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# Effect of Vitamin E Supplementation on Plasma Lipid, Apolipoprotein and Lipoprotein Profiles in Patients on Peritoneal Dialysis and Hemodialysis

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## Abstract

***Background and Aims:*** Dyslipidemia is one of the well known risk factor for cardiovascular disease in patients on dialysis. The aim of the present study was to assess the influence of vitamin E therapy on lipid profile in patients on hemodialysis (HD) and peritoneal dialysis (PD).

***Methods:*** This was a case-control study. The study was performed on 34 HD patients, 13 PD patients and 22 healthy volunteers with a mean age of 45.57 ± 8.54 years. HD patients were divided into two groups, i.e. treatment (n=19) and control (n=15). Vitamin E was administered, 300 mg/day, to the HD treatment group and PD patients for 20 weeks. Plasma total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, and lipoprotein(a) were examined before and after vitamin E treatment.

***Results:*** Before vitamin E treatment, the levels of high-density lipoprotein cholesterol were significantly lower in the HD patient group (35.91±10.54 mg/dl) and PD group (37.92±7.19 mg/dl) than the healthy group (44.27±8.33 mg/dl), (p=0.008). Before the treatment the levels of lipoprotein(a) were significantly higher in the HD group (28.12±10.85 mg/dl) and PD group (31.64±15.12 mg/dl) than the healthy group (22.09±9.05 mg/dl), (p=0.008). Lipid and lipoprotein levels in HD and PD groups were not changed significantly after vitamin E treatment.

***Conclusions:*** Vitamin E supplementation is not effective on lipid and lipoprotein levels in patients on HD and PD.

***Keywords:*** Vitamin E, Hemodialysis, Peritoneal Dialysis, Lipids, Lipoprotein

## Introduction

Chronic kidney disease is associated with characteristic alterations of lipoprotein metabolism and dyslipidemia which is characterized by elevated concentration of triglyceride, very-low density lipoprotein cholesterol (VLDL-C), low high-density

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lipoprotein cholesterol (HDL-C), and low or normal levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), and alterated apolipoprotein profile (1-4).

The most important cause of mortality in patients with renal failure undergoing hemodialysis is cardiovascular disease related to atherosclerosis (5-6). Dyslipidemia is an important factor in the development of glomerulosclerosis and tubulointerstitial lesions, and it contributes to the high incidence of coronary artery disease or atherosclerotic coronary heart disease in dialysis patients (6-9).

Several medications have been studied to improve the dyslipidemia in dialysis patients (10-11). The effects of vitamin E supplementation on altering lipoprotein levels in dialysis patients have not been extensively investigated. Vitamin E has an antioxidative activity, which can neutralize free oxygen radicals and can block membrane lipid peroxidation (12-15). In patients on dialysis, factors related to dialysis and factors related to uremic condition contribute to the pathogenesis of oxidative stress and atherosclerosis (5-6, 14, 16).

In our study we aimed at exploring the effects of vitamin E on lipid profile and investigating its possible efficacy in end stage renal disease patients who were undergoing hemodialysis and peritoneal dialysis.

## Materials and Methods

A prospective, case-control study was performed in 69 individuals. Individuals were divided into four groups as shown in Figure 1: healthy controls (n=22), HD controls (n=15), HD treatment (n=19) and PD treatment group (n=13). Dialysis patients had all been treated in the Department of Medicine, Division of Hemodialysis and Peritoneal Dialysis Units of Nephrology, Trakya University School of Medicine, in Tekirdag Dialysis Center of Turkish Renal Foundation and in Dialysis Center of Edirne State Hospital. The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee.

Patients who had been subjected to dialysis for less than 6 months, users of cigarettes, lipid lowering agents, carnitine and vitamin E, as well as those having diabetes mellitus, collagenous disease, active hepatitis, amyloidosis, or malignancy were excluded.

The hemodialysis (HD) treatment group and the peritoneal dialysis (PD) patients received 300 mg vitamin E (Ephynal capsule, Roche, Istanbul, Turkey) orally once a day after a meal. The patients in the HD control group were followed for 20 weeks without making any alteration to their original treatment. Hemodialysis treatment (4 hours a day, 3 times a week) and continuous ambulatory peritoneal dialysis treatment (4x2 lt daily), which had been administered previously, did not change. Laboratory tests were analysed at the beginning and at the end of the 20-week vitamin E treatment. Pre- and post-treatment plasma vitamin E, total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), and lipoprotein(a) [Lp(a)], fasting blood glucose, urea, creatinine, uric acid, hemoglobin and albumin levels of all groups were measured. Blood samples were always taken after 8-10 hours of fasting and prior to dialysis. Complete blood count and routine biochemical analyses were performed on the same day and serum samples for further tests were put into tubes with an eppendorf and stored at -80 $^{o}$C in a refrigerator. The body-mass index was calculated as the weight divided by the square of the height in meters. Plasma vitamin E measurements were made by spectrophotometry (520 nm). Complete blood counts were performed with an Abbott Cell-DYN-3500R apparatus. Lp(a) was measured in serum samples by nephelometric agglutination assay (N Latex Lp(a) Reagent; Dade Behring). Serum levels of ApoA-I and ApoB were evaluated by nephelometric assays with antiserum specific for ApoA-I and ApoB (Dade Behring Inc., Newark, DE, USA).

Serum levels of total cholesterol and TG levels were measured using enzymatic, colorimetric tests on the autoanalyzer (Abbott Laboratories Inc.,

**Table 1.** Baseline clinical and biochemical characteristics of the study patients.

| Characteristics | Healthy Control (n=22) | HD Control (n=15) | HD Treatment (n=19) | PD Treatment (n=13) |
|---|---|---|---|---|
| Age (years) | 44.95±9.42 | 46.86±8.51 | 45.57±13.68 | 43.30±17.58 |
| Female gender | 11 (50%) | 7 ( 47%) | 9 ( 46%) | 6 (46 %) |
| Body mass index (kg/m$^2$) | 25.10±3.75 | 23.46±3.10 | 23.23±3.72 | 24.43±3.60 |
| Systolic BP(mmHg) | 114.54±7.54* | 138.66±22.63 | 138.42±29.48 | 136.15±23.64 |
| Diastolic BP(mmHg) | 72.95 ± 7.01** | 82.66 ± 10.32 | 82.89 ± 13.26 | 81.15 ± 12.60 |
| Serum urea (mg/dL) | 31.41± 4.72*** | 161.93± 31.05 | 166.26± 43.64 | 140.92± 43.61 |
| Serum creatinine (mg/dL) | 0.73 ± 0.14*** | 9.34 ± 3.12 | 9.02 ± 2.84 | 9.66 ±3.24 |
| Hemoglobin (mg/dL) | 13.55 ± 1.63*** | 8.51 ± 1.33 | 8.85 ± 1.89 | 8.92 ± 1.23 |
| Serum albumin (g/dL) | 4.89 ± 0.42*** | 3.70 ± 0.27 | 3.64 ± 0.35 | 3.57 ± 0.20 |
| Serum uric acid (mg/dL) | 3.09 ± 0.45*** | 6.44 ± 1.75 | 4.98 ± 1.61 | 5.21 ± 1.09 |
| Serum glucose (mg/dL) | 86.36 ± 13.03 | 74.06 ± 16.01 | 85.36 ± 13.65 | 100.23 ±20.02 |
| Duration of dialysis (months) | | 35.52 ± 30.66 | 35.73 ± 32.57 | 29.00 ± 21.44 |

**BP**, Blood Pressure; Values are expressed as mean±SD (range) or number (%) of patients.

* p=0.002 healthy control group versus HD control, HD treatment and PD treatment groups

** p=0.001 healthy control group versus HD control, HD treatment and PD treatment groups.

*** p<0.001 healthy control group versus HD control, HD treatment and PD treatment groups.

Abbott Park, IL, USA). HDL-C was determined after selective pre-cipitation of the VLDL-C and LDL-C fractions. LDL-C was calculated using the Friedewald formula.

***Statistics***

Comparisons of continuous variables between groups were performed using Student's t-test for normally distributed data and the Mann-Whitney U-test or Kruskal Wallis Test for non-normally distributed data. All tests were two-sided, and a p value of <0.05 was considered statistically significant. All data are expressed as mean ± SD, unless otherwise noted. Analyses were performed using SPSS software version 7.5 for Windows.

## Results

The study was carried out with 69 individuals: 36 male and 33 female. The baseline characteristics of the study patients are shown in Table I.

There was no difference between the patients in the causes of end stage renal disease. The causes of end stage renal disease in the patient group as a whole were chronic glomerulonephritis in 15 patients (31.91%), hypertensive nephrosclerosis in 7 (14.89%), vesicoureteral reflux in 4 (8.51%), polycystic kidney disease in 2 (4.25%) and chronic interstitial nephritis in 12 (25.53%). The cause of end stage renal disease could not be determined in 7 patients (14.8 %). Systolic (p=0.002) and diastolic (p=0.001) blood pressure of the patient groups were higher than that of the healthy control group. Biochemical data of the healthy control and the patient groups were compared and higher urea (p<0.001), creatinine (p<0.001) and uric acid (p<0.001) values were found in the patient groups and the albumin values (p<0.001) and hemoglobin levels

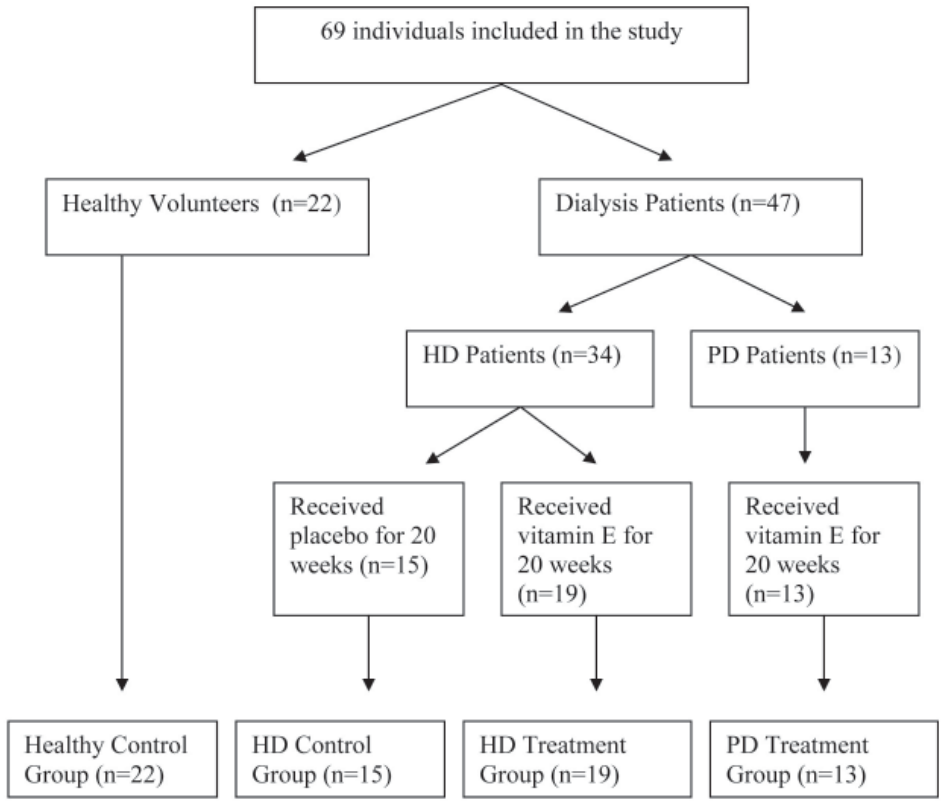


**Figure 1.** Enrollment Flow

($p<0.001$) were higher in the healthy control group. Baseline and follow-up total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, ApoA-1, ApoB, Lp(a) and vitamin E levels were shown in Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, and Figure 10, respectively.

No side-effects were observed during the study. Throughout the study any significant alteration was not observed in the other biochemical values of patients enrolled in the study, except in uric acid values of the PD group. Serum uric acid level was decreased from 5.21 ± 1.09 to 4.16 ± 0.94 mg/dL ($p=0.007$) in PD treatment group. With the vitamin E treatment, there was no significant difference in serum albumin

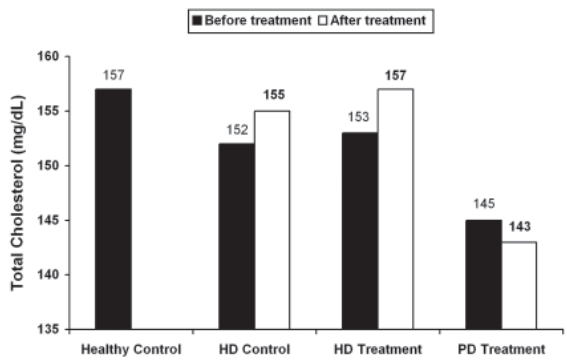


**Figure 2.** Total cholesterol levels of study patients before and after Vitamin E supplementation.

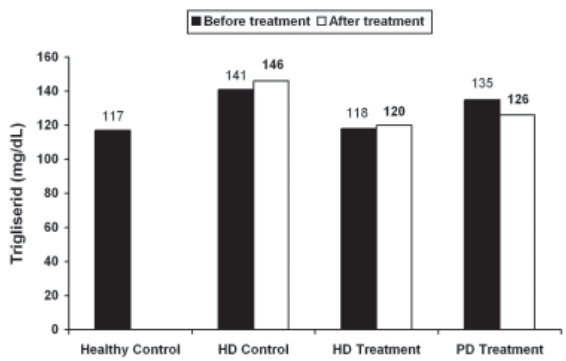


**Figure 3.** Trigliserid levels of study patients before and after Vitamin E supplementation.

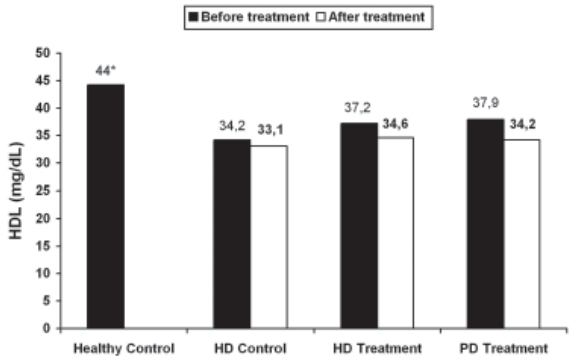


**Figure 4.** HDL levels of study patients before and after Vitamin E supplementation.
* p<0.008 Healthy control vs. HD control, HD treatment, and PD treatment

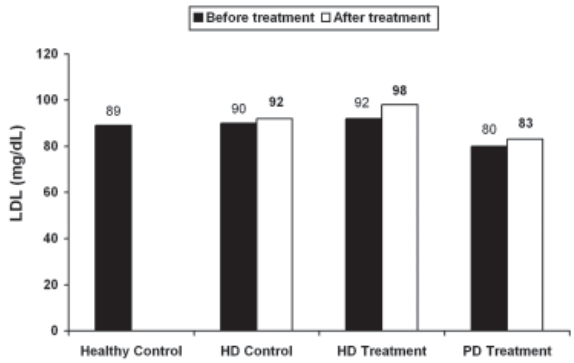


**Figure 5.** LDL levels of study patients before and after Vitamin E supplementation.

levels in treatment groups. Serum albumin level was decreased from 3.70 ± 1.09 to 3.65 ± 0.32 g/dL in HD control group (p=0.570); increased from 3.64 ± 0.35 to 3.72 ± 0.30 g/dL (p=0.208) in HD treatment group, and increased from 3.57 ± 0.20 to 3.65 ± 0.19 g/dL in PD group (p=0.384). Serum vitamin E increased from 0.93±0.16 to 1.09±0.14 mg/dL (p=0.001) in the HD treatment group.

***Lipid levels***

As shown in Figure 4, baseline levels of HDL-C were significantly lower in the HD patient group (HD treatment and HD control together) (35.91±10.54 mg/dl) and PD group (37.92±7.19 mg/dl) than the healthy group (44.27±8.33 mg/dl), (p=0.008). Other baseline lipid levels were not statistically significant between the groups. After vitamin E treatment lipid levels in HD and PD groups were not changed significantly. However, there was a non-significant increase in LDL-C levels (Figure 5); and there was a non-significant decrease in HDL-C levels (Figure 4) in PD treatment and HD treatment groups.

***Lipoprotein levels***

As shown in Figure 9, baseline levels of Lp(a) were significantly higher in the HD group (HD treatment and HD control together) (28.12±10.85 mg/dl) and PD group (31.64±15.12 mg/dl) than the healthy

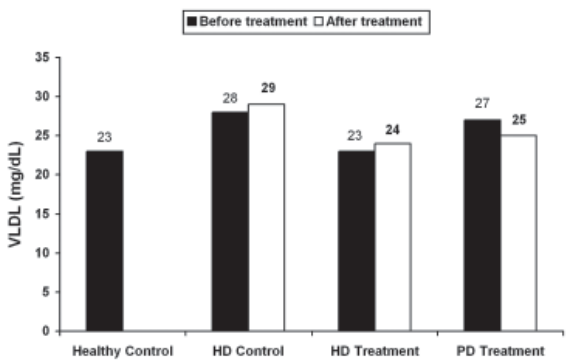


**Figure 6.** VLDL levels of study patients before and after Vitamin E supplementation

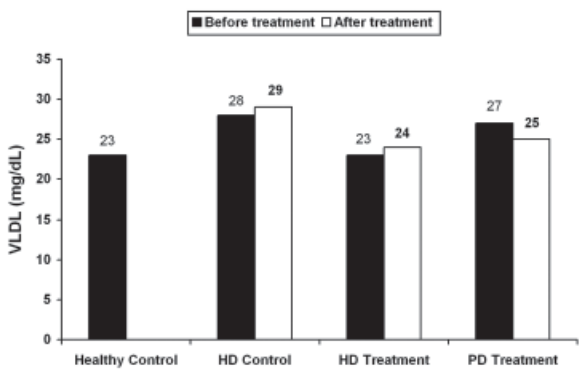


**Figure 7.** ApoA1 levels of study patients before and after Vitamin E supplementation

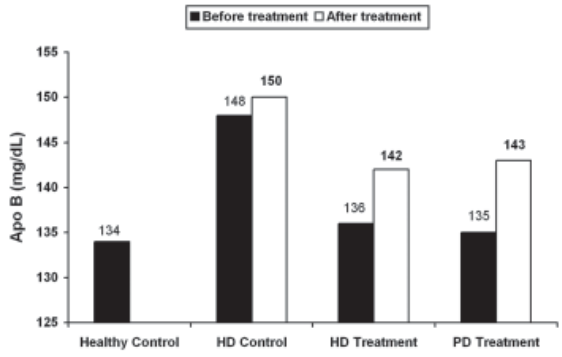


**Figure 8.** ApoB levels of study patients before and after Vitamin E supplementation

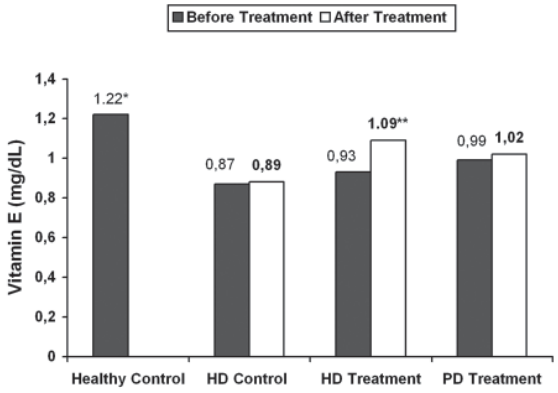


**Figure 10.** Vitamin E levels of study patients before and after Vitamin E supplementation.
* p<0.001 Healthy control vs. HD control, HD treatment, and PD treatment.
** p=0.001 HD treatment after treatment vs. HD treatment before treatment.

group (22.09±9.05 mg/dl), (p=0.008). Other baseline lipoprotein levels were not statistically significant between the groups. Lipoprotein levels in HD and PD groups were not changed significantly after vitamin E treatment. However, there was a non-significant increase in ApoA-I, and ApoB levels; and there was a non-significant decrease in Lp(a) levels in PD treatment and HD treatment groups (Figure 7, Figure 8, and Figure 9, respectively).

## Discussion

The main novel finding in this study was that using a daily oral supplement of 300 mg vitamin E for 20 wk is not effective on lipid, apolipoprotein and lipoprotein profiles in both patients on maintenance HD and PD. The levels of total and LDL-C cholesterol in HD patients are usually low or within normal ranges, which correlated with our study (1, 3-4). In reported studies, 20 to 40% of PD patients have been shown to have elevated total cholesterol and LDL-C (1, 4). Even when the concentration of LDL-C is normal, an increased oxidized LDL levels have been reported in dialysis patients (1, 6, 10). Oxidized LDL particules have atherogenic effects (3, 5). Unfortunately, in our study we have not studied the levels of oxidized LDL levels. In our study the levels of triglycerides, VLDL-C, and apolipoproteins were not different between the groups. However in literature we found that in most of the studies, the levels of triglycerides and ApoB levels are increased while ApoA-I levels were decreased (2-3, 16-17).

In a study by Senti et al (18) lipid profiles in 101 HD patients and 101 healthy controls were investigated. They found that HD patients had significantly higher levels of serum triglycerides, VLDL-C, and lower levels of LDL-C and HDL-C than controls. Regarding apolipoproteins, serum ApoB concentrations were

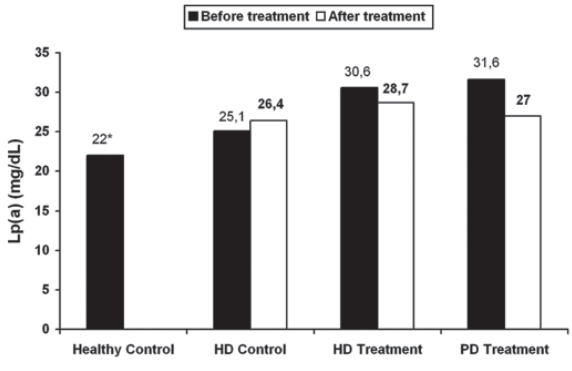


**Figure 9.** Lp(a) levels of study patients before and after Vitamin E supplementation.
*p<0.008 Healthy control vs. HD treatment, and PD treatment

decreased. Seventy-eight of the 101 chronic kidney disease patients had normal serum cholesterol and triglycerides. High triglycerides are accompanied by high levels of ApoB and triglyceride-rich lipoprotein VLDL-C (19). Hypertriglyceridemia is usually more pronounced in PD patients (1, 4). In reported studies, 25 to 50% of PD patients have elevated triglycerides and Apo B (1, 3, 19). ApoB is present in VLDL-C, intermediate density lipoproteins, large buoyant LDL, and small dense LDL. ApoB-containing particles can enhance the risk of atherothrombosis (20). Usually 90% of all ApoB in blood is found in LDL-C. ApoA-I is the major apolipoprotein in HDL particles. ApoA-I also manifests anti-inflammatory, antioxidant, and anti-atherogenic effects (20).

Lipid lowering medications in dialysis are statins, fibrates, and other drugs such as niacin, polyunsaturated fatty acid, sevelamer, and ezetimibe (10, 19). The effects of vitamin E on cholesterol levels and atherosclerosis have been studied in numerous laboratory, population, and clinical trials (21-26). However, very limited reports were available on the effect of vitamin E supplementation on lipids, lipoproteins, and apolipoproteins in patients undergoing dialysis (12-13, 23-24, 26).

In this article, we addressed the issue of whether vitamin E dietary supplementation affects lipoprotein metabolism in the patients on maintenance HD and PD. In the present study, we chose vitamin E supplementation as a prophylactic agent for dyslipidemia in dialysis patients for the following reasons: it leads to (i) reduced ex vivo LDL oxidizability (15), (ii) reduced in vivo lipid peroxidation (14, 16), (iii) is an effective antioxidant and has been proposed for the prevention or treatment of numerous health conditions, often based on its antioxidant properties (13-14, 16, 21, 23), (iv) the antioxidant reserve in dialysis patients is significantly lower than in healthy subjects (16), (v) some studies suggested that abnormal lipoprotein metabolism and lipid oxidation are related to the cardiovascular disease in dialysis patients (6, 8, 21-22), and (vi) in a few experimental and human studies it was shown that dietary vitamin E supplementation may have positive effect on lipid profile (12-15, 25-29). Atherosclerosis and cardiovascular disease are the primary causes of increased morbidity and mortality in dialysis patients (5-6). Atherosclerosis is an inflammatory process that is accelerated under circumstances of oxidative stress. It has been suggested that atherosclerosis might be delayed by an effective supplementation of the antioxidant system such as vitamin E (21-23). In a study by Rimm et al (22) they found evidence of an association between a high intake of vitamin E and a lower risk of coronary heart disease in men. For reduction of oxidative stress, high-dose supplementation with 800 IU/d vitamin E can be useful. We have previously reported in a placebo-controlled study that 300 mg/day Vitamin E therapy for 20 weeks is effective in decreasing the lipid peroxidation in patients on HD (14). In literature there is a few animal studies about the effect of vitamin E on lipit profiles. Rainwater et al (29) showed that dietary vitamin E supplementation for 7 wk on baboons caused 2 paradoxical effects on HDL-C metabolism: higher ApoA-I concentrations and lower HDL-C sizes. Lucas et al (27) studied the the dose-dependent effects of vitamin E supplementation on lipid parameters in ovariectomized rats. They found that vitamin E supplementation moderately improves lipid parameters in ovarian hormone-deficient rats. Dehim et al (30) found that vitamin E does not modulate plasma lipid profile in orchiectomized rats. In another experimental study, Mazur et al (28) shown that Vitamin E deficiency had no significant effect on plasma lipid, lipoprotein and apolipoprotein concentration in rats. Some studies have studied the effects of vitamin E on lipid profiles in patients with normal renal function. In a study by Badiou et al (31) which evaluates the effects of fenofibrate and/or vitamin E (500 mg/day) on lipoproteine profile in 36 HIV-positive adults they presented that three months of vitamin E supplementation only improves LDL-C resistance to oxidation and addition to fenofibrate results in a

slightly greater effect. Total cholesterol, HDL-C, LDL-C, triglycerides, ApoA-I, ApoB, ApoCIII, lipoprotein composition, LDL-C size were not effected by vitamin E supplementation (15). In a study by Noma et al (25) the effects of 600 mg/day vitamin E on lipid profile was studied in 28 hyperlipidemic patients with normal renal function. They found that serum Lp(a) levels in all patients decreased significantly after 2 months of vitamin E treatment. In addition, Howard et al (32) documented no significant change in serum HDL-C with vitamin E therapy.

In a study by Islam et al (12) it was shown that vitamin E supplementation (800 IU per day) for 12 weeks decreased the oxidative susceptibility of LDL-C in renal failure patients on dialysis. In our study, lipid and lipoprotein levels in HD and PD groups were not changed significantly after 20 week dietary supplementation of vitamin E. However, there was a non-significant increase in ApoA-I, LDL-C, and ApoB levels; and a non-significant decrease in Lp(a) and HDL-C levels in PD treatment and HD treatment groups. The increase in ApoA-I and the decrease in Lp(a) levels may have positive effects to protection against cardiovascular disease, but increase in ApoB and LDL-C and decrease in HDL-C levels may have negative effect on cardiovascular system. A decrease in HDL-C concentration, increased levels of Lp(a) and ApoB make dialysis patients more vulnerable to cardiovascular disease (7-9, 20). Our study results are compatable with the following three studies: In a study by Chapkin et al (33) seven patients on dialysis were given 600 IU of vitamin E daily for 4 wk (33). The level of total, free, and esterified cholesterol and triglyceride in whole serum and HDL-C were measured. No significant change was noted in any of the parameters. Mortzzavimoghaddam et al (34) presented that oral vitamin E supplementation at a dose of 400 mg/d for 90 days, had no effect on the levels of serum cholesterol, triglyceride, HDL-C and LDL-C in 26 uremic patients undergoing maintenance HD. In a double-blind randomised placebo-controlled study in 23 HD and 21 PD patients, it was shown that 800 IU/day vitamin E supplementation for 12 weeks may be effective on lipid oxidisability in HD patients. On the other hand vitamin E had no effect on serum total cholesterol, triglyceride, LDL-C, ApoB, and oxLDL (13). However, Khajehdehi et al (24) tested the effect of vitamins on the lipid profile of patients on regular HD and showed that HDL-C increased and the ratio of LDL-C to HDL-C decreased significantly after vitamin E therapy. In chronic renal insufficiency, the loss of vitamins possessing antioxidative characteristics considerably increases due to the large number of metabolic abnormalities, reduction in intake due to a diet restriction, loss through dialysis, voiding and changes to vitamin carrying proteins and lipids due to increased production of reactive oxygen species. Therefore, changes occur in water-and-fat soluble vitamin levels, such as Vitamin E. Altered vitamin E levels have also been detected in uremic patients (35). Some authors have investigated intraerythrocyte vitamin E levels and demonstrated they were lower in HD patients (36). Our findings are comparable with the sources reporting reduced plasma vitamin E levels in dialysis patients. The present study has several limitations: We did not measure levels of small, dense LDL. Small sample size is another study limitation. The results from this study should be generalized with caution, since it was conducted at a single medical center.

In conclusion, the results of this study suggest that 20 weeks of vitamin E dietary supplementation had no effect on lipid profile and lipoproteins in patients on PD and HD.

## Acknowledgement

None of the authors have any conflict of interest for the present study. The abstract form of this study has been presented in 35. Kongress Der Gesellschaft für Nephrologie, in Basel, Switzerland at 18-21 September 2004.

## Conflict of Interest

None of the authors have any conflict of interest in the present study.

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