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CLINICAL STUDY

The Effects of Vitamin E-Coated Membrane Dialyzer Compared to Simvastatin in Patients on Chronic Hemodialysis

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Abstract

Background: We investigated the effects of the use of vitamin E-coated membrane (VEM) dialyzer in comparison to simvastatin on markers of chronic inflammation, oxidative stress, and endothelial cell apoptosis in ten patients on chronic hemodialysis (HD), aiming at distinguishing the different treatment effects and their time sequence on these pathogenetic routes. *Methods*: Ten HD patients were sequentially submitted to a 6-month treatment with the use of VEM and 10 mg of simvastatin daily, interrupted by a 3-month washout period. At baseline, at 3, and 6 months of each trial, serum C-reactive protein (CRP), apolipoprotein (Apo) A1 and B, lipoprotein-a [Lp(a)], high-sensitivity interleukin-6 (hsIL-6), monocyte chemoattractant protein-1 (MCP-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble E-selectin (sE-selectin), soluble Fas (sFas), soluble Fas ligand (sFasL), and plasma oxidized low-density lipoproteins (oxLDL) levels were determined. *Results*: VEM treatment resulted in a significant decrease in CRP, IL-6, sICAM-1 at 3 months, and oxLDL at 6 months, compared to baseline. Simvastatin resulted in a significant decrease in CRP, which correlated with decreases in both total ($r = 0.87$, $p < 0.05$) and low-density lipoprotein cholesterol, IL-6, sICAM-1, sVCAM-1, oxLDL, and sFas at 6 months, compared to baseline. Simvastatin effects on sVCAM-1 (mean difference = 652 ng/mL; 95% CI = 294 to 2686; $p < 0.05$) and sFas (mean difference = 1284 pg/mL; 95% CI = 510 to 1910; $p < 0.05$) differed significantly from the corresponding VEM effects. *Conclusions*: The 6-month use of VEM resulted in more direct and immediate anti-inflammatory effects compared with those caused by the 6-month treatment with simvastatin. Simvastatin caused a more intense decrease in the markers of inflammation, which was in part correlated with its lipid-lowering effects.

Keywords: apoptosis, hemodialysis, inflammation, oxidative stress, simvastatin, vitamin E dialyzers

INTRODUCTION

Driven by the observation that several markers of inflammation, oxidative stress, and endothelial cell apoptosis have been shown to represent potent early indicators of atherosclerosis and independent predictors of mortality in patients on chronic hemodialysis (HD),[1] various anti-inflammatory and anti-oxidative treatment approaches have been studied over the last years, aiming at the reduction of cardiovascular risk. Earlier studies have shown that both the use of vitamin E-coated membrane (VEM) dialyzers[2] and 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA)-reductase inhibitors, or statins,[3–5] can have anti-inflammatory and anti-oxidative effects in HD patients.[6–8] The primary objective of the present prospective, randomized, crossover study was to compare the effects of both treatments on sensitive markers of inflammation, oxidative stress, and endothelial cell apoptosis in patients on HD, aiming at distinguishing the different treatment effects and their time sequence on these pathogenetic routes.

SUBJECTS AND METHODS

Patients

Ten patients (5 males, mean age 63 years, range 45–76) were recruited from University Department of Nephrology at Hippokration General Hospital, Thessaloniki, Greece. Inclusion criteria were (1) treatment with standard chronic HD for at least 6 months, (2)

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hypercholesterolemia documented by at least two plasma determinations on fasting condition or indication for hypolipidemic treatment according to 2001 NCEP-ATP III guidelines (primary prevention for patients with a fasting plasma low-density lipoprotein cholesterol (LDL-C) level $\geq$ 130 mg/dL and two other risk factors; secondary prevention for patients with a fasting plasma LDL-C level $\geq$ 100 mg/dL and coronary disease), (3) clinically stable health condition, and (4) age 18–85 years. Exclusion criteria were: use of antioxidant, hypolipidemic, non-steroid anti-inflammatory drugs, or corticosteroids during the last 3 months, malignancy, cachexia, liver disease, alcohol abuse, hypothyroidism, active inflammation, considerable iron overload, and rheumatological disorders. The study had a randomized, crossover design and lasted 15 months. Five patients received 10 mg of simvastatin for 6 months. During the 6-month period, all patients were dialyzed with a cellulose 1.2–1.5 m^2 hollow fiber dialyzer. Five patients were submitted to HD with the use of a vitamin E-coated regenerated cellulose 1.2–1.5 m^2 hollow fiber Clirans® E (CL-E; Terumo Corp., Japan) dialyzer (exclusively low- or medium-flux) for 6 months. This was followed by a 3-month washout period off initial treatment and then the alternative treatment for 6 months. The study complied with the declaration of Helsinki, was approved by the hospital ethics committee, and informed consent was taken from all participants. During the study, there was no dialyzer reuse. All patients were receiving standard HD therapy three times a week for 4 hours, with bicarbonate dialysate at a flow of 500 mL/min from a central supply system and low-molecular weight heparin as anticoagulant. Dialysis prescription was guided by a goal of achieving a value of $\geq$0.65 for the urea reduction ratio and a value of Kt/V $\geq$ 1.2. The above indices of adequacy of dialysis were calculated by the formula [(pre-dialysis urea)–(post-dialysis urea)/pre-dialysis urea] and by the second-generation Daugirdas equation, respectively. Blood samples were taken from a peripheral vein under fasting conditions, in the morning of a mid-week routine dialysis day, at baseline, after 3 and after 6 months of both treatments. Serum and plasma samples were separated from clotted blood by immediate centrifugation (1500 $\times$ *g* for 10 min), aliquoted, and stored immediately at –70°C until assayed.

Statistical Analysis

Results are expressed as mean $\pm$ SD or median and range, depending on the normality of the distributions of each parameter. Baseline and end point data were compared using repeated measures analysis of variance (ANOVA), with the two treatment modalities further compared using paired *t*-test if the ANOVA showed a significant difference. Pre- and post-treatment data were compared using paired *t*-test. Significant correlations were identified with the use of regression analysis. Statistical analysis was performed with the use of SPSS v. 13.0.0 statistical software (SPSS Inc., Chicago, IL, USA).

Laboratory Methods

Serum albumin, urate, total cholesterol (T-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C) were determined by routine techniques, and serum apolipoprotein (Apo) A1, ApoB, and lipoprotein-a [Lp(a)] by immunoturbidimetric method, with the use of an automated analyzer (Olympus AU560, Hamburg, Germany). Normal range for ApoA1 was 105–175 (males) and 105–205 mg/dL (females), for ApoB 60–140 (males) and 55–130 mg/dL (females), and for Lp(a) 0–30 mg/dL (both sexes). LDL-C was calculated with the use of the Friedewald formula [LDL-C = T-C – triglycerides/5-HDL-C].

Serum C-reactive protein (CRP) levels were measured by nephelometry (normal values $\leq$5mg/L). Serum levels of high-sensitivity interleukin-6 (hsIL-6), monocyte chemoattractant protein-1 (MCP-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble E-selectin (sE-selectin), soluble Fas (sFas), soluble Fas ligand (sFasL), and plasma levels of oxidized low-density lipoproteins (oxLDL) were determined by enzyme-linked immunosorbent assay (ELISA), as described previously.[7]

RESULTS

The primary renal disease was glomerulonephritis in three patients, diabetes mellitus in two patients, tubulointerstitial nephritis in two patients, adult dominant polycystic kidney disease in one patient, vascular renal disease in one patient and was unknown in one patient. Three patients were active smokers, a state defined as the regular use of smoke products over the last 5 years. Five patients had a history of documented cardiovascular disease (CVD) (coronary artery disease, stroke, or peripheral vascular disease) and seven patients had arterial hypertension and were receiving antihypertensive treatment. During both treatments, all patients tolerated treatments well and no meaningful adverse effects were documented that could have justified termination of the therapies. In addition, during the treatment with simvastatin, creatine-phosphokinase as well as liver aminotransferases remained within normal levels in all patients (data not shown).

Laboratory data during the study are shown in Table 1. Values at the beginning of each treatment phase (baseline and washout) did not differ for any parameter. The median age of the study patients was 64 years (range 28–76). Mean BP was 109 $\pm$ 10 mmHg. The mean BMI was 24.3 $\pm$ 1.8 kg/m^2. As expected, simvastatin but not VEM treatment resulted in significant changes in lipids from as early as the 3rd month of the study (Table 1). At 3 months, the use of VEM resulted in a significant decrease in CRP (25%) and sICAM-1 (29%) and a slight decrease in IL-6 (14%). Moreover, a remarkable change in oxLDL (31%) was additionally observed at 6 months

Table 1. Laboratory parameters of the patient groups at baseline and after 3 and 6 months of treatment with VEM versus simvastatin.

		VEM		Simvastatin	
Parameters	Baseline	At 3 months	At 6 months	At 3 months	At 6 months
Albumin (g/dL)	3.9 ± 0.5	3.9 ± 0.3	4.1 ± 0.3	3.8 ± 0.2	3.8 ± 0.4
T-C (mg/dL)	234 ± 23	231 ± 20	238 ± 20	172 ± 24*	166 ± 43*
HDL-C (mg/dL)	39 ± 16	38 ± 6	42 ± 8	40 ± 10	40 ± 16
LDL-C (mg/dL)	152 ± 24	148 ± 19	153 ± 13	103 ± 22*	97 ± 33*
Triglycerides (mg/dL)	215 ± 74	224 ± 67	218 ± 72	146 ± 50*	147 ± 40*
ApoA1 (g/L)	110 ± 20	111 ± 13	113 ± 18	130 ± 23*	130 ± 24*
ApoB (g/L)	133 ± 33	129 ± 46	132 ± 35	122 ± 32	104 ± 35*
ApoB/A	1.2 ± 0.3	1.2 ± 0.2	1.18 ± 0.3	0.9 ± 0.3	0.8 ± 0.3*
Lp(a) (μmol/L)	9.2 ± 12.8	9.0 ± 6.1	8.9 ± 7.0	7.7 ± 4.0	4.4 ± 1.6*
CRP (mg/L)	7.9 ± 5.3	5.9 ± 1.7*	4.2 ± 2.3*	7.4 ± 5.3	3.3 ± 0.6*
hsIL-6 (pg/mL)	5.8 ± 4.1	5.0 ± 2.8*	4.1 ± 3.8*	5.1 ± 3.8	2.0 ± 1.2*
sICAM-1 (ng/mL)	429 ± 118	304 ± 75*	314 ± 77*	415 ± 119	320 ± 74*
sVCAM-1 (ng/mL)	2671 ± 720	2448 ± 683	2686 ± 1257	2653 ± 695	1711 ± 464*
sE-selectin (ng/mL)	82 ± 34	82 ± 38	90 ± 40	82 ± 24	86 ± 33
MCP-1 (ng/mL)	503 ± 76	499 ± 81	492 ± 99	484 ± 64	486 ± 80
oxLDL (U/L)	45 ± 13	43 ± 9	31 ± 9*	41 ± 11*	34 ± 5*
sFas (pg/mL)	22013 ± 5283	19548 ± 5286	18802 ± 5075	19548 ± 5286	17518 ± 4161*
sFasL (pg/mL)	95 ± 26	100 ± 26	104 ± 41	105 ± 55	91 ± 38

Notes: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; hsIL-6, high-sensitivity interleukin-6; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein-a; MCP-1, monocyte chemoattractant protein-1; oxLDL, oxidized low-density lipoproteins; sE-selectin, soluble E-selectin; sFas, soluble Fas; sFasL, soluble Fas ligand; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1. Data are presented as mean ± SD.
*$p < 0.05$ compared to baseline.

Table 2. Comparison of 6-month changes in the parameters studied in patients treated with VEM versus simvastatin.

Parameter	VEM	Simvastatin	Δ	Comparison 95% CI	*p*-Value
T-C (mg/dL)	4 ± 14	−56 ± 24	60	40 to 84	0.0001
LDL-C (mg/dL)	1 ± 18	−47 ± 23	48	18 to 72	0.004
Triglycerides (mg/dL)	3 ± 7	−68 ± 54	71	30 to 128	0.008
ApoA1 (g/L)	3 ± 24	7 ± 20	−4	−25 to 22	0.89
ApoB (g/L)	−1 ± 32	−16 ± 36	15	−11 to 72	0.13
ApoB/A	−0.02 ± 0.25	−0.2 ± 0.2	0.18	−0.08 to 0.5	0.23
Lp(a) (μmol/L)	−0.3 ± 2.7	−2.9 ± 7.2	2.6	−2.4 to 9.6	0.21
CRP (mg/L)	−3.7 ± 4.1	−3.3 ± 4.6	−0.4	−4.7 to 5.4	0.87
hsIL-6 (pg/mL)	−1.7 ± 7.0	−1.7 ± 1.6	0	−5.0 to 5.9	0.86
sICAM-1 (ng/mL)	−115 ± 69	−136 ± 158	21	−102 to 205	0.48
sVCAM-1 (ng/mL)	−15 ± 174	−830 ± 843	652	294 to 2686	0.02
oxLDL (U/L)	−14 ± 15	−9.2 ± 7.7	−4.8	−19 to 11	0.55
sFas (pg/mL)	−3211 ± 850	−4495 ± 780	1284	510 to 1910	0.04

Notes: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CRP, C-reactive protein; hsIL-6, high-sensitivity interleukin-6; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein-a; oxLDL, oxidized low-density lipoproteins; sFas, soluble Fas; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1. Data are expressed as mean ± SD. Comparison of mean differences (with 95% confidence intervals of the difference) for each variable were estimated using Student's *t*-test: Δ negative numbers for all variables favor VEM treatment, while positive numbers favor simvastatin treatment.

(Table 1), as well as a slight decrease in sFas (15%), which however just failed to reach statistical significance. With simvastatin treatment, on the other hand, no significant changes in the markers of inflammation or apoptosis were observed at 3 months of treatment. Simvastatin treatment resulted in a significant decrease in CRP (58%), IL-6 (65%), sICAM-1 (25%), sVCAM-1 (27%), and sFas (20%) and a gradually remarkable change in oxLDL (24%) (Table 1) at 6 months, compared to baseline.

At 6 months, beyond its effects on lipids (Table 2), simvastatin was found to exert more significant effects on sVCAM-1 (mean difference = 652 ng/mL; 95% CI = 294 to 2686; $p < 0.05$) and sFas (mean difference = 1284 pg/mL; 95% CI = 510 to 1910; $p < 0.05$), compared to the effects caused by VEM. Furthermore, serum CRP reduction after simvastatin treatment correlated with decreases in both total ($r = 0.87$, $p < 0.05$) and LDL-C concentration ($r = 0.86$, $p < 0.05$).

DISCUSSION

In line with the results of earlier studies,[6–13] the main finding of this study is that both treatments confer anti-oxidative and anti-inflammatory effects in patients on HD, albeit in different order. Thus, the anti-inflammatory effects of VEM treatment preceded its anti-oxidative effects, whereas simvastatin caused at first a significant reduction in oxLDL in parallel with its lipid-lowering effects, which were later followed by its anti-inflammatory effects, which seemed to be more intense compared with the respective effects of VEM treatment, and was accompanied by beneficial changes in the markers of endothelial cell dysfunction (sVCAM-1) and apoptosis (sFas). Furthermore, the 6-month simvastatin-induced change in CRP was found to correlate with the 6-month change in total and LDL-C. The findings of this study apparently reflect the different mechanisms by which the two treatments exert their anti-inflammatory effects. The effects of VEM are exerted through in situ scavenging of free oxygen radicals by vitamin E coating, amelioration of the stimulation of circulating leukocytes and the decrease in the production of the inflammatory cytokines. It is interesting that some of these effects are common regardless of the administration route of vitamin E, as is detailed elsewhere.[11] Furthermore, the time-sequence of the effects taken place with the simvastatin treatment in this study, as well as the correlation of the change in CRP with the change of total and LDL-C, supports the hypothesis that anti-inflammatory effects of simvastatin are, at least in part, secondary to its lipid lowering effects. The mechanisms through which statins might affect endothelial cell apoptosis are the confinement of inflammation, the increase in the bioavailability of nitric oxide and their anti-oxidative effects.[14,15] It is interesting that the effects of both treatments on the markers of inflammation, oxLDL as well as lipids, lasted for no more than 3 months, since during the washout period they returned to baseline levels. We believe that this finding reflects the active and ongoing inflammatory and oxidative mechanisms working in these patients and signifies the need for a continuous intervention in order to suppress these atherogenic mechanisms.

As long as inflammation, oxidative stress, and apoptosis are pathways known to contribute to the atherogenesis process from the early stages of chronic kidney disease (CKD), the observed anti-inflammatory, anti-oxidative, and anti-apoptotic effects of both treatments studied herein provide evidence of potential cardiovascular prevention in CKD and HD patients. Despite the unexpected discrepancy between the anticipated cardiovascular benefits either from the dietary supplementation with α-tocopherol or from statin treatment and the results of major prospective primary and secondary prevention clinical trials over the last years,[16–19] we believe that as long as prevention is applied by definition before or at early stages of a disease, it would seem quite paradoxical to expect significant cardiovascular effects at later stages of the atherogenesis process, especially when it refers to patients with accelerated atherosclerosis, such as patients already on HD. Although the number of the patients studied herein was small and additional factors, such as smoking, might have contributed to their state of inflammation and oxidative stress, we believe that the serial measurement design of the study counterbalances these confounders. Practically, although both treatments studied herein were shown to exert significant anti-inflammatory and anti-oxidative effects, the use of statins at early stages of CKD seems to be a far more appealing approach for cardiovascular prevention, probably in most ESRD patients regardless of their lipid status, than the use of VEM, which of course cannot be applied at earlier stages of the disease.

In conclusion, the present prospective, crossover study provides preliminary evidence regarding the differences in the effects and mechanisms between the two treatments in hyperlipidemic HD patients. Specifically, the 6-month use of VEM and simvastatin resulted in similar anti-inflammatory and anti-oxidative effects which, however, appeared more directly and immediately with the VEM treatment compared to the simvastatin treatment. Simvastatin, on the other hand, caused a more intense anti-inflammatory response, which was in part correlated with its preceding lipid-lowering effects. These results might be of therapeutic importance in CKD patients.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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