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# **Vitamin E in Hemodialysis Patients**

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Anca Elena Rusu

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## **Abstract**

End-stage renal disease patients treated with hemodialysis are characterized by a special diet, increased oxidative stress, cardiovascular morbidity and mortality, as well as many other complications such as inflammation-malnutrition syndrome, muscle cramps, and anemia. Worldwide efforts are focused on reducing hemodialysis complications to increase survival in these patients. In vitro and in vivo studies proved that vitamin E has many beneficial effects such as: decreases reactive oxygen species synthesis, improves antioxidant defense system, inhibits lipids peroxidation and reduces atherosclerosis, and ameliorates anemia treatment. Mechanisms of action are complex and not fully understood. However, there are particularities in regards of vitamin E intake, metabolism, and clearance in patients treated with hemodialysis. Supplementation of vitamin E in these patients has been intensively studied, and it is still under debate. Oral administration and vitamin E-coated membranes for dialysis have been tried. Clinical practice guidelines tried to underline when and how much vitamin E to be given to be safe and cost-beneficial. The current chapter aims to synthesize all these issues.

**Keywords:** hemodialysis, vitamin E deficiencies, oxidative stress, anemia, cardiovascular diseases, vitamin E supplementation

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## **1. Introduction**

Hemodialysis (HD) patients are a special population with many particularities in regard of nutrition, metabolism, inflammation and oxidative stress, morbidity, and mortality. Contacts with extracorporeal dialysis membranes generate inflammation and oxidative stress and the entire cascade of complications. Intake, metabolism, and clearance of many nutrients are limited or disturbed, and vitamin E is one of them. On the other hand, beneficial effects of vitamin E come to recommend its supplementation in order to limit oxidative stress and other complications in hemodialysis patients.

## 2. Particularities of HD patients

- dietary restrictions
- increased oxidative stress (as displayed in **Figure 1**)
- increased inflammation markers and malnutrition inflammation syndrome
- muscle cramps during dialysis
- disturbances in lipid profile
- increased cardiovascular risk

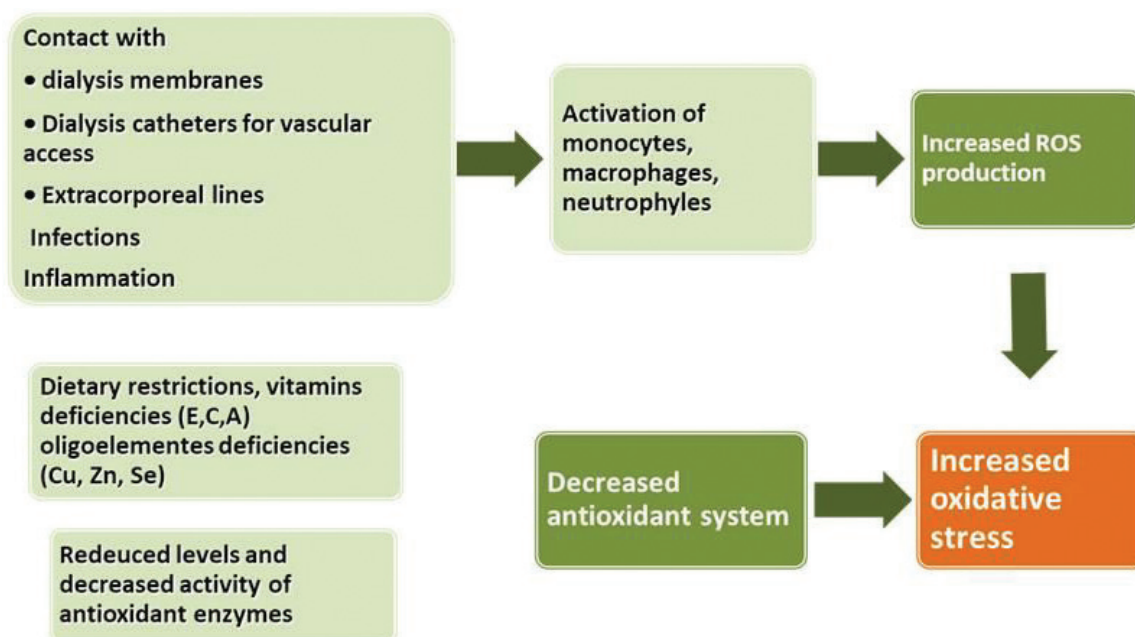


Figure 1. Oxidative stress in hemodialysis patients.

## 3. Status of vitamin E in HD patients

The level of vitamin E in HD patients is influenced by dietary intake, particularities in metabolism and clearance. The plasma level of vitamin E is usually normal, even though there are studies that found predialysis low levels of alpha-tocopherol. However, the number of patients included was small and similar results have not been identified in other larger studies. Gastro-intestinal disturbances in uremic patients might lead to poor absorption and this could be an explanation for low plasma levels of vitamin E identified in some HD patients, while increased consumption is another one [1–4].

Profile of vitamin E status in these patients is as follows:

- limited intake
- not cleared by dialysis

- metabolism disturbances
- normal/reduced plasma levels
- reduced level in cellular membranes

### 3.1. Intake

Usually, HD patients have sufficient daily dietary intake of vitamin E, but sources of vitamin E are limited and mainly represented by vegetable oils. Many other sources are restricted in

Food	Portion size	Vitamin E (milligrams of alpha-tocopherol)	A/ARP/NA in hemodialysis patients	Additional observations
<i>Fats and oils</i>				
Vegetable oil, wheat germ	5 mL (1 tsp)	7	NA	High content of phosphorus
Vegetable oil (sunflower, safflower)	5 mL (1 tsp)	2	A	—
<i>Vegetables and fruits</i>				
Spinach, cooked	½ cup	3–4	ARP	High content of potassium
Tomato sauce	125 mL (½ cup)	2	NA	High content of potassium
Pumpkin, canned	1 cup	3	NA	High content of potassium
Collard greens	1 cup	2	ARP	High content of potassium
Avocado	½ fruit	4	NA	High content of potassium
Mango	1 whole	1.9	NA	High content of potassium
Asparagus, cooked	1 cup	2.2	NA	High content of potassium
Red peppers, raw	1/2	2	ARP	High content of potassium
<i>Grains products</i>				
Cereal, wheat germ	30 g (1/4 cup)		ARP	High content of phosphorus
<i>Meat and alternatives</i>				
Tuna, canned with oil	75 g	2	ARP	High contents of phosphorus
Sardines, canned with oil	75 g	2	ARP	High contents of phosphorus
Herring, cooked	75 g	1.5	ARP	High contents of phosphorus
Egg, cooked	2 large	2.5	ARP	High contents of phosphorus and lipids
<i>Nuts and seeds</i>				
Sunflower seeds	¼ cup	8–10	NA	High contents of phosphorus
Almonds	¼ cup	9	NA	High contents of phosphorus
Peanuts	¼ cup	3	NA	High contents of phosphorus
Peanut butter	2tbsp	3	NA	High contents of phosphorus
Hazelnuts	¼ cup	5	NA	High contents of phosphorus

**Table 1.** Sources of vitamin E for hemodialysis patients.

these patients because of its increased phosphorus and/or potassium content. **Table 1** displays vitamin E containing foods which are allowed (A), allowed with restricted portions size (ARP), or not allowed (NA) in patients undergoing chronic hemodialysis [4–6].

### 3.2. Metabolism and clearance

Vitamin E is a lipophilic vitamin. Hemodialysis membranes remove only hydrophilic substances, so that alpha-tocopherol cannot be cleared by hemodialysis. It should be unlikely that vitamin E levels should be low in these patients as long as the intake is adequate, but abnormalities in absorption and metabolism of alpha-tocopherol have been reported.

Tocopherol is metabolized to carboxyethyl-hydroxychromans (CEHC), which are water-soluble compounds excreted by the kidneys. These metabolites accumulate in uremic patients, but as they are water soluble, they might be removed by dialysis membranes also. This could be an explanation for the results of a study from USA that found that even though CEHC levels increased after 30 days of alpha-tocopherol supplementation, they did not increase any more with further treatment [4, 7].

A reduction of vitamin E in cellular membranes has been noted in HD patients, suggesting that a decreased uptake of alpha-tocopherol by different tissues is happening, but the mechanism is not known. Some studies showed a disproportion between plasma tocopherol and lipids, as well as a low level of gamma-tocopherol and CEHC accumulation in patients undergoing chronic hemodialysis.

## 4. Effects of vitamin E in hemodialysis patients

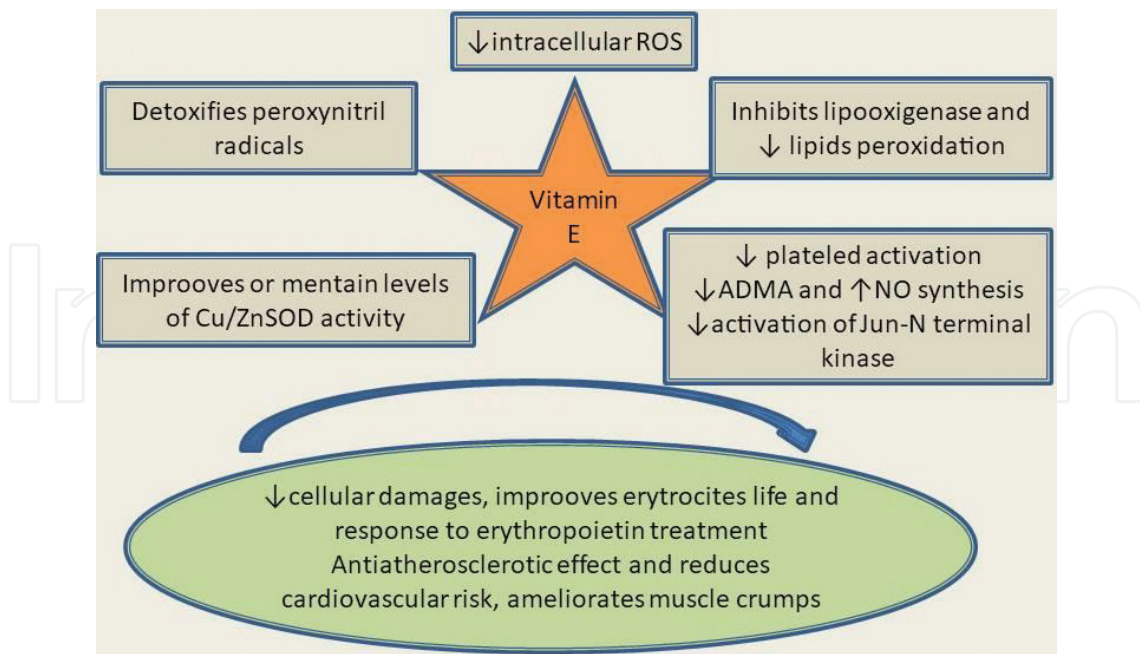
- antioxidant agent
- antiatherosclerotic
- hypolipidemic
- ameliorates recurrent muscle cramps
- reduces erythropoietin doses

A schematic representation of mechanisms leading to these effects of vitamin E in hemodialysis patients is displayed in **Figure 2**.

### 4.1. Antioxidant agent

Increased reactive oxygen species (ROS) production was observed in hemodialysis patients, in response to inflammation and extracorporeal membranes. Markers of lipid peroxidation are increased in these patients, while catalase and superoxide dismutase activity are decreased.

5-lipoxygenase branch of the arachidonate cascade is only responsible for membrane peroxidation, oxidative stress, and apoptosis of leucocytes in hemodialysis patients.



**Figure 2.** Effects of vitamin E on hemodialysis patients.

Vitamin E might directly inhibit 5-lipoxygenase in peripheral blood monocytes and partially control the lipid peroxidation and oxidative stress [8, 9].

Early studies showed that vitamin E acts as a scavenger for ROS in hemodialysis patients. Other researchers found that gamma-tocopherol is a detoxifier of peroxynitrile radicals. More recent in vitro studies found that vitamin E-coated dialysis membranes reduce intracellular ROS in monocytes and maintain normal activity of Cu/Zn superoxide dismutase [4, 10–12].

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide (NO) synthase and it is increased in hemodialysis patients. Vitamin E acts as an inhibitor of ADMA and increases the activity of NO synthase [13, 14].

Pertosa et al. demonstrated that vitamin E-coated dialysis membranes reduce activation of Jun N-terminal kinase [15].

#### 4.2. Antiatherosclerotic effect

Vitamin E acts at the cellular level interfering with reactions implied in the progression of atherosclerosis such as:

- reduces smooth muscle cell proliferation;
- inhibits platelet aggregation and monocyte adhesion induced by superoxide anions;
- reduces lipids peroxidation in monocytes;
- decreases oxidized low-density lipoproteins uptake;
- reduces activation of Jun-N terminal kinase;



- decreases ADMA and increases NO synthase activity and NO synthesis; and
- reduces cytokine production.

All these listed above have been found in small in vitro or in vivo studies [8–17].

There are two large controlled trials on patients with renal failure, SPACE and HOPE studies, that found either a significant reduction in cardiovascular risk and myocardial infarction in end-stage renal disease patients treated with oral alpha-tocopherol as compared to placebo, or similar effect of vitamin E treatment and ramipril on cardiovascular outcome in patients with mild and moderate renal failure [18, 19].

#### **4.3. Hypolipidemic effect**

It was demonstrated that vitamin E reduces lipid peroxidation and it decreases electronegatively charged LDL-subfraction, but if it also reduces the triglycerides or total cholesterol, it is uncertain. Some studies found that short-term high doses of vitamin E had no benefits in a majority of renal patients in regards to their circulating levels of high-density lipoprotein cholesterol [16, 17].

#### **4.4. Ameliorates muscle cramps**

Vitamin E-deficient muscle in animals has been shown to provide increased susceptibility to peroxidative damage.

Radical-mediated oxidative damage of skeletal muscle membranes has been implicated in the fatigue process. Moreover, in hemodialysis patients, ROS-mediated damages occur during hemodialysis-induced muscle hypoperfusion and ischemia, as well as because of activation of macrophages and leukocytes passing dialysis membranes. Vitamin E is a major chain-breaking antioxidant that has been shown to reduce contraction-mediated oxidative damage. Vitamin E deficiency would adversely affect muscle contractile function, resulting in a more rapid development of muscular fatigue during exercise [4, 20].

#### **4.5. Erythropoietin doses reduction**

Anemia is an important cause of morbidity and mortality in chronic hemodialysis patients. Treatment with erythropoiesis-stimulating agents is influenced by many factors that can induce erythropoietin resistance, such as:

- bleeding
- iron deficiency
- folate and vitamin B12 deficiency
- inflammation
- oxidative stress

An imbalance between oxidant and antioxidant system in hemodialysis patients is well known. Any studies found low levels of superoxide dismutase and decreased activity of

erythrocyte superoxide dismutase in erythrocyte membranes, leading to increased reactive oxygen species production, increased anemia, and resistance to erythropoietin treatment. Some authors found that vitamin E supplementation was followed by increased activity of erythrocyte superoxide dismutase, improving anemia and erythropoietin responsiveness in these patients [4, 10, 21].

## **5. Vitamin E supplementation in hemodialysis patients**

### **5.1. Oral supplementation**

The European Best Practice Guidelines on Renal Nutrition recommend a daily supplement of 400–800 IU for the secondary prevention of cardiovascular events and recurrent muscle cramps [4, 20, 22].

### **5.2. Vitamin E-coated membranes**

Vitamin E-coated membranes were used in hemodialysis to increase membrane biocompatibility and to reduce reactive oxygen species production [23–28].

Effects of vitamin E-coated dialysers [23–28]:

- reduce the levels of advanced glycation end products
- reduce reactive oxygen species
- prevent monocyte activation
- improve the functional capacity of white blood cells population
- reduce lipid peroxidation
- reduce intima-media thickness into carotid artery
- reduce the percentage of dysmorphic red blood cells
- reduce erythropoietin doses

Disadvantages of vitamin E-coated membranes:

- expansive
- not widely available

## **6. Side effects of vitamin E supplementation**

Usually, no side effects have been seen using doses of 400–800 UI/d, even though, in prolonged administration, some of the effects listed below could be possible [20, 22]:

- accumulation of metabolites;



- paradoxical pro-oxidant effects due to the reduction of antioxidant defense system components;
- bleeding, diarrhea, blurry vision, and headache are rare.

In conclusion, vitamin E proved its antioxidant effects in hemodialysis patients, decreasing ROS synthesis and cellular damages, reducing lipid peroxidation, platelet aggregation and limiting atherosclerosis, improving antioxidant defense and ameliorating anemia treatment in hemodialysis patients. It is safe to use doses of vitamin E that should not exceed 1000 Ui/d in selected hemodialysis patients, especially to reduce cardiovascular risk, improve muscle cramps, and reduce required erythropoietin doses.

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