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Effects of High-dose Vitamin E Supplementation on Markers of Cardiometabolic Risk and Oxidative Stress in Patients with Diabetic Nephropathy

A Randomized Double-blinded Controlled Trial

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Original Paper

Introduction. Patients with diabetic nephropathy (DN) may benefit from vitamin E's antilipid and antioxidant activities. This study aimed to evaluate the effects of high-dose vitamin E supplementation on markers of cardiometabolic risk and oxidative stress in patients with DN.

Materials and Methods. This randomized controlled trial was carried out on 54 patients with DN that were randomly divided into 2 groups to receive vitamin E supplement (800 IU/d) or placebo for 12 weeks. Fasting blood samples were obtained at baseline and after the 12-week intervention to determine markers of cardiometabolic risk and oxidative stress.

Results. Vitamin E supplementation, compared with the placebo, resulted in a significant reduction in serum total cholesterol (-14.3 ± 29.9 mg/dL versus -0.8 ± 13.1 mg/L, P = .03), low-density lipoprotein cholesterol (-16.4 ± 28.5 mg/dL versus 0.1 ± 17.2 mg/L, P = .01), and ratio of total cholesterol to high-density lipoprotein cholesterol ratio (-0.5 ± 0.7 versus 0.1 ± 0.5, P = .001), and a significant elevation in vitamin E levels (39.7 ± 12.4 nmol/mL versus -0.5 ± 1.3 nmol/mL, P < .001) and high-density lipoprotein cholesterol levels (1.4 ± 3.7 versus -2.1 ± 5.1 mg/L, P = .006). It also resulted in a significant elevation in plasma glutathione levels.

Conclusions. Our study demonstrated that high-dose vitamin E supplementation for 12 weeks had favorable effects on lipid profile and glutathione levels of patients with DN, except for triglycerides, very low-density lipoprotein cholesterol, nitric oxide, and total antioxidant capacity levels.

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INTRODUCTION

Dyslipidemia is a metabolic disorder characterized by diverse lipid profiles, such as hypertriglyceridemia, hypercholesterolemia, and decreased high-density lipoprotein cholesterol (HDLC) levels,[1] and is emerging as an independent risk factor for the development of kidney disease in diabetic nephropathy (DN).[2,3] Previous studies strongly suggested that hyperlipidemia could result in glomerulosclerosis and tubulointerstitial fibrosis and induce renal injury by promoting the intrarenal generation of reactive oxygen species and free radicals and by glomerular infiltration of monocytes and macrophages.[4] In addition, increased biomarkers of oxidative stress are associated with the development of late diabetic complications.[5]

Antioxidants administration has demonstrated a beneficial role in the prevention of the diabetic complications. Diabetes mellitus (DM) forms a good model of dyslipidemia and chronic oxidative damage, and thus it is a particularly suitable for antioxidant supplementation.[6] In an animal study, supplementation with d-α-tocopherol significantly improved insulin resistance, serum triglycerides, very low-density lipoprotein cholesterol (VLDL), and malondialdehyde concentrations.[7] Earlier, it was reported that d-α-tocopherol could regulate gene expression related to lipid metabolism and peroxisome proliferator activated-receptor-γ.[6,8] Vitamin E supplementation for 16 weeks among maintenance hemodialysis patients significantly improved lipid profiles.[9] Furthermore, vitamin E supplementation at dosages of 200 IU/d and 300 IU/d for 4 months provided marked benefits in reducing oxidative stress concentrations and improving lipid profiles in women with metabolic syndrome.[10] However, vitamin E supplementation for 120 days in orchiectomized rats significantly reduced oxidative stress without modulating lipid profiles or inflammatory response.[11]

Considering that the pathogenesis of DN may be correlated with increased markers of cardiometabolic risk and oxidative stress and since there is evidence that vitamin E intake has antilipid and antioxidant actions, we hypothesized that high-dose vitamin E supplementation might help DN population to control their markers of cardiometabolic risk and oxidative stress. This investigation was aimed to evaluate the effects of high-dose vitamin E supplementation on markers of cardiometabolic risk and oxidative stress among DN patients.

MATERIALS AND METHODS

Participants

This randomized double-blinded placebo-controlled clinical trial was conducted on 54 patients with DN, aged 40 to 85 years old, referred to Shahid Beheshti Clinic in Kashan, Iran, from May 2017 to August 2017. We defined DN as diabetic kidney disease with a proteinuria level greater than 0.3 g/24 h, with or without circulating levels of serum creatinine.[12] Patients matching any of the following criteria were excluded: vitamin E supplementation within the past 3 months, pregnancy, and chronic liver disease (abnormal liver enzymes levels). Based on suggested formula for clinical trials, we calculated that we needed 23 participants in each group considering a type 1 error of 0.05, a type 2 error of 0.20, and 3.5 mg/dL as standard deviation and 2.9 mg/dL as the distinction in mean of low-density lipoprotein cholesterol (LDLC) level as the key variable.[13] Assuming 4 dropouts in each group, the final sample size was determined to be 27 participants per group.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and written informed consent was taken from all of the participants. The research protocol was approved by the research ethics committee of Kashan University of Medical Sciences and was registered by the Iranian Registry of Clinical Trials (http://www.irct.ir; IRCT201706055623N117).

Study Design

All of the participants were stratified based on sex, number and type of hypoglycemic medications, duration of DM, body mass index (BMI), and age. They were randomly allocated into 2 groups to take either 800 mg/d of vitamin E supplement or placebo (n = 27 in each group) for 12 weeks. Vitamin E supplements and placebos (similar in shape and size to vitamin E capsule) were manufactured by Zahravi Pharmaceutical Company (Tabriz, Iran). Randomization and allocation into 2 groups were done using a random number table by one of the investigators who had no clinical involvement in the research. Compliance to the intake of vitamin E supplement and placebo was assessed by vitamin E levels using an enzyme-linked immunosorbent assay method.

Assessment of Anthropometric Measures

Weight and height of the participants were determined in an overnight fasting status using a standard scale (Seca, Hamburg, Germany) at baseline and after the 12-week treatment. Body mass index was calculated as weight in kilograms divided by squared height in meters.

Assessment of Outcomes

Lipid profile was considered as the primary outcome, and biomarkers of oxidative stress were considered as the secondary outcomes. Ten

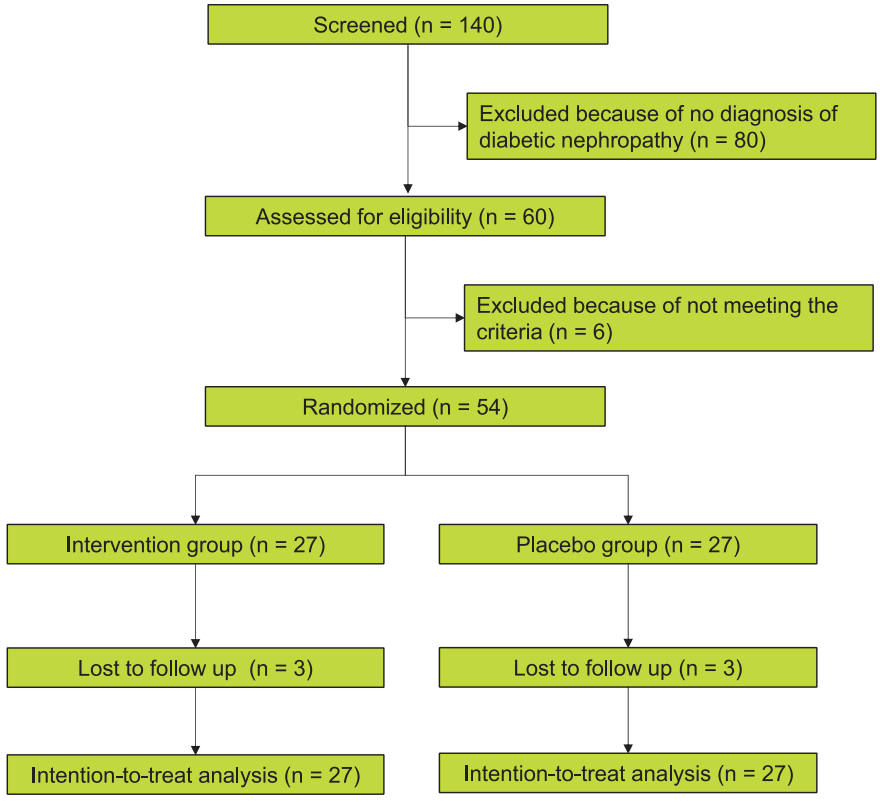
milliliter fasting blood samples were collected at baseline and after the 12-week intervention at Kashan Reference Laboratory, Kashan, Iran. Serum vitamin E levels were assessed by an enzyme-linked immunosorbent assay kit (Crystal Day, Shanghai, China) with inter- and intra-assay coefficient variances of 5.3 and 6.8%, respectively. Enzymatic kits (Pars Azmun, Tehran, Iran) were applied to evaluate serum triglycerides, VLDLC, total cholesterol, LDLC, HDLC, and fasting plasma glucose concentrations. All inter- and intra-assay coefficient variances for lipid profile and fasting plasma glucose were less than 5%. The plasma nitric oxide (NO) levels were determined using the Griess method.[14] The plasma total antioxidant capacity (TAC) level was assessed using the method of ferric-reducing antioxidant power developed by Benzie and Strain.[15] Total glutathione (GSH) was determined using the method of Beutler et al.[16] Malondialdehyde levels were determined using the thiobarbituric acid reactive substances spectrophotometric test.[17] Coefficient variances for plasma NO, TAC, glutathione, and malondialdehyde were lower than 5%, respectively. Hemoglobin A1c levels in the whole blood were quantified by Glycomat kit (BiocodeHycel, Massy, France) using the method of exchange chromatography.

Statistical Analysis

To evaluate normal distribution of the variables in the study, we applied the Kolmogrov-Smirnov test. The analyses were conducted based on intention-to-treat principle. To detect differences in anthropometric measures as well as in macro- and micro-nutrient intakes between the two groups, we applied independent samples Student *t* test. To determine the effects of vitamin E supplementation on biochemical parameters, we used the 1-way repeated measures analysis of variance. Adjustment for confounding variables was done by the analysis of covariance using general linear models. A *P* value less than .05 was considered significant. All statistical analyses were done using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Among the participants of each group, 3 withdrew from the study due to personal reasons (Figure). Finally, 48 patients (24 in the vitamin E group



Summary of patient flow diagram.

and 24 in the placebo group) completed the trial. However, we did the analysis based on intention-to-treat principle, and all 54 patients (27 patients in each group) were included in the final analysis. There were no significant differences between the two groups in the mean age, height, weight, or BMI at baseline and after the trial, or in duration of DM, using antidiabetic and antilipidemic medication (Table 1).

Based on the 3-day dietary records obtained throughout the trial, we found no significant difference in the mean dietary macro- and micro-nutrient intakes (data not shown). After the 12-week intervention, compared with the placebo, vitamin E supplementation resulted in a significant reduction in serum total cholesterol (-14.3 ± 29.9 mg/dL versus -0.8 ± 13.1 mg/L, P = .03), LDLC (-16.4 ± 28.5 mg/dL versus 0.1 ± 17.2 mg/L, P = .01), and total cholesterol-HDLC ratio (-0.5 ± 0.7 versus 0.1 ± 0.5, P = .001), and a significant elevation in vitamin E levels (39.7 ± 12.4 nmol/mL versus -0.5 ± 1.3 nmol/mL, P < .001) and HDLC levels (1.4 ± 3.7 versus -2.1 ± 5.1 mg/L, P = .006; Table 2). In addition, vitamin E supplementation resulted in a significant elevation in plasma glutathione levels (72.7 ± 160.8 µmol/L versus -42.8 ± 127.8 µmol/L, P = .005) compared with the placebo. Supplementation with vitamin E had no significant effects on other lipid profiles and biomarkers of oxidative stress compared with the placebo.

There was a significant difference in baseline levels of HDLC (P = .001) between the two groups. Therefore, we adjusted the analysis for baseline of biochemical variables, age, and baseline BMI. When we controlled the analysis for baseline values of biochemical variables, age and baseline BMI, the difference in changes in HDLC between the two groups became nonsignificant (P = .15), while other findings did not change (Table 3).

DISCUSSION

In the current study, we assessed the effects of high-dose vitamin E supplementation on markers of cardiometabolic risk and oxidative stress among patients with DN. We found that high-dose vitamin E supplementation for 12 weeks among DN patients had favorable effects on lipid profiles and glutathione levels except triglycerides, VLDLC,

Table 1. Characteristics of Study Participants*

Characteristic	Placebo Group (n = 27)	Vitamin E Group (n = 27)	*P*
Sex			
Male	8 (29.6)	8 (29.6)	> .99
Female	19 (70.4)	19 (70.4)	
Age, y	64.5 ± 9.2	62.2 ± 9.8	.38
Height, cm	163.8 ± 6.8	161.6 ± 8.7	.31
Body weight, kg			
Baseline	83.3 ± 16.1	80.7 ± 14.1	.52
At the end of trial	83.8 ± 16.2	80.9 ± 13.9	.47
Body mass index, kg/m^2			
Baseline	31.1 ± 6.1	30.9 ± 4.7	.88
At the end of trial	31.2 ± 6.0	30.9 ± 4.6	.82
Smoking	2 (7.4)	2 (7.4)	> .99
Diabetes mellitus			
Type 1	3 (11.1)	3 (11.1)	> .99
Type 2	24 (88.9)	24 (88.9)	
Duration of diabetes, y	16.1 ± 3.3	16.4 ± 2.8	.72
Insulin therapy	22 (81.5)	21 (77.8)	.73
Antidiabetic medication			
Monotherapy	3 (11.1)	3 (11.1)	
Combination therapy	24 (88.9)	24 (88.9)	> .99
Antilipid medication			
Monotherapy	16 (59.3)	17 (63.0)	
Combination therapy	3 (11.1)	4 (14.8)	.79
Hypertension	25 (92.6)	25 (92.6)	> .99

*Data are mean ± standard deviation or frequency (percentage).

Table 2. Markers of Cardiometabolic Risk and Oxidative Stress at Baseline and After the 12-week Intervention in Patients With Diabetic Nephropathy That Received Either Vitamin E Supplement or Placebo*

Parameter	Placebo Group (n = 27)			Vitamin E Group (n = 27)			*P*
	Baseline	End of Trial	Change	Baseline	End of Trial	Change	
Vitamin E, nmol/mL	46.4 ± 15.9	45.9 ± 15.8	-0.5 ± 1.3	48.5 ± 14.6	88.2 ± 22.2	39.7 ± 12.4	< .001
Triglycerides, mg/dL	198.7 ± 100.3	204.7 ± 80.7	6.0 ± 82.1	212.7 ± 96.5	216.4 ± 110.9	3.7 ± 66.0	.90
Very low-density lipoprotein cholesterol, mg/dL	39.7 ± 20.1	40.9 ± 16.1	1.2 ± 16.4	42.5 ± 19.3	43.3 ± 22.2	0.7 ± 13.2	.90
Total cholesterol, mg/dL	166.8 ± 31.0	166.0 ± 33.1	-0.8 ± 13.1	168.4 ± 31.5	154.1 ± 27.4	-14.3 ± 29.9	.03
Low-density lipoprotein cholesterol, mg/dL	81.3 ± 32.4	81.4 ± 30.5	0.1 ± 17.2	86.5 ± 26.2	70.1 ± 30.3	-16.4 ± 28.5	.01
High-density lipoprotein cholesterol, mg/dL	45.7 ± 6.9	43.6 ± 5.9	-2.1 ± 5.1	39.4 ± 5.7	40.8 ± 6.8	1.4 ± 3.7	.006
Ratio of total cholesterol to high-density lipoprotein cholesterol	3.7 ± 0.7	3.8 ± 0.7	0.1 ± 0.5	4.3 ± 0.9	3.8 ± 0.7	-0.5 ± 0.7	.001
Nitric oxide, µmol/L	61.1 ± 9.2	64.5 ± 10.5	3.3 ± 10.2	62.1 ± 9.1	62.7 ± 10.2	0.6 ± 9.3	.30
Total antioxidant capacity, mmol/L	1118.3 ± 242.0	1155.3 ± 381.9	37.0 ± 364.5	1070.8 ± 131.8	1155.7 ± 184.3	84.9 ± 162.6	.53
Glutathione, µmol/L	688.2 ± 107.6	645.4 ± 157.1	-42.8 ± 127.8	717.3 ± 176.0	790.0 ± 245.5	72.7 ± 160.8	.005
Fasting plasma glucose, mg/dL	118.7 ± 26.4	120.9 ± 23.8	2.2 ± 11.9	114.6 ± 28.8	115.4 ± 32.2	0.8 ± 15.2	.70
Hemoglobin A1c, %	8.0 ± 1.1	7.8 ± 1.1	-0.2 ± 0.4	7.8 ± 1.0	7.3 ± 0.8	-0.4 ± 0.6	.12

*Data are mean ± standard deviation or frequency (percentage).

NO, and TAC. To our knowledge, this is the first report of high-dose vitamin E supplementation on markers of cardiometabolic risk and oxidative stress in patients with DN.

Diabetic nephropathy is associated with metabolic disturbances, inflammation, and oxidative stress.[18] We found that taking vitamin E supplements for 12 weeks by patients with DN were correlated with a significant reduction in serum total cholesterol, LDLC, and total cholesterol-HDLC, and a significant elevation in HDLC levels compared with the placebo, but did not affect triglycerides and VLDLC levels. Supporting our study, vitamin E supplementation for 4 months in a hemodialysis population led to a significant reduction in total cholesterol and LDLC concentrations, but did not affect other lipid fractions.[19] In addition, vitamin E plus symbiotic supplementation was beneficial in lowering triglycerides, total cholesterol, and LDLC among patients with nonalcoholic fatty liver disease.[13] Vitamin E and omega-3 fatty acids cosupplementation for 12 weeks in women with polycystic ovary syndrome significantly improved lipid profiles.[20] Cosupplementation of 150 mg of vitamin E, 200 mg of vitamin C, 200 mg of magnesium, and 30 mg of zinc for 3 months in patients with type 2 DM significantly increased HDLC and apo A1, but did not affect other lipid profiles.[21] However, vitamin E supplementation at a dose of 400 IU/d for 8 weeks did not influence total cholesterol or LDLC levels in hypercholesterolemic patients receiving lovastatin or simvastatin.[22] Diabetic nephropathy is strongly linked with dyslipidemia in diabetic patients.[23] Previous studies have found even more robust lipid disorders correlated with nephropathy than with cardiovascular disease.[24] Vitamin E intake inhibits signal transduction pathways including protein kinase C.[25] Vitamin E supplementation may stimulate the proliferator activated-receptor-γ transduction pathway,[26] which in turn decrease cholesterol levels.

The current study demonstrated that vitamin E supplementation among patients with DN were associated with a significant increase in plasma glutathione levels compared with the placebo, but did not increase plasma TAC and NO concentrations. In agreement with our study, vitamin E supplementation at a dose of 600 mg/d for 3 months ameliorated oxidative stress through

Table 3. Adjusted Changes in Metabolic Variables in Patients With Diabetic Nephropathy That Received Either Vitamin E Supplement or Placebo*

Parameter	Placebo Group (n = 27)	Vitamin E Group (n = 27)	*P*
Vitamin E, nmol/mL	-0.3 ± 1.7	39.6 ± 1.7	< .001
Triglycerides, mg/dL	4.2 ± 13.6	5.4 ± 13.6	.95
Very low-density lipoprotein cholesterol, mg/dL	0.9 ± 2.7	1.1 ± 2.7	.95
Total cholesterol, mg/dL	-0.9 ± 4.1	-14.2 ± 4.1	.02
Low-density lipoprotein cholesterol, mg/dL	-0.6 ± 4.3	-15.7 ± 4.3	.01
High-density lipoprotein cholesterol, mg/dL	-1.3 ± 0.9	0.6 ± 0.9	.15
Ratio of total cholesterol to high-density lipoprotein cholesterol	-0.008 ± 0.1	-0.4 ± 0.1	.03
Nitric oxide, μmol/L	3.2 ± 1.8	0.7 ± 1.8	.33
Total antioxidant capacity, mmol/L	50.5 ± 53.1	71.5 ± 53.1	.78
Glutathione, μmol/L	-42.3 ± 28.6	72.2 ± 28.6	.007

*Data are mean ± standard deviation or frequency (percentage). Results were obtained from the analysis of covariance test adjusted for baseline values plus age and baseline body mass index.

increasing levels of glutathione in patients with type 1 DM.[27] In addition, vitamins E and C cosupplementation with exercise protected against fibromyalgia-induced oxidative stress through upregulation of an antioxidant redox system in the plasma and erythrocytes of individuals with fibromyalgia.[28] Supplementation with combined vitamin E (400 IU/d) and vitamin C (500 mg/d) for 2 months significantly decreased lipid peroxidation and strengthened the antioxidant defense system in patients with cardiovascular disease through significant increases in superoxide dismutase and glutathione peroxidase activity.[29] Furthermore, in another study, vitamin E supplementation significantly improved biomarkers of oxidative stress.[30] However, no significant differences were observed in erythrocyte superoxide dismutase and glutathione peroxidase activities, glutathione, and plasma TAC, lipid peroxides and glutathione peroxidase activity following the supplementation of vitamin E at a dosage of 400 IU twice a day for 8 weeks in patients with chronic obstructive pulmonary disease.[31] Overproduction of intracellular reactive oxygen species and free radicals contributes to several microvascular and macrovascular complications of DN, and increase the production of inflammatory cytokines.[32]

This study had few limitations. First, sample size was low. Future studies with longer duration of the intervention and a larger sample size are needed to confirm the validity of our findings. Second, we did not evaluate the effects of vitamin E supplementation on the mean daily proteinuria and gene expression related to biomarkers of inflammation and oxidative stress.

CONCLUSIONS

Our study demonstrated that high-dose vitamin E supplementation for 12 weeks among DN patients had favorable effects on lipid profiles and glutathione levels except for triglycerides, VLDLC, NO, and TAC.

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CONFLICTS OF INTEREST

None declared.

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