

# Improvement of Plasma Lipoprotein Profiles During High-Flux Dialysis<sup>1,2</sup>

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## ABSTRACT

Patients undergoing maintenance hemodialysis therapy have increased mortality due to cardiovascular disease. One possible etiologic factor for this increased mortality is the lipid abnormalities associated with chronic renal failure. These include elevated triglyceride (TG) and decreased high-density lipoprotein (HDL) concentrations. Lipoprotein profiles of patients undergoing chronic hemodialysis with either saponified cellulose ester (CE) ( $N = 9$ ) or polysulfone (PS) high-flux dialysis membranes ( $N = 10$ ) were compared. Patients in each group received similar amounts of heparin during the dialysis. CE-dialyzed patients showed no alteration in serum TG, HDL, low-density lipoprotein, or total cholesterol when predialysis and postdialysis values were compared. PS patients, on the other hand, had a significant decrease in TG concentrations ( $P < 0.01$ ) as well as a significant rise in HDL ( $P < 0.01$ ). These changes might signify activation of lipoprotein lipase (LPL) during dialysis. LPL activity in PS sera was significantly greater than LPL in CE sera. Moreover, sera from PS patients inhibited LPL much less than did sera from CE patients. These findings suggest that a circulating substance not dialyzable with cellulosic

membranes inhibits LPL in uremic subjects and is removed during dialysis with a PS membrane. Alternatively, the greater biocompatibility of PS may produce less LPL inhibitory cytokines during dialysis. The improvement of lipoprotein profiles in patients receiving dialysis with PS membranes may, in the long term, lead to less morbidity and mortality from atherosclerotic disease.

**Key Words:** Chronic renal failure, hemodialysis, lipoprotein metabolism, atherosclerosis, triglyceride, high-density lipoprotein

Patients undergoing hemodialysis for end-stage renal failure have increased mortality due to cardiovascular disease (1). These patients also have elevated concentrations of triglyceride (TG) and decreased concentrations high-density lipoprotein (HDL) in serum (2). It is well known that concentrations of HDL are inversely related to risk for developing atherosclerosis (2), and several studies have shown that, in some populations, elevated TG levels are positively correlated with the incidence of cardiac events (3). Therefore, an objective of therapy for any patient undergoing dialysis should include normalization of lipoprotein levels.

The cause of the lipoprotein abnormalities accompanying chronic renal failure has only been partially elucidated. One known defect in patients undergoing hemodialysis is that their TG clearance rate is slower than normal (2). This may relate to changes in the activity of lipoprotein lipase (LPL), the rate-limiting enzyme for the hydrolysis of lipoprotein-TG. LPL is synthesized primarily in muscle and adipose tissue and is bound to the luminal surface of capillary endothelium, where it interacts with circulating lipoproteins. When LPL is released into the bloodstream after an iv injection of heparin (4), it causes an acute decrease in TG levels. Heparin-induced lipolysis is markedly diminished in dialysis patients (2), an observation that is consistent with their reductions in adipose tissue and postheparin plasma LPL activities (2). LPL activity is positively correlated with HDL concentrations (2). This relationship is true because LPL both increases HDL cholesterol content and decreases HDL catabolic rate (5). Thus, it is not surprising that in dialyzed patients TG concentrations are directly correlated with lipid clearance rates and LPL activity and HDL concentrations are inversely correlated with lipid clearance rates and LPL activity (6).

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Moreover, exercise and fibric acid medications such as clofibrate and gemfibrozil increase LPL activity, reduce serum TG, and increase HDL in dialysis patients (2,7).

High-flux, polysulfone (PS) membranes, recently introduced for chronic hemodialysis (8), are more permeable to larger molecules than are the older, cellulose-based membranes. Furthermore, these membranes cause less activation of cellular and humoral inflammatory processes than do the older cellulosic membranes (9). Patients undergoing hemodialysis may have progressive worsening of lipid and lipoprotein abnormalities (7). Dumler *et al.* (10), however, reported that patients undergoing high-flux dialysis with PS membranes for an average of 18 months had decrements in TG and total cholesterol concentrations. Therefore, dialysis with PS and cellulosic membranes might have different effects on plasma lipoprotein concentrations.

In this report, we compare lipoprotein profiles of patients undergoing dialysis with saponified cellulose ester (CE) and PS membranes. Our data show that high-flux dialysis with PS membranes leads to decreased TG and increased HDL concentrations in association with increased LPL activity.

## SUBJECTS AND METHODS

Subjects with chronic renal failure of various etiologies who were undergoing dialysis with either CE ( $N = 9$ ) or PS membranes ( $N = 10$ ) were studied. All subjects used dialysate with bicarbonate as a buffer. Three of the patients (numbers 1, 2, and 4) were studied while being dialyzed with each membrane. Patients were excluded if they were acutely ill, if they were taking medications that raise or lower lipids, or if they were undergoing lifestyle changes that affect lipid metabolism (*i.e.*, new exercise program or diet). This study was approved by the Institutional Review Boards of Beth Israel Medical Center and Mount Sinai School of Medicine. Informed consent was obtained from all subjects.

After an overnight fast, a 10-mL (predialysis) blood sample was drawn from the arterial dialysis catheter. During the dialysis, the patients did not eat but were allowed small amounts of water. Each subject was weighed immediately before and after the dialysis. Patients received a bolus of 1,000 to 6,000 U of heparin followed by an infusion of 500 to 1,500 U/h. The heparin dose was determined by periodic partial thromboplastin time determinations.

Postdialysis samples were obtained 30 to 120 s after the completion of the procedure. Blood drawing was delayed to allow equilibration in the graft. Ten milliliters of blood was withdrawn and discarded. A second 10-mL sample was then obtained and used for our analyses. This protocol was used to prevent the dilution of the sample by saline. Blood was al-

lowed to clot at 4°C. The serum was separated from the cells by centrifugation at 2,500 rpm at 7°C in a Damon Model IEC/PR-J refrigerated centrifuge and then decanted into polyethylene tubes (Fisher Scientific, Pittsburgh, PA) and stored at -80°C.

## Analytic Methods

TG and cholesterol were determined by colorimetric assays (11,12) (Triglyceride Assay Kit #210-75 and Total Serum Cholesterol Assay Kit #225-26; Diagnostic Chemicals, Ltd., Monroe, CT). HDL cholesterol was determined by the enzymatic measurement of cholesterol in plasma supernatants after the precipitation of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) by phosphotungstic acid and magnesium ions (HDL-cholesterol Kit #215-33; Diagnostic Chemicals). LDL cholesterol was estimated by the subtraction of HDL and TG/5 from the total cholesterol. This analysis assumes that a large amount of plasma cholesterol is not circulating in cholesterol-rich  $\beta$ -VLDL or remnant lipoproteins. Because none of our subjects had marked hypertriglyceridemia, this assumption is probably correct. Apoproteins were measured by single radial immunodiffusion (13) with agarose gel plates that contained wells impregnated with antiapolipoprotein antibodies (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan).

## Lipoprotein Lipase Assays

LPL activity was measured with a gum-arabic stabilized emulsion and heat-inactivated human serum as a source of apolipoprotein apoCII activator (14). All assays were performed in triplicate. Postheparin samples contain both LPL and hepatic TG lipase (HTGL); therefore, the specific measurement of LPL was performed by the inhibition of HTGL activity with a previously described specific antiserum (15). A standard source of human postheparin plasma obtained from a normal volunteer 10 min after the iv injection of 60 U/kg body wt of heparin (Elkins-Sinn, Inc., Cherry Hill, NJ) was used for studies of LPL inhibition. All assays of LPL and HTGL in the patients' serum samples were performed together, thus eliminating any interassay variability.

## Statistical Methods

Comparison of predialysis and postdialysis measurements was made by a paired *t* test. Mean values for different treatment groups were compared by a two-tailed *t* test.

## RESULTS

### Patients

A total of 16 patients (6 men and 10 women) were studied (Table 1). CE-dialyzed patients were on av-

TABLE 1. Patient characteristics

Patient No. <sup>b</sup>	Age/Sex	Months of Dialysis	Weight Decrease (kg)	Diagnosis	Associated Conditions
CE Dialysis (N = 9)					
1	70/M	2	2.8	Chronic GN	HTN, CAD
2	26/F	54	0.95	Lupus	SLE, HTN
3	69/M	22	2.7	Chronic IN	Gout, HTN
4	33/M	0.75	1.4	Unknown	HTN
5	40/F	15	1.93	Unknown	HTN, CHF
6	72/F	108	3.7	Unknown	HTN, DM, CAD, CHF
7	87/F	44	2.7	Unknown	HTN, CHF
8	90/F	7	3.7	Unknown	HTN, COPD, CHF
9	29/F	48	2.8	Unknown	HTN
Average ± SE	57.3 8.5	33.4 11.5	2.52 0.31		
PS Dialysis (N = 10)					
1	70/M	3	2.1	Chronic GN	HTN, CAD
2	26/F	55	0.8	SLE nephritis	SLE, HTN
4	33/M	2	1.4	Unknown	HTN
10	70/F	22	2.1	Nephrosclerosis	DM, HTN, CAD
11	34/F	33	1.7	Unknown	Lymphoma
12	37/F	9	1.3	Polycystic	
13	59/M	25	3.4	Unknown	HTN, gout, sickle trait
14	68/M	43	1.7	Diabetes	DM, HTN, CAD
15	48/F	31	1.8	Diabetes	DM
16	50/F	28	1.5	Myeloma	
Average ± SE	49.5 5.3	25.1 5.4	1.79 0.22		

<sup>a</sup> Abbreviations: IN, interstitial nephritis; HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GN, glomerulonephritis; SLE, systemic lupus erythematosus; DM, diabetes mellitus.

<sup>b</sup> Patients 1, 2, and 4 were studied while on each type of dialysis.

average  $57.3 \pm 5.3$  yr old, whereas PS patients were  $49.5 \pm 5.3$  yr old ( $P =$  not significant [NS]). The CE-dialyzed group had been in end-stage renal failure for  $33.4 \pm 11.5$  months; the average time of renal failure in the PS group was  $25.1 \pm 5.4$  months ( $P =$  NS). The CE patients had been receiving dialysis for  $33.4 \pm 11.5$  months. The PS-dialyzed group had been on dialysis treatment (of any kind) for  $25.1 \pm 5.4$  months; PS dialysis in this group was for  $6.4 \pm 1.5$  months.

Weight changes during dialysis are listed in Table 1. CE-dialyzed patients lost  $2.52 \pm 0.31$  kg/dialysis, and PS-dialyzed patients lost  $1.79 \pm 0.22$  kg/dialysis ( $P =$  NS). Dialysis treatments appeared to be similarly effective in removing excess body water.

#### Changes in Plasma Lipoproteins During Dialysis

Lipoprotein concentrations before and after dialysis with CE ( $N = 9$ ) and PS ( $N = 10$ ) dialysis membranes are given in Table 2 and summarized in

Figure 1. Mean TG concentrations in subjects undergoing PS dialysis decreased from 126 to 81 mg/dL ( $P = 0.01$ ). A decrease was found in 9 of 10 patients. One PS subject had TG concentrations change by 42%, from 364 to 210 mg/dL, during a single dialysis. TG concentrations showed no significant change during CE dialysis. Predialysis concentrations were nearly identical in PS and CE patients.

Total cholesterol concentrations were greater in PS sera after dialysis. Baseline cholesterol concentrations in the PS group ( $160.5 \pm 13.1$  mg/dL) and CE group ( $153.5 \pm 9.9$  mg/dL) were not different. Although cholesterol did not significantly change in CE patients ( $153.5 \pm 9.9$  mg/dL, predialysis;  $160 \pm 11.6$  mg/dL, postdialysis), mean serum cholesterol concentrations in PS patients increased from 161 to 185 mg/dL during dialysis ( $P < 0.02$ ). Aside from the increase in HDL cholesterol (see below), this increase was also due to a 6% increase in LDL. LDL cholesterol did not change significantly during CE dialysis.

HDL cholesterol concentrations increased during

TABLE 2. Individual changes in plasma lipids

Patient No.	Cholesterol		TG		HDL Cholesterol	
	Pre	Post	Pre	Post	Pre	Post
<b>CE Dialysis (N = 9)</b>						
1	144	138	67	112	37	29
2	126	115	68	60	43	41
3	117	136	113	149	26	34
4	195	191	156	96	40	41
5	178	217	70	76	56	81
6	159	159	106	77	35	37
7	133	143	66	101	38	40
8	187	192	346	361	25	28
9	142	156	125	159	19	24
Average ± SE	154	161	124	132	35	39
<i>P</i>	9.9	11.6	31.5	32.4	3.9	5.6
<i>P</i>	0.19		0.50		0.22	
<b>PS Dialysis (N = 10)</b>						
1	153	173	113	59	29	41
2	129	137	49	44	40	48
4	188	207	126	64	33	47
10	131	144	83	51	23	41
11	110	192	364	210	29	33
12	178	190	102	82	46	51
13	140	138	54	57	55	53
14	164	175	168	99	40	46
15	163	199	64	31	45	65
16	250	291	134	116	50	70
Average ± SE	161	184	126	81	39	49
<i>P</i>	13.1	15.1	30.6	17.3	3.4	3.7
<i>P</i>	0.012		0.013		0.0017	

<sup>a</sup> Values predialysis (Pre) and postdialysis (Post) are in milligrams per deciliter. *P* values were calculated by paired *t* test.

<sup>b</sup> Patients 1, 2, and 4 were studied while on each type of dialysis.

PS dialysis. Baseline HDL cholesterol in the PS group ( $38.9 \pm 3.4$  mg/dL) was slightly, but not significantly, higher than in the CE group ( $35.4 \pm 3.9$  mg/dL). After high-flux dialysis with PS membranes, HDL cholesterol was  $49.3 \pm 3.3$  mg/dL. This 27% increase in HDL cholesterol concentration was significant ( $P < 0.01$ ). A smaller, not statistically significant, increase in HDL was observed in CE patients. Therefore, dialysis with PS membranes resulted in a concomitant decrease in TG and an increase in HDL cholesterol concentrations.

#### Apolipoprotein Concentrations Before and After Dialysis

Because HDL cholesterol increased during PS dialysis, we were especially interested in whether the concentration of the major protein component of HDL, apoAI, changed. As shown in Table 3, which gives the average predialysis and postdialysis apoAI, apoB, apoE, apoCII, and apoCIII concentrations in five patients from each group, no significant change in

apoAI or other apolipoproteins was found. The increase in HDL cholesterol without a change in apoAI suggests that the composition of the HDL molecule had been altered.

#### Effects of Dialysis on Lipase Activity

Acute decreases in TG accompanied by increases in HDL cholesterol occur during activation of the lipolytic cascade mediated by LPL. Both groups received the same amount of heparin; the PS group received  $59.8 \pm 9.7$  U/kg, and the CE group received  $51.3 \pm 13$  U/kg ( $P = \text{NS}$ ) (Table 1). LPL and HTGL were measured in serum samples obtained at the conclusion of dialysis from a subgroup of our patients. PS dialysis ( $N = 6$ ) was associated with more LPL activity than CE dialysis ( $N = 7$ ) (Figure 2). HTGL activity was also greater in the PS serum samples.

This greater amount of LPL activity in PS sera could have been due to an increase in LPL protein or to the removal of an LPL inhibitor by the dialysis treatment. To test for the presence of an inhibitor,

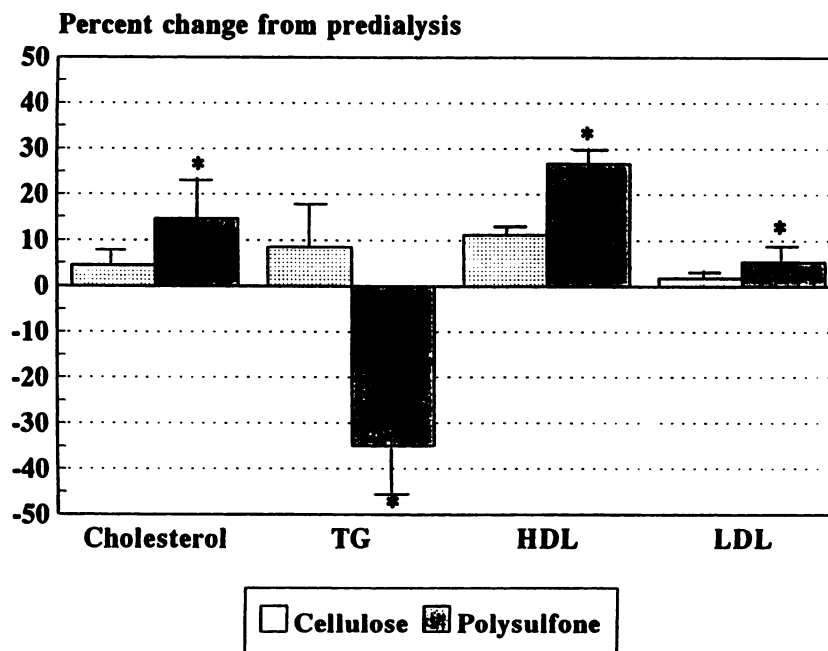


Figure 1. Changes in lipoprotein profiles during dialysis.

TABLE 3. Apolipoprotein concentrations predialysis and postdialysis

	AI	All	B	CII	CIII	E
<b>CE Dialysis (N = 5)</b>						
Pre	90 ± 14	26 ± 4.6	56 ± 11	2.3 ± 0.6	10.3 ± 1.3	3.6 ± 0.4
Post	115 ± 9.7	23 ± 2.3	58 ± 9.7	3.4 ± 1.7	12.1 ± 1.5	4.2 ± 1.2
P	0.079	0.67	0.56	0.53	0.20	0.61
<b>PS Dialysis (N = 5)</b>						
Pre	98 ± 3.6	23 ± 1.7	66 ± 12	2.5 ± 0.4	12.7 ± 2.1	4.9 ± 0.9
Post	112 ± 5.5	23 ± 0.9	61 ± 10	2.7 ± 0.5	11.4 ± 2.0	4.5 ± 1.0
P	0.12	0.95	0.69	0.62	0.19	0.20

<sup>a</sup> Values are average ± SE in milligrams per deciliter. Average apolipoprotein concentrations from patients 1, 2, 3, 4, and 5 (CE group) and 1, 2, 10, 11, and 12 (PS group). None of the predialysis (Pre) versus postdialysis (Post) changes in apolipoproteins were statistically different.

serum samples from patients undergoing PS and CE dialysis were added to an assay containing a standard sample of human postheparin plasma. The addition of 50  $\mu$ L of serum from PS patients decreased LPL activity by  $18 \pm 4.2\%$ . Serum samples from CE patients caused significantly more inhibition of LPL activity ( $34 \pm 7.8\%$ ;  $P < 0.05$  versus PS). Serum samples from two patients receiving both treatments were compared. In both cases, inhibition was greater with serum obtained while the patients were dialyzed with CE membranes. Thus, it appears that dialysis with PS membranes is associated with more LPL activity and this is due, at least in part, to less LPL inhibition by serum.

## DISCUSSION

This study shows that high-flux dialysis with PS membranes is associated with beneficial changes in lipoprotein profiles. No significant change in TG or HDL concentrations were found during dialysis with CE membranes. In contrast, dialysis with PS membranes decreased TG levels and increased HDL cholesterol levels in plasma. Although HDL cholesterol increased, plasma apoAI, the major protein component of HDL, did not change. Because apoAI is a marker for the number of HDL particles, it is likely that after dialysis with PS membranes each HDL particle contained more cholesterol. Thus, the rapid

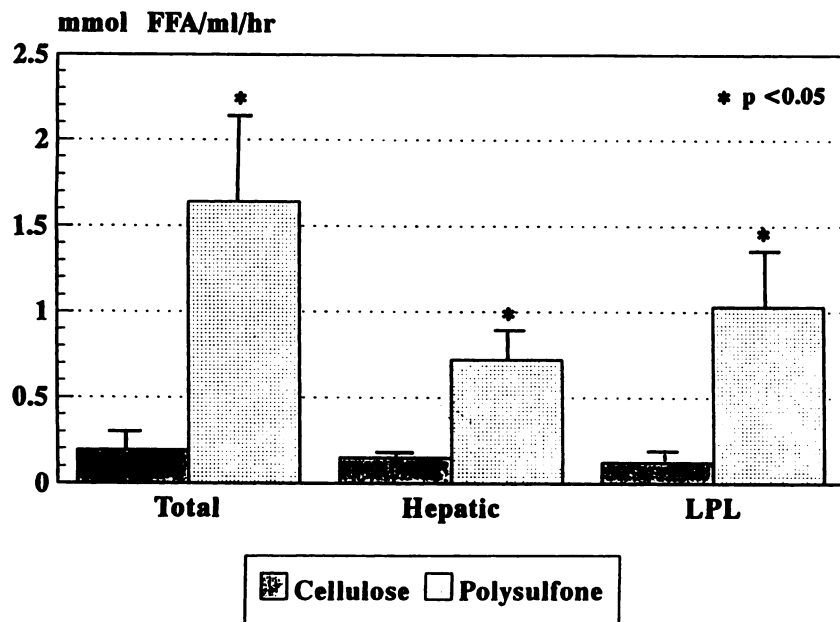


Figure 2. Postdialysis lipase activity.

changes in HDL cholesterol during PS membrane dialysis are consistent with a redistribution of cholesterol from the TG-rich VLDL.

Acute decreases in TG accompanied by increases in HDL cholesterol are seen during acute activation of LPL with heparin infusion and after the addition of apoCII, the necessary cofactor for LPL actions, into patients with a genetic deficiency of apoCII (16). Immunologic inhibition of LPL produces the opposite effects on circulating lipoproteins (17). Several inhibitors of LPL have been described. Concentrations of one of these, apoCIII, were identical in our two groups of patients (Table 2). A circulating nondialyzable LPL inhibitor has been described in sera of patients with chronic renal failure (18,19). This poorly characterized inhibitor is precipitated by trichloroacetic acid, suggesting that it is a protein and is not associated with plasma lipoproteins (19). We hypothesize that this LPL inhibitor is a middle-range molecule that is removed by dialysis with PS, but not CE, membranes.

The beneficial effects on lipoprotein profiles were after the first dialysis with PS membranes and persisted throughout the study period (for up to 4 months). Therefore, a single dialysis may be sufficient to improve LPL actions. Additionally, because both CE and PS patients received a similar amount of heparin, our findings are not consistent with the theory that the repeated administration of heparin to dialysis patients causes dyslipidemia by depleting tissue stores of LPL.

Our data suggest that a more physiologic dialysis treatment that removes larger molecules and activates inflammatory systems less also improves lipo-

protein abnormalities in dialysis patients. We hypothesize that if the improvement in lipoproteins found in our study is maintained, it might have a favorable effect on cardiac morbidity and mortality in patients on chronic hemodialysis.

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