION AND FUTURE PERSPECTIVES

CVD, in regard to the highest mortality and morbidity rates, is the leading cause of death, which reflects 31% of all deaths in 2012. The increase of major risk factors such as obesity and diabetes in industrialized but also developing countries further increases the burden of vascular diseases. Vitamin E is a crucial nutrient and a number of studies have determined inverse correlation between the levels of vitamin E and diseases such as CVD. As reviewed in detail by Azzi et al. (11) and Galli et al. (13), studies using cell culture and animal models have resolved the possible molecular mechanisms that are modulated by vitamin E and its metabolites in various diseases. On the basis of promising *in vitro* and *in vivo* investigations, a number of large scaled human studies were performed and followed up over years. Beside the studies that observe the beneficial effect of vitamin E in reducing cardiovascular risk, some studies have not reported any beneficial outcome.

In recent years, our understanding of vitamin E has significantly improved. A number of evidence now exist demonstrating that catabolized (long- and short-chain metabolites) and phosphorylated (α-, γ-TP) products play key roles in the regulation of biological processes crucial for CVD. Further scientific investigations of these new class of regulatory metabolites, both at cellular level as well as the clinical one, will reveal major gaps in our knowledge and offer crucial pharmacological and pathophysiological discoveries against CVD. Although, failure in correlating the data obtained from *in vitro/in vivo* studies to clinical trials still remains a major bump in the road. We believe determining the key players involved in cellular and molecular mechanisms, which are altered by vitamin E, is certain to bring new therapeutic strategies to prevent the progression of the disease. However, importance of understanding the metabolomics identification of vitamin E derivatives should not be underestimated. As we discussed in this review, several factors based on the selection of individuals, pathophysiological conditions, timing of intervention, and gene polymorphisms might affect outcome of vitamin E against CVD. Therefore dietary/supplemental doses should be considered with regard to these factors to improve the therapeutic value in the concept of individualized medicine strategies.

Beside the factors mentioned above, novel therapeutic approaches of vitamin E include its delivery as nanoparticle lipid-based drug carrier (111, 112). Lewis et al. (113) showed vitamin E loaded nanoparticles inhibited well-identified features of atherosclerosis, such as foam cell formation and inflammatory signaling, in cultures of endothelial cells, SMCs, and primary human macrophages. Such emerging studies

might be an important point of consideration against CVD, which makes vitamin E supplementation more effective.

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