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Lipoperoxidation and hemodialysis

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Abstract

It has been suggested that hemodialysis patients may be under increased oxidative stress and may therefore benefit from the long-term use of antioxidants (particularly for the reduction of the risk of heart disease). The aim of this study was, first, to evaluate the effect of hemodialysis by itself on lipid and lipoprotein oxidation profiles and, second, to analyze the effect of vitamin C supplementation in patients with end-stage renal disease starting hemodialysis. Forty-one patients with end-stage renal disease were enrolled and randomized to receive 1000 mg/d vitamin C or matching placebo before starting hemodialysis. We measured lipid profile and the susceptibility of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) to oxidation using copper ions at the moment of inclusion and after 1 year. All lipoperoxidation parameters were included. Hemodialysis by itself improved the lipid profile, lowering total cholesterol (176.4 ± 48.4 to 154.2 ± 28.8 mg/dL, $P < .01$), LDL cholesterol (94.1 ± 39.6 to 76.1 ± 26.6 mg/dL LDL, $P < .03$), and phospholipids levels (196.5 ± 36.7 to 182.9 ± 36.1 mg/dL, $P < .05$) in all patients on maintenance hemodialysis. The HDL cholesterol was also decreased (49.4 ± 19.8 to 43.4 ± 24.1 mg/dL HDL, $P < .03$). No significant differences were detected between patients receiving vitamin C and those receiving placebo. Thiobarbituric acid reactive substances (TBARS) and lipoperoxides increased in patients after a year of hemodialysis, but the difference was lower in those administered vitamin C for a year—TBARS LDL (in nanograms per gram LDL): 0.25 ± 0.20 to 0.38 ± 0.2 in vitamin C–treated subjects and 0.28 ± 0.17 to 0.46 ± 0.21 in those treated with placebo ($P < .007$); TBARS HDL (in nanograms per gram HDL): 0.22 ± 0.12 to 0.34 ± 0.30 in patients receiving vitamin C and 0.20 ± 0.18 to 0.28 ± 0.19 in those receiving placebo ($P = .071$). Hemodialysis by itself seems to improve the lipid profile in patients with a previous prooxidative state such as uremia. Although our results failed to demonstrate significant differences between vitamin C–treated and untreated patients, and despite the small number of patients, the trend toward a decrease in oxidation products due to vitamin C supplementation may be beneficial for oxidation parameters. This area remains controversial and under active investigation. Further research is necessary before a firm conclusion can be reached.

1. Introduction

Oxidative stress defines an imbalance between the formation of reactive oxygen species and antioxidative defense mechanisms. There is mounting evidence indicating that uremia in general is associated with enhanced oxidative stress and a high incidence of premature atherosclerosis [1]. Uremia-associated dyslipidemia, hypertension, and the cause of renal disease, for example, diabetes, have also been implicated as underlying mechanisms. The relative risk of death from myocardial infarction has been reported to be at least 5 times greater in patients receiving some form of renal replacement therapy than in the general population [2]. It has been suggested that renal replacement therapy in uremic patients on hemodialysis or peritoneal dialysis may contribute to oxidative stress and reduce antioxidant levels in these patients [3-5]. Loss or deficiency of antioxidant activity (eg, vitamin E deficiency) may also contribute to enhanced oxidative stress in uremia. Boaz et al [6] reported reduced cardiovascular end points and myocardial infarction in hemodialysis patients with prevalent cardiovascular disease supplemented with 800 IU/d vitamin E. In hemodialysis patients, reduced plasma total vitamin C concentration has been demonstrated [4,7]. This deficiency is probably due to a dietary restriction of fresh fruit and vegetables to avoid hyperkalemia, and the loss of the vitamin during dialysis sessions [7-10]. Some authors have identified vitamin C as a predictor of cardiovascular event rate in dialysis patients[11]. However, the results of studies on the use of antioxidant supplements are inconsistent.

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Schulz et al [11] failed to detect any acute reduction in lipoprotein antioxidative defense by activated cells during hemodialysis in a study of 12 patients. These authors did not find a link between cuprophane membranes and a mechanism that might contribute to accelerated atherosclerosis in hemodialysis. However, the significance of enhanced oxidative stress in renal patients has been further elucidated in clinical end point studies. Unfortunately, only a few antioxidant intervention studies with clinical end points have been published.

The aim of our study was to evaluate the effect of hemodialysis by itself on lipid and lipoprotein oxidation profiles and, secondly, to assess whether the antioxidative effect of vitamin C may help prevent atherosclerosis in hemodialysis patients.

2. Methods

2.1. Patients

We studied several parameters of lipid antioxidative protection in patients with end-stage renal disease at baseline (before starting chronic hemodialysis) and 1 year after, comparing the results of oral daily treatment with 1 g of vitamin C vs placebo. Some nutritional (serum albumin) and inflammatory (C-reactive protein [CRP]) parameters were recorded.

Forty-one consecutive patients who started hemodialysis in our hospital, in the same year, were enrolled in the study after giving informed consent. Only 34 patients ended the study (11 women and 23 men; mean age, 57 ± 17 years). Fourteen were smoker patients (41%), and 20 were nonsmoker patients (59%). The mean body mass index was 24.5 ± 4. Two patients died as a result of cardiovascular complications, 3 received a renal transplantation, and 2 patients were transferred to another hospital and were lost to follow-up.

Twenty-eight patients (82%) were on antihypertensive drug treatment (β-blockers, n = 6; calcium channel blockers, n = 10; angiotensin-converting enzyme inhibitors, n = 5; others, n = 7).

Diabetic subjects, patients with malignant tumors or acute infection illnesses, and those receiving immunosuppressive therapy or hypolipidemic treatment were excluded from the study.

2.2. Methods

Venous blood samples were obtained from 34 patients during the last outpatient-clinic visit before the first hemodialysis session. Patients were randomized to receive 1 g/d of vitamin C or matching placebo. Patients were followed for a median of 365 days; during this time, hemodialysis was performed 3 times weekly with hemophan or cellulose-acetate membranes. New venous blood samples were obtained at the end of this period before the middle-week dialysis session.

Whole blood (10 mL) was collected in standard agar tubes without anticoagulant (Vacutainer; Becton Dickinson, Grenoble, France) and centrifuged (3000*g*, 4°C, 10 minutes). After centrifugation, the plasma was stored for biochemistry, hematology, and hemostasis analysis using a HITACHI 747 and Boehringer Mannheim reagents (Mannheim, Germany). Plasma apolipoprotein (apo) A and B were determined by immunoturbidimetry (TinaQuant, Boehringer Mannheim). Lipoprotein (a), using immunoprecipitation (SPQ TM Test System, Minnesota, USA), and lipoperoxides (LPO) were measured by spectrophotometric technique at 365 nm of absorbance. C-reactive protein concentrations were measured with a high-sensitivity assay (Denka Seiken, Tokyo, Japan, high-sensitivity CRP assay). Albumin was determined by the bromocresol purple dye-binding method.

Plasma thiobarbituric acid reactive substances (TBARS) were also measured. We used the fluorometric TBARS method by absortion of 548 nm emission. This widely used parameter of lipid peroxidation is operationally defined as the amount of chromogenic condensation products formed in plasma after the addition of thiobarbituric acid against a titration curve constructed with malondialdehyde standard.

2.3. Low- and high-density lipoprotein and isolation

Low- and high-density lipoproteins (HDL and LDL) were obtained through preparative lipoprotein ultracentrifugation in a Beckman SW 41 rotor at 40 000 rpm and 10°C for 24 hours (Lipid Research Clinics–Quanlitop, Immuno, Vienna, Austria).

2.4. Lipoprotein composition

Protein, total cholesterol, free cholesterol, triglyceride, and phospholipid contents of crude LDL and HDL were measured in the samples by HITACHI 747 and Boehringer Mannheim reagents. The TBARS and LPO were also determined for each lipoprotein fraction.

2.5. Lipoprotein oxidation

Isolated LDL and HDL were diluted with phosphate-buffered saline to a concentration of 50 μg of protein per milliliter. Copper (II) chloride was added to give a final concentration of 2 μmol/L Cu^{2+} ions and incubated at 37°C. Conjugated diene (CD) production was monitored by continually recording absorbance at 234 nm in a spectrophotometer. The output from the spectrophotometer was used to compute the lag time to the onset of oxidation.

2.6. LDL and HDL vitamin E content

The LDL and HDL samples were analyzed for vitamin E content following the Tsen methodology using α-tocopherol as standard and at 534nm of absorbance.

3. Statistics

Results are expressed as means ± standard deviation (SD). A paired Student-Fisher *t* test was used to estimate

Table 1
Lipidic profile at baseline and 1 year after dialysis

	Group A (vitamin C)		Group B (placebo)		*P* (differences *a* − *b*)
	Before HD[a]	After 1 y HD[b]	Before HD[a]	After 1 y HD[b]	
Total cholesterol (mg/dL)	183.3 ± 57.3	164.8 ± 30.6	170.2 ± 39.1	144.8 ± 24.2	.70
Triglycerides (mg/dL)	132.6 ± 86.5	151.3 ± 171	144.7 ± 60.8	114.7 ± 46	.21
Phospholipids (mg/dL)	198.3 ± 44.7	188.3 ± 44.5	195 ± 29.2	178.1 ± 27	.61
LDL cholesterol (mg/dL)	100.3 ± 50.5	79.4 ± 30.9	88.6 ± 27	73.1 ± 22.6	.75
HDL cholesterol (mg/dL)	50.2 ± 23.1	47.2 ± 31.3	48.7 ± 16.8	40 ± 15.6	.62
LPO (mg/dL)	20.9 ± 15.7	85.8 ± 96.1	26.6 ± 30.9	47.3 ± 26.7	.071
Lp (a) (mg/dL)	48.4 ± 49.2	52.9 ± 62.5	38.3 ± 52	31.4 ± 45.6	.38

HD indicates hemodialysis; Lp (a), lipoprotein (a).

differences between the 2 groups (group A = treated with vitamin C, group B = not treated with vitamin C) before starting hemodialysis therapy and 1 year later. *P* values < .05 were considered as significant. A descriptive analysis was performed with the SPSS program (SPSS, Chicago, IL).

4. Results

Lipid profiles improved after a year of hemodialysis therapy (1 year after inclusion) in both groups (vitamin C–treated and nontreated patients)—total cholesterol: 176.4 ± 48.4 to 154.2 ± 28.8 mg/dL (*P* < .01); LDL cholesterol: 94.1 ± 39.6 to 76.1 ± 26.6 mg/dL (*P* < .03); and phospholipids levels: 196.5 ± 36.7 to 182.9 ± 36.1 mg/dL (*P* < .05). The HDL cholesterol was also decreased—49.4 ± 19.8 to 43.4 ± 24.1 mg/dL (*P* < .03). Serum lipoprotein profiles of both groups are shown in Table 1. There were no differences in lipid profile between the groups after a year of starting hemodialysis.

No differences in baseline lipoprotein (a) were found between groups A and B, but a nonsignificant decrease was observed in both groups 1 year after starting hemodialysis.

The LDL and HDL lag phases, initial absorbances, and CDs were quite similar in treated and untreated patients (Table 2).

The TBARS levels were high 1 year after hemodialysis treatment in both groups, but the increase was smaller in the vitamin C group—TBARS LDL (in nanograms per gram LDL): 0.25 ± 0.20 to 0.38 ± 0.2 in vitamin C group and 0.28 ± 0.17 to 0.46 ± 0.21 in the placebo group (*P* < .007); TBARS HDL (in nanograms per gram HDL): 0.22 ± 0.12 to 0.34 ± 0.30 in the vitamin C group and 0.20 ± 0.18 to 0.28 ± 0.19 in the placebo group (*P* = .071) (Table 3).

A year after starting hemodialysis, the levels of vitamin E had fallen considerably in patients treated with the antioxidant (Table 4).

As regards albumin and CRP levels, there were no differences between the groups either at baseline or after 1 year of hemodialysis treatment (Table 5).

No differences in baseline hemoglobin, hematocrit, ferritin, and erythropoietin dose were found between groups A and B; but a nonsignificant increase was observed in both groups 1 year after starting hemodialysis in hemoglobin (from 9.3 ± 0.5 to 10.2 ± 0.3g/dL, *P* = .09), hematocrit (29.8% ± 1.2% to 33% ± 0.9%, *P* = .07), and ferritin levels (278 ± 68 to 350 ± 29, *P* = .08). We also observed a nonsignificant decrease in erythropoietin dose (277 ± 61 to 229 ± 76 U/[kg wk], *P* = .09).

5. Discussion

Considering the description of the “elephant in uremia,” Himmelfarb et al [12] propose oxidative stress as a unifying concept of cardiovascular disease in this condition.

Table 2
Lag phase and CD evolution

	Group A (vitamin C)		Group B (placebo)		*P* (differences *a* − *b*)
	Before HD[a]	After 1 y HD[b]	Before HD[a]	After 1 y HD[b]	
Lag time/LDL	42 ± 23	46 ± 17	37 ± 20	41 ± 14	.79
Lag time/HDL	27 ± 35	17 ± 7	20 ± 14	18 ± 13	.51
Tmax/LDL	86 ± 29	93 ± 27	82 ± 29	86 ± 24	.88
Tmax/HDL	63 ± 45	59 ± 12	68 ± 21	66 ± 24	.98
CD initial/LDL	49 ± 18	48 ± 16	46 ± 22	49 ± 15	.70
CD initial/HDL	64 ± 42	52 ± 37	46 ± 39	51 ± 24	.27
CD final/LDL	108 ± 25	107 ± 16	115 ± 41	114 ± 15	.92
CD final/HDL	110 ± 43	97 ± 13	124 ± 46	105 ± 13	.83
Rate propagation/LDL	2.07 ± 0.7	1.75 ± 0.5	2.2 ± 1.1	1.87 ± 0.6	.80
Rate propagation/HDL	1.4 ± 0.7	1.35 ± 0.5	1.8 ± 0.96	1.46 ± 0.7	.042

Conjugated dienes in micromoles per gram protein; lag time and Tmax (time needed to reach maximal absorbance) in minutes; rate propagation in micromoles per CD per minute.

Table 3
The TBARS and fluorescent compounds levels

	n	Group A (vitamin C)		Group B (placebo)		*P* (differences *a* − *b*)
		Before HD[a]	After 1 y HD[b]	Before HD[a]	After 1 y HD[b]	
TBARS LDL (ng/g LDL)	32	0.25 ± 0.20	0.38 ± 0.2	0.28 ± 0.17	0.46 ± 0.21	.007
TBARS HDL (ng/g HDL)	30	0.22 ± 0.12	0.34 ± 0.30	0.20 ± 0.18	0.28 ± 0.19	.071
CF LDL (ng/g LDL)	34	8 ± 4.5	22.3 ± 14.6	11.7 ± 10	18 ± 9.9	.001
CF HDL (ng/g HDL)	30	5.1 ± 3.4	13.2 ± 7.4	6.6 ± 6	11.3 ± 9.5	.001

CF indicates fluorescent compounds.

Oxidative stress is frequently considered in terms of "total quantity of oxidized products" compared with "total quantity of antioxidants." As Wratten et al [13] report, this commonly leads to either an underestimation or an overestimation of its physiologic importance.

Several authors [14,15] have reported an intensification of lipid peroxidation in patients with chronic renal failure treated with maintenance hemodialysis and suggest that hemodialysis by itself can accelerate atherosclerosis by increasing lipid peroxidation. In contrast, our findings showed a significant decrease in total cholesterol, LDL cholesterol, and phospholipids in patients on maintenance hemodialysis, despite the absence of malnutrition or inflammation shown by the lack of any modification of albumin or CRP (Table 5). This suggests that the lipoprotein profile is not substantially modified by hemodialysis treatment and in fact may even improve. Similar results have been proposed in other clinical trials [16,17] that conclude that dialysis may improve the proatherogenic milieu of uremia. As Okubo et al [18] reported, we have found HDL cholesterol level to be decreased. However, non–HDL cholesterol serum was the marker considered as a significant and independent predictor of cardiovascular mortality in hemodialysis patients [19]. Because of it, we should bear in mind the existence of other processes related to dialysis therapy, such as the prolonged use of catheters for vascular access and the use of bioincompatible membranes that may contribute to a proinflammatory and prooxidative state [20].

Several studies have suggested that the oxidative modification of LDL might explain the accelerated atherosclerosis in hemodialysis patients in the absence of major increases in native LDL. One might therefore expect lag times to be shorter in these patients [21]. In our patients, we did not observe a reduction in LDL or HDL lag time after 12 months on maintenance dialysis. Nor did we see differences in any parameters of copper-induced lipoprotein oxidation between patients treated with the antioxidant and those who received placebo.

As regards total TBARS, markers of oxidative stress, some authors have found high levels of lipoperoxidation product in dialyzed patients and have therefore assumed that an increase in LPO also occurred [22-25]. In agreement with these reports, we found an increase in TBARS and LPO 12 months after hemodialysis therapy in all of our patients, although the differences were not significant.

During hemodialysis session, the concentration of water-soluble antioxidants like vitamin C is very low [26]. Ascorbate is not present in lipoproteins; therefore, the major antioxidants protecting LDL against oxidation are lipid soluble, such as α-tocopherol [27]. Ascorbic acid can recycle α-tocopherol from the tocopheroxyl free radical, thereby permitting vitamin E to function again as a free radical chain-breaking antioxidant. These 2 antioxidants work together to scavenge antioxidants. Hemodialysis patients, in addition, have a net decrease of water-soluble antioxidants during the dialysis session because of diffuse loss during hemodialysis. Therefore, it might be expected that a supplementation of this water-soluble vitamin would improve lipoperoxidation parameters. Although vitamin C might be carefully evaluated [28], some reports have detected a decrease in plasma TBARS levels using vitamin C supplementation on diet compared with baseline controls [26,29]. Interestingly, in our study, TBARS levels were not higher 1 year after hemodialysis in our vitamin C–treated patients compared with the patients of placebo group; but these results did not achieve statistical significance. This finding could be probably related to the vitamin C supplementation, although it is difficult to know because of the lack of vitamin C levels in our study.

Table 4
Vitamin E levels

	Before HD		After 1 y HD	
	Group A	Group B	Group A	Group B
Vitamin E (μmol)/g LDL	1.82	0.98	1.05	2.96
Vitamin E (μmol)/g HDL	1.10	1.59	0.43	1.60

Table 5
Nutritional and inflammation parameters

	Group A (vitamin C)		Group B (placebo)		*P* (diff *a* − *b*)
	Before HD[a]	1 y after HD[b]	Before HD[a]	1 y after HD[b]	*P*
Serum albumin (g/L)	39 ± 4	40 ± 4	38 ± 3	40 ± 3	.81
CRP (mg/L)	9.1 ± 11	10.2 ± 12	8.9 ± 10	9 ± 11	.85

diff = differences.

It is well known that vitamin E is the main lipid phase antioxidant [30]. This suggests that a high LDL vitamin E content could result in increased resistance to oxidation. Our results showed that the lipoprotein–vitamin E content was higher 12 months after hemodialysis only in the patients who were not treated with vitamin C, although the differences between lipoperoxidation parameters were not significant. This finding contrasts with other studies in which vitamin C supplementation resulted in a significant increase in α-tocopherol [26].

The poor results for LDL oxidation might indicate that during the aqueous-removal process of hemodialysis, the supplementation with a hydrophilic substance like vitamin C does not confer benefit probably because of losses. In this case, the addition of liposoluble antioxidants like vitamin E could probably increase the level of antioxidant to raise lipoprotein resistance to oxidation [6].

Some reports have demonstrated a beneficial effect of vitamin C on indices of anemia [31]. Our results did not show any differences between groups, probably because of the small number of patients. The nonsignifcant improvement in the anemia parameters after a year of starting hemodialysis may be attributed to a better management of anemia compared with predialysis time.

Despite the most current data supporting the conclusion that long-term, high-dose use of vitamin C therapy is safe for dialysis patients, controlled studies of the impact of vitamin C supplements on the occurrence of possible adverse effects, especially the risk of oxalosis, are needed.

In conclusion, hemodialysis by itself seems to improve lipid profile in patients with a previous prooxidative state such as uremia. Although our results failed to demonstrate significant differences in the oxidative state, the tendency to decrease oxidation products (like TBARS) by supplementation of vitamin C may have a small beneficial effect in relation to oxidation parameters. When patients are on maintenance hemodialysis, the administration of lipophilic antioxidant substances is probably advisable. “In vivo,” many unresolved questions remain concerning the efficacy of antioxidant vitamin supplementation in the prevention of oxidative damage. This area remains controversial, and additional research is necessary in this area before a firm conclusion can be reached.

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