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REVIEW

Vitamin E in renal therapeutic regimens

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Abstract Administration of vitamin E in children with immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis (FSGS) and type I diabetes demonstrated potential towards ameliorating progression. Oral vitamin E therapy reduced endothelial dysfunction, lipid peroxidation and oxidative stress in patients with chronic kidney failure (CKF). Moreover, the use of vitamin E-bonded hemodialyzers reduced atherosclerotic changes, erythropoietin dosage and muscular cramps in patients on hemodialysis (HD). However, several controlled clinical trials failed to document beneficial effects on the study subjects' cardiovascular and renal outcomes. A recent report of increased all-cause mortality in adult patients receiving high dose vitamin E therapy has caused considerable concern and debate. These issues regarding the efficacy and safety of vitamin E in renal therapeutic regimens will be reviewed in this article.

Keywords Vitamin E · Alpha-tocopherol · Glomerulosclerosis · IgA nephropathy · Chronic renal insufficiency

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Introduction

Vitamin E (VE), particularly in the form of α-tocopherol, has been proposed for the prevention or treatment of numerous health conditions [1–13], often based on its antioxidant [14, 15] and anti-inflammatory properties [15, 16]. However, review of the available scientific evidence revealed that, apart from the treatment of VE deficiency [17–19], there are no definitively proven medicinal uses of VE supplementation beyond the recommended daily allowance. Meanwhile, there is a growing interest in the possible benefits of VE in kidney diseases with high oxidative stress [7, 12, 13, 20–22]. Oxidative stress occurs when the production of oxidants exceeds the capacity of the enzymatic and non-enzymatic antioxidant systems. Increased production of reactive oxygen species (ROS) and reduced antioxidant defense mechanisms have been demonstrated in chronic kidney diseases (CKD), CKF and HD patients [23–26]. Recent concerns have been raised about the safety of VE supplementation, particularly in high doses (≥400 IU/day) [27]. This article will review the use of high dose VE in various renal therapeutic regimens.

Insights from animal models of kidney diseases

Reactive oxygen molecules play important roles in the pathogenesis and progression of kidney diseases [23–26]. This was demonstrated in experimental nephropathies [28, 29]. The lipophilic VE, based on its potent antioxidant properties, was tried in many animal models of kidney diseases to reduce renal damage. Several investigators [30–34] proved the renal protective effects of VE in experimental models of glomerulosclerosis. Trachtman et al. [30] found that VE (100 IU/kg) significantly decreased glomer-

ulosclerosis and tubulointerstitial scarring in chronic puromycin aminonucleoside nephropathy, which is an experimental analogue of focal segmental glomerulosclerosis (FSGS). In the rat remnant kidney, transforming growth factor beta-1 (TGF-β1) and glomerulosclerosis were significantly reduced by dietary administration of VE [31, 32]. Mune et al. [33] demonstrated that VE plus probucol reduced mesangial cell proliferation and sclerotic injury in experimental glomerulosclerosis accelerated with hyperlipidemia. In the rat Adriamycin model of CKF, the development of glomerulosclerosis and tubulointerstitial lesions were attenuated by dietary VE supplementation [34].

In an experimental model of IgA nephropathy, Trachtman et al. [35] documented increased oxygen-free radical release. They also found that administration of α-tocopherol (100 IU kg^{-1} day^{-1}) ameliorated kidney functional deterioration and glomerular damage. This protective effect was associated with a decrease in kidney cortical malondialdehyde (MDA) content [35]. Increasing the dosage in excess of 150 IU/kg did not elicit further benefits [36, 37]. In pigs subjected to 12 weeks of unilateral renal arterial stenosis, Chade et al. [38] showed that vitamin E at 100 IU kg^{-1} day^{-1} significantly improved renal hemodynamics, and reduced inflammation and fibrosis of the ischemic kidneys.

Antioxidant treatment with VE normalized diabetes-induced renal dysfunction such as albuminuria and glomerular hypertension in streptozotocin-induced diabetic rats [39]. It also normalized the increased diacylglycerol levels, protein kinase C activities [40], and TGF-β1 [41] and F(2)-isoprostane levels [42]. Increased F(2)-isoprostane synthesis during diabetes appears to be responsible in part for the increase in renal TGF-β1, a well-known mediator of diabetic nephropathy [42].

Antioxidant intervention improved renovascular endothelial function in experimental hypercholesterolemia by decreasing oxidation of low density lipoproteins (LDL) and increasing bioavailability of nitric oxide (NO) [43]. Pigs fed for 3 months on a high cholesterol diet supplemented daily with vitamins E (100 IU/kg) and C (1,000 mg) had preserved renal vascular response to endothelium-dependent vasodilators and significantly decreased LDL oxidizability [43]. Such beneficial effects can potentially prevent kidney damage induced by hypercholesterolemia.

Natural vitamin E exists in eight different "isomers": four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ) [44]. Alpha-tocopherol is the most biologically active form of VE in humans [44]. The VE used in most of the above animal studies was the synthetic form of α-tocopherol (all rac-α-tocopherol, formerly called dl-α-tocopherol) where 1 IU≅1 mg of the vitamin.

Insights from clinical studies of kidney diseases

Currently, there is much interest in the benefits of VE in kidney diseases with high levels of oxidant stress and/or depletion of natural antioxidant defense systems. Several clinical studies have demonstrated beneficial roles of VE in kidney diseases [7, 12, 21, 22, 45–51]. Almost all of these clinical trials used the synthetic form of α-tocopherol. The renal protective effects of α-tocopherol described in these trials were linked mainly to its antioxidant and anti-inflammatory properties. Vitamin E preserves the integrity of biological membranes, stabilizes their permeability and fluidity [14, 52, 53], and prevents apoptosis due to oxidative stress [54]. Also, it promotes neutral endothelial vasoactivity [55], decreases adhesion of monocytes to endothelium, and decreases superoxide production by activated phagocytes [56]. It inhibits neutrophil chemotaxis [57] and platelet aggregation [58]. Moreover, VE therapy, especially at high doses, decreases the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), the chemokine IL-8 and plasminogen activator inhibitor-1 (PAI-1) [14–16]. C-reactive protein (CRP), a prototypic marker of inflammation, is a risk marker for cardiovascular diseases (CVD), and it could contribute to atherosclerosis. Alpha-tocopherol has been shown to decrease CRP levels in patients with CVD and in those with risk factors for CVD. The mechanisms that account for non-antioxidant effects of α-tocopherol include the inhibition of protein kinase C, 5-lipoxygenase, tyrosine-kinase and cyclo-oxygenase-2 [15, 16].

Vitamin E in chronic kidney failure (CKF)

The incidence and prevalence of cardiovascular (CV) risk factors, complications and mortality are high in children with CKF [59–66]. Early identification and intervention to treat modifiable risk factors and asymptomatic CVD may lead to prevention of CVD in children with CKF and to a decrease in CV morbidity and mortality in young adults who develop CKD during childhood. Vitamin E therapy may be considered as a means of correcting the deficient plasma antioxidant status in CKF and thus attenuating the development of CVD. However, it should be noted that a large-scale, multi-national, controlled trial showed that VE had no effect on CV events in adult patients with chronic renal insufficiency [67], while another randomized controlled study noted reduction in primary CV endpoint risk in HD patients [12].

Uremic patients have an increased incidence of LDL peroxidation, endothelial dysfunction and atherogenesis [68–71]. The increased oxidative stress and impaired

Table 1 Tolerable upper intake levels of vitamin E [77]

Age (years)	mg/day	IU/day[a]
1–3	200	300
4–8	300	450
9–13	600	900
14–18	800	1,200
>18	1,000	1,500

IU International unit
[a] D-α-tocopherol, where 1 mg=1.5 IU

antioxidant defense system characteristic of CKF are contributing factors to such events [68–72]. Recently, Zwolinska et al. [72] reported increased oxidative stress and lipid peroxidation in children with CKF as evidenced by increased erythrocyte MDA and plasma organic hydroperoxide (OHP) concentrations. Endothelial dysfunction is one of the possible mechanisms determining atherosclerosis acceleration in uremic patients. Reduced endothelium-dependent vasodilation was demonstrated in the brachial artery of pre-dialysis children with severe CKF [73] and in uremic adults [74].

Endothelial nitric oxide (NO) exerts a protective effect against vascular atherosclerotic damage. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial NO synthase and a proposed CV risk factor, was found to be elevated in CKD [69]. Reduced NO production caused by ADMA can induce endothelial dysfunction in uremic patients [69]. Saran et al. [75] showed that VE therapy had the potential to lower ADMA concentrations in CKD patients, implying increased NO bioavailability and potentially limiting atherosclerosis. Many studies reported significant therapeutic effects of VE in ameliorating major co-morbidity of CKF, such as endothelial dysfunction [75], LDL peroxidation [20, 45, 51], atherosclerosis [76], and anemia [49, 50]. The optimal dose and duration of VE that may be helpful in studying prevention or slowing CKF in children is yet undefined but it should not exceed the tolerable upper intake levels for age (Table 1) [77].

Studies on VE metabolism in CKF and HD patients revealed variable results [72, 78, 79]. In the face of the usual deficient dietary intake of VE in CKF, tocopherols were found to be low, normal or high (Table 2). The progressive deterioration of kidney function was associated with increased plasma carboxyethyl-hydroxychromans (CEHC): the hydrosoluble VE metabolites [78, 79]. These metabolites have significant anti-inflammatory and antioxidative properties. Although increased CEHC may seem to correct antioxidant imbalance in CKF, the markedly increased oxidative stress and its augmentation by HD calls for therapeutic antioxidant supplementation. Whether CEHC accumulation could play a role in the context of the therapeutic effects of VE in uremic patients remains a matter of speculation and deserves further investigation. In children with moderate CKF and those on HD, plasma levels of VE were decreased, while erythrocyte VE levels were not different from the controls [72].

Vitamin E in dialysis patients

The characteristic state of oxidant/antioxidant imbalance in uremia is increased after HD initiation [72, 80, 81]. Recent studies [46–48, 80, 81] have documented significant production of ROS in HD patients. Activation of peripheral blood cells interacting with the dialyzer membrane is proposed to be an important contributor to excessive generation of ROS [81]. Thus, VE orally or via the dialysis membrane may lower oxidative stress and risk of CVD in dialysis patients.

Oral vitamin E supplementation

The Secondary Prevention with Antioxidants of Cardiovascular Events (SPACE) study reported 54% reduction in primary CV endpoint risk in HD patients with pre-existing CVD who received 800 IU/day of natural VE [12]. Moreover, VE administration (400 mg/day) alleviated subjective muscle cramps during HD in a randomized, controlled trial [82]. In CAPD patients, VE supplementation at 400 mg/day resulted in reduction of oxidative stress evidenced by significant decrease in plasma MDA concentrations [83]. However, the erythrocyte antioxidant enzymes, superoxide dismutase, glutathione peroxidase, and catalase concentrations did not change after 6 weeks of VE treatment [83]. In a randomized, controlled trial in

Table 2 Serum vitamin E in CKF and HD patients

Study		α-tocopherol	γ-tocopherol	α-CEHC	γ-CEHC
Himmelfarb et al. [78]	HD patients	Normal	High	High	High
Galli et al. [79]	HD patients	Low	Low	High	High
	CKF[a] patients	Normal	Normal	High	High

CEHC Carboxyethyl-hydroxychromans (hydrosoluble vitamin E metabolites)
[a] CKF patients included three subgroups with different extents of kidney damage [CrCl, ml/min: (1) 2–10, (2) 10–20, and (3) 20–45]

HD and peritoneal dialysis patients, Diepeveen et al. [51] demonstrated that treatment with α-tocopherol (800 IU/day) plus atorvastatin (40 mg/day) reduced LDL oxidizability, lowered total cholesterol, triglycerides, LDL cholesterol, and apolipoprotein B.

Vitamin E-coated dialyzers (VE-CD)

The use of VE-CD demonstrated beneficial effects on markers of oxidative stress [20, 84–86], endothelial dysfunction [20, 87], cytokine induction [88], and atherosclerosis [76, 89] in patients on HD. However, to the best of our knowledge, direct benefits of these expensive dialyzers on CV morbidity or mortality have not been proved yet. Morimoto et al. [20] demonstrated significant reduction in ADMA plasma levels after 6 months of using VE-CD. ADMA is an independent predictor of overall mortality and CV outcome in HD patients [90]. In a crossover study, Maccarrone et al. [91] showed that oral VE or VE-CD resulted in reduction of apoptosis, mitochondrial uncoupling, and cytochrome C release from peripheral blood mononuclear cells. Nakamura et al. [89] demonstrated that VE-CD and LDL apheresis prevented accelerated atherosclerosis in HD patients, as evidenced by significant decrease in carotid arterial intima-media thickness, arterial stiffness, reduced plasma concentrations of CRP, and IL-6 after 10 weeks of treatment compared to baseline values and compared to patients receiving conventional membrane dialysis and LDL apheresis. Similarly, significant reduction in carotid intima-media thickness was reported by Kobayashi et al. [76] in a randomized, prospective, controlled study using VE-CD for 1 year. In a crossover controlled study, the use of VE-CD resulted in a trend towards diminishing leg cramps, but this did not reach statistical significance [92].

Enrichment of plasma with VE after use of VE-CD [93, 94] could not be explained by a release of VE from dialysis membrane as in vitro studies did not show any transfer of VE from the dialysis membrane [95]. It was hypothesized that VE-CD, by scavenging oxygen free radicals in situ, decreased the local oxidative stress and thereby contributed to a sparing effect towards circulating VE [93]. On the other hand, Mune et al. [96] did not report any significant difference in plasma VE concentration between two groups of HD patients, one dialyzed with VE-CD and the other with classical membranes.

Vitamin E in uremic anemia

Increased oxidative stress during HD aggravates dialysis anemia, reduces RBC survival, impairs the effect of erythropoietin (EPO), and increases the susceptibility to hemolysis. Antioxidants were tested as a collateral therapy for anemia in patients on HD and encouraging results were obtained with oral VE [49, 50, 97–99] and VE-CD [76, 100]. Indeed, they reduced oxidative damage to RBCs and resulted in a sparing effect on EPO dosage requirement. In uremic children, Nemeth et al. [99] found that vitamin E supplementation (15 mg kg^{-1} day^{-1}) combined with recombinant human EPO therapy resulted in a significant elevation in hemoglobin and hematocrit within 2 weeks of such combined therapy compared with EPO monotherapy. This beneficial effect of the combined therapy is likely due to reduction in oxidative stress as evidenced by the decrease in oxidized glutathione/reduced glutathione ratio [99].

Kobayashi et al. [76] found a significant reduction in EPO dosage associated with 1 year of treatment with the VE-CD compared to the conventional cellulose dialyzers. Usberti et al. [100] found that VE-CD plus glutathione (1,200 mg intravenously after each dialysis session) reduced oxidative stress, as evidenced by reduced MDA, ROS and oxidized LDL [100]. Thus anemia was better controlled even after reduction of EPO dosage due to the significant increase in RBC survival. The rise in hemoglobin was correlated with a rise in plasma concentration of VE [100]. On the contrary, Triolo et al. [101] did not observe any change in dosage of EPO or hematological parameters after 12 months of HD with VE-CD, despite better control of oxidative stress. However, this was not a controlled study and the sample size was only 10 patients [101].

Vitamin E in diabetes mellitus (DM)

Numerous reports have demonstrated that oxidative stress induced by diabetes plays an important role in the development and progression of diabetic microvascular complications including nephropathy [102–104]. Vitamin E therapy, especially at high doses, clearly shows beneficial effects as regards LDL oxidation, endothelial dysfunction, inflammatory markers, pro-inflammatory cytokines, and CRP and PAI-1 levels in diabetic patients [11, 105–110]. However, supportive evidence from large clinical trials that this therapy can prevent diabetic microvascular or CV complications is lacking. The Heart Outcomes Prevention Evaluation study did not find any benefit of VE in microvascular or CV events in high risk adult patients with type II DM [111]. Table 3 summarizes clinical trials using VE in children and adolescents with type I DM. A placebo-controlled trial noted that high doses of VE (1,800 IU/d) normalized renal hyperfiltration and abnormalities of retinal blood flow in patients with <10 years duration of type I DM [112]. In the IMDIAB IX trial [113], nicotinamide and VE improved overall metabolic control and the residual beta-cell function, as measured by C-peptide secretion, in

Table 3 Randomized controlled clinical trials of vitamin E in children and adolescents with type 1 diabetes

Study	Daily dose	Duration	Effect of vitamin E
Skyrme-Jones et al. [11]	1,000 IU	3 months	Improved endothelial vasodilator function
Pinkney et al. [107]	500 IU	3 months	Increased flow-mediated vasodilatation
Bursell et al. [112]	1,800 IU	4 months	Normalized retinal blood flow and creatinine clearance
IMDIAB IX [113]	15 mg/kg	2 years	Preserved baseline C-peptide secretion for up to 2 years after diagnosis

children and adolescents with recent-onset type I DM for up to 2 years after diagnosis [113]. Residual C-peptide secretion is associated with reduced prevalence of late diabetic complications [114]. Therefore in young patients with recent-onset type I DM, prolongation of such secretion by early use of VE therapy along with intensive insulin therapy could be of value in preventing diabetic nephropathy.

In type II DM, the usual antioxidant doses of VE and C improved endothelial dysfunction and microalbuminuria [115]. Farvid et al. [116] reported that a combination of VE, vitamin C, magnesium and zinc supplementation had significant effects in decreasing urinary albumin excretion, mean blood pressure, fasting serum glucose and MDA concentrations in type II diabetic patients.

Vitamin E in renal transplant recipients

Renal transplant recipients (RTRs) have elevated oxidative stress and a high incidence of CV morbidity and mortality [117, 118]. Although only a small number of studies have examined the effects of antioxidant supplementation in these patients, most have reported beneficial findings [21, 119–121]. Blackhall et al. [122] reviewed five studies [21, 119–121, 123] that investigated the effects of antioxidant supplementation in RTRs; aside from one study that supplemented with tomato juice [123], the other four studies (including two using VE [21, 119]) reported decreases in markers of oxidative stress. Rabl and colleagues [119] studied the effects of a preoperative multivitamin infusion on markers of lipid peroxidation and reperfusion damage during kidney transplantation in a randomized controlled trial. They gave intravenous infusion of vitamins E and C to 16 RTRs (antioxidant group). The plasma MDA increased significantly after the onset of reperfusion in the control group while the antioxidant group did not show such an increase, and this marker decreased by 20% compared with baseline values. These findings agreed with studies reporting that antioxidants were effective at preconditioning tissue against ischemic reperfusion injury [124, 125].

The effects of VE supplementation (500 mg/day) for 6 months in RTRs in the presence or absence of chronic rejection (CR) were studied by Vela et al. [21] in an uncontrolled trial. Vitamin E therapy decreased the elevated MDA in 23 patients with CR, and the renal function remained stable during the period of study as demonstrated by creatinine and diethylenetriamine penta-acetic acid (DTPA) clearances. Available evidence to date would suggest that patients with high levels of oxidant stress or depletion of natural antioxidant defense systems, such as RTRs, may be the most likely to benefit from antioxidant therapy. Still, large-scale, prospective, placebo-controlled trials with clinical end-points are needed before valid generalization of such therapy in RTRs can be made.

Blackhall et al. [126] recently reported that anti-oxidant supplementation with vitamin C, VE and β-carotene resulted in a 24% decrease in cyclosporine A (CsA) trough levels in RTRs. This issue needs further research for confirmation. The injudicious use of these vitamins might evoke rejection if they indeed decrease blood CsA concentrations.

Vitamin E in specific nephropathies

IgA nephropathy

Scientific evidence suggests that ROS play a role in the pathogenesis of IgA nephropathy [29, 127, 128]. Chan et al. [7] conducted a randomized, placebo-controlled prospective study in children with biopsy-proven IgA nephropathy from a network of pediatric nephrology programs across the United States. The duration of treatment was a minimum of 1 year, and VE dose was 400 IU/day in children weighing <30 kg, and twice that dose for those >30 kg. The authors demonstrated that VE treatment significantly lowered proteinuria in the early stages of IgA nephropathy when the glomerular filtration rate (GFR) was nearly normal. This therapy had no effect on the incidence of hematuria. There was a trend toward stabilization of GFR in the VE-treated patients. Yet, long-term treatment and follow-up are needed to determine whether this antioxidant therapy is associated with preservation of renal function in IgA nephropathy.

Focal segmental glomerulosclerosis (FSGS)

There is a similarity between glomerulosclerosis and atherosclerosis; the glomerular lesions in FSGS are akin

to plaques in atherosclerosis [129]. The intriguing histological and immunohistochemical similarities between the evolving fatty streaks in the atherosclerotic vessel wall and the progressive glomerular lesion leading to glomerulosclerosis suggest analogous pathobiologic mechanisms [129]. Thus pharmacological strategies that prevent atherosclerosis may be expected to limit glomerulosclerosis. Alpha-tocopherol prevents oxidative damage of the endothelium and oxidation of LDL, i.e., the crucial initial steps in the pathogenesis of atherosclerosis. It showed beneficial effects in experimental glomerulosclerosis. Tahzib et al. [22] showed that VE therapy was a useful adjunct in treatment of children with FSGS in whom proteinuria was refractory to standard medical management. Their protocol consisted of 200 IU of oral VE twice daily to 11 children with FSGS and 9 children with miscellaneous kidney diseases for 3 months. Vitamin E therapy lowered the protein/creatinine ratio in 91% of children with FSGS. In contrast, no beneficial impact on urinary protein excretion was detected in children with miscellaneous renal diseases.

Cyclosporine A (Cs-A) nephrotoxicity

Although the mechanisms of Cs-A nephrotoxicity are not completely defined, there is evidence that ROS, lipid peroxidation, and release of thromboxane and prostaglandins contribute to its pathogenesis [130]. Review of evidence in experimental animal studies points to the possibility of prevention of Cs-A–mediated renal injury by VE treatment [131–133]. In experimental CsA nephrotoxicity, VE treatment reduced ROS, vasoconstrictive thromboxane, and tubulointerstitial fibrosis [131–133]. No patient data are yet available on this issue but Barany et al. [134] demonstrated that in healthy volunteers, the hemodynamic changes brought about by a single dose of Cs-A were ameliorated by 6 weeks of vitamin E (800 IU/day). This is a critically important area for investigation.

Differential efficacy of vitamin E

Recent prospective, controlled clinical trials failed to verify a consistent beneficial effect of VE on CVD [67, 135–137]. It was found that VE had no effect on CV events in adult patients with chronic renal insufficiency in the HOPE study [67]. Another report from the same study [135] indicated that Ramipril, but not VE, significantly decreased the risk of CV outcomes in these patients. The causes of differential effectiveness of VE in epidemiological [138, 139], clinical [67, 135–137], and experimental studies are not clearly defined. There is a paradox between the dramatic responses to VE in animal studies and the lack of efficacy in some human studies. This is possibly related to many variables such as nature and dosage of VE, timing of therapy, stage of the disease, age of patients, and degree of renal insufficiency among other factors.

Vitamin E supplements are available in natural and synthetic forms. The natural form (RRR-α-tocopherol, formerly called D-α-tocopherol) may have biological activity different from that of the synthetic form [14]. Importantly, unlike most large-scale randomized controlled trials of VE, the HOPE study used the natural form and thus, the neutral findings in this trial may refute the hypothesis of a differential clinical effect between natural and synthetic α-tocopherol. Recently, another debate has arisen concerning γ-tocopherol [140]; human trials with VE have almost always been done with α-tocopherol. Supplementation with large amounts of α-tocopherol (1,200 IU/day) decreases blood levels of γ-tocopherol [14, 140]. It has become evident that γ-tocopherol may possess anti-inflammatory and specific free-radical–scavenging action beyond the activities of α-tocopherol. Gamma-tocopherol is particularly more potent than α-tocopherol at inhibiting the catalytic function of cyclooxygenase (COX) in macrophage cells [141]. Additionally, γ-tocopherol may, in certain circumstances, provide greater protection against reactive nitrogen species than does α-tocopherol [142]. Additional research is needed in this area.

There is no clear-cut age or disease-specific VE dosage. The dose used in the HOPE study was 400 IU/day and that used in GISSI study [136] was 300 mg/day (synthetic form equivalent to 300 IU/day); both were associated with null effects. Beneficial effects were observed with higher doses in the CHAOS study (400–800 IU/day) [143] and in the SPACE study (800 IU/day) [12]. The issue of under-dosage based on body weight should be of concern in future studies. The preferential effect of VE in end-stage renal disease shown in the SPACE study was speculated to be related to increased bioavailability of CEHC [122].

Another important issue is that VE may be more effective in the early stages of the disease than in the advanced irreversible stages. The ability of VE to inhibit LDL oxidation in vitro has been shown unequivocally and served as the basis for the assumption that VE is also able to inhibit early atherogenic events. To date, the clinical trials undertaken have mostly enrolled elderly patients with established atherosclerosis or those at high risk of developing the disease, and thus these studies—at least in part—failed to show unequivocally that VE reduces CVD. The reported beneficial effects of VE were in observational studies in primary prevention settings, and animal studies that started VE at a very early stage of disease. Thus, clinical trials starting VE therapy during the early stages of disease are likely to show significant beneficial outcome.

Table 4 Large scale randomized controlled studies with evidence of vitamin E safety

Study	Population	Daily dosage	Duration	Safety observations
GISSI [136]	11,324	300 mg	3.5 years	No adverse effects reported
PPP [150]	4,495	300 mg	3.6 years	No adverse effects reported
HOPE [10]	9,541	400 IU	4.5 years	No significant adverse effects
Taylor et al. [151]	1,193	500 IU	4 years	No significant adverse effects
HPS [137]	20,536	600 mg	5 years	No safety concerns
CHAOS [143]	2,002	400 or 800 IU	510 days	0.55% of patients discontinued treatment because of adverse effects with no difference between active and control groups

GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, *PPP* Collaborative Group of the Primary Prevention Project, *HOPE* Heart Outcomes Prevention Evaluation Study, *HPS* Heart Protection Study Collaborative Group, *CHAOS* Cambridge Heart Antioxidant Study

Alpha-tocopherol, when it reacts as an antioxidant in vivo, is converted to the tocopheroxyl radical during the chain-breaking reaction. If not reduced by a co-antioxidant, the tocopheroxyl radical can react with lipids to generate lipid radicals, thereby promoting the chain instead of breaking it [14, 44, 144]. Therefore, α-tocopherol probably requires a co-antioxidant to have a beneficial effect and to prevent this pro-oxidant potential.

Evidence of vitamin E safety

Miller et al. [27] recently conducted a meta-analysis of selected publications and reported that VE in high doses (≥400 IU/day) carried an increased risk for all-cause mortality in adult patients with serious chronic conditions. Their study [27] caused considerable debate and was criticized by many experts. The Miller report was in adults and can not be extrapolated to children. There is no published evidence of increased mortality in children using VE therapy. Furthermore, three other meta-analyses found no evidence that VE supplementation up to 800 IU/day significantly increased or decreased CVD mortality or all-cause mortality [145–147].

Table 5 Doses of vitamin E used in different pediatric studies

Daily dose	Disease
50 IU	Anemia of prematurity [6]
400 IU	FSGS [22]
400–800 IU	IgA nephropathy [7]
15 mg/kg	Anemia in CKF [99]
5–10 IU/kg	Cystic fibrosis [154]
100–200 IU/kg	Chronic cholestasis [155–157]
15–25 IU/kg[a]	
100–200 IU/kg	Abetalipoproteinemia [158, 159]
1,200–3,000 IU	Ataxia with isolated vitamin E deficiency (AVED) [18, 19, 160, 161]

[a] A water-soluble oral form of VE, d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)

Generally, vitamin E is well tolerated, and many studies have reported no increased mortality [145–151]. The Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study used mega-doses of VE (2,000 IU/day) and did not reveal increased mortality over 13 years of observation [148]. The Alzheimer's Disease Cooperative Study (ADCS) used VE (2,000 IU/day) and did not demonstrate safety concerns [149]. Recently, the Women's Health Study reported a 24% reduction in CV deaths in women taking 600 IU of VE daily, but no change in total mortality rate [2]. Table 4 shows some large-scale randomized controlled studies of VE that indicated absence of significant adverse effects [10, 136, 137, 143, 150, 151].

Moreover, the U.S. Institute of Medicine of the National Academy of Sciences concluded from hundreds of studies that VE is safe in daily dosages of 200–800 mg (Table 1) and is associated with minimal side effects and enjoys excellent patient tolerability [77]. Long-term use of VE at very high doses may increase the risk of bleeding, due to inhibition of platelet aggregation and antagonism of vitamin K-dependent clotting factors. Caution is advised in patients with bleeding disorders or those taking drugs that may increase the risk of bleeding. Dose adjustments may be necessary in these cases [152, 153].

Table 6 Biological activities of vitamin E [77, 162]

Vitamin E		IU/mg
Synthetic	D,L-α-tocopherol acetate	1.00
	D,L-α-tocopherol	1.10
Natural	D-α-tocopherol acetate	1.36
	D-α-tocopherol	1.49

Therapeutic dosage in children

No disease-specific VE dosage has been definitely established in children, but previous pediatric clinical trials could serve as a guide (Table 5) [7, 22, 99, 154–161]. However, therapeutic doses of VE should not exceed the tolerable upper intake limits for age (Table 1) [77]. Also, equivalents of natural and synthetic VE (Table 6) [162] and possible drug interactions have to be taken into account when prescribing high doses of VE.

Summary

In recent years, research attention has focused on the use of vitamin E as an antioxidant for cardiac and renal protection. Although earlier observational studies reported significant decreases in cardiovascular morbidity and mortality in individuals consuming large doses of vitamin E, these findings had not been supported in large-scale, randomized, placebo-controlled clinical trials in adults. Vitamin E may be more effective in the early stages of disease than in the advanced stages experienced by most adult patients in clinical trials reported to date. The therapeutic use of vitamin E in high doses should be approached cautiously in patients with bleeding disorders or those taking drugs that may increase the risk of bleeding. It is speculated that vitamin E could emerge as an adjuvant therapy in early stages of kidney diseases with elevated oxidative stress or compromised antioxidant defenses. Yet its efficacy as a renal therapeutic agent in children awaits the results of long-term, large controlled clinical trials before clear-cut conclusions can be drawn.

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