

Profiles of inflammatory markers and lipoprotein subclasses in patients undergoing continuous ambulatory peritoneal dialysis

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Disclaimers

Nothing to declare.

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Running title: Lipoprotein and inflammatory markers in CAPD patients

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Abstract

Background: Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) often have inflammation and dyslipidemia that accelerate to atherosclerosis. This study aimed to evaluate chronic inflammation and dyslipidemia in CAPD patients.

Methods: We measured inflammatory markers and lipoprotein subclasses in 20 CAPD patients (12 men and 8 women, aged 59.5 ± 9.9 y) and 20 gender -matched controls. Lipoproteins were separated by high-performance liquid chromatography (HPLC) using an anion-exchange column.

Results: High-sensitivity C-reactive protein and serum amyloid A protein (SAA) were higher among CAPD patients vs. controls (1.6 ± 2.2 vs. 0.8 ± 1.2 mg/l, $p < 0.05$; 11.9 ± 12.8 vs. 4.5 ± 2.4 mg/l). HPLC analysis revealed that chylomicron, VLDL, and IDL cholesterol levels were higher among CAPD vs. controls. In contrast, HDL cholesterol was lower among CAPD patients vs. controls. In the subgroup analysis, SAA levels were significantly lower among patients receiving CAPD for > 3 y than among controls. However, IDL cholesterol was consistently higher among CAPD patients vs. controls.

Conclusions: CAPD patients have chronic inflammation and dyslipidemia. IDL cholesterol is the only lipoprotein subclass that is consistently elevated regardless of CAPD duration. More attention should be paid to dyslipidemia in the management of the CAPD patients.

1. Introduction

Patients with end-stage renal disease (ESRD) have high risks of death and hospitalization [1]. Hemodialysis (HD) markedly reduces short-term mortality in ESRD patients, as does continuous ambulatory peritoneal dialysis (CAPD). However, patients on these treatments still have high long-term mortality from cardiovascular disease (CVD) [2]. Diabetic nephropathy, chronic glomerulonephritis, and nephrosclerosis are the major causes of ESRD [3, 4], and these diseases often occur with co-morbid conditions of hypertension, dyslipidemia and inflammation [5-7], all of which promote the initiation and development of atherosclerosis synergistically. In addition to the control of blood pressure, management of dyslipidemia and inflammation are important factors in the reduction of long-term mortality in HD and CAPD patients.

CAPD is suitable as a home-based treatment for adults below the age of retirement. Although the total number of patients receiving dialysis treatment (HD plus CAPD) has been increasing year after year, the proportion of CAPD patients is less than 4% of all the patients receiving dialysis [4]. The obstructive factors for the dissemination of CAPD include the possible risk of peritonitis and exit-site infection. In addition, the hypertonic dialysis solution used in CAPD may cause adverse effects due to the high level of glucose, which may lead to an elevation in TG-rich lipoproteins [8]. These factors are likely to change as the duration of CAPD use. This study aimed to evaluate inflammation and dyslipidemia in the CAPD patients. To measure lipoprotein concentrations, we used high-performance liquid chromatography (HPLC) using an anion-exchange

column, which can separate intermediate-density lipoprotein (IDL) quantitatively and accurately [9, 10].

2. Materials and Methods

2.1. Subjects

The study subjects were 20 patients with ESRD who were being treated with CAPD (CAPD group, 12 men and 8 women). All were outpatients at Niigata University Medical and Dental Hospital. CAPD was carried out at home. All patients used hypertonic dialysis solutions. The CAPD group was divided into 3 subgroups based on the number of months of CAPD treatment: subgroup I, 0.5 to 10 months, $n = 7$; subgroup II, 14 to 29 months, $n = 7$; and subgroup III, 36 to 42 months, $n = 6$. Primary diseases in the CAPD group were chronic glomerulonephritis ($n = 5$), diabetic nephropathy ($n = 5$), IgA nephropathy ($n = 3$), nephrosclerosis ($n = 2$), and others ($n = 5$). We excluded patients who suffered from malignancies or overt acute inflammation associated with clinical symptoms such as cough, sputum, and sore throat.

For the controls, we enrolled 20 gender -matched normolipidemic healthy subjects (control group, 12 men and 8 women). At entry to the study, written informed consent was obtained from all subjects. The study protocol was approved by the ethics committee of the Niigata University Graduate School of Medical and Dental Sciences and complied with the Declaration of Helsinki revised in 2008.

2.2. Blood samples

Blood samples were obtained from the cubital vein after a minimum 12-hour overnight fast. Serum was separated by a 10-min centrifugation at 800×

g at room temperature. An aliquot of serum was mixed with stock solution (sucrose 760g/l, EDTA2K 1.5g/l, 3 : 1, v/v) for lipoprotein stabilization and frozen at -80°C until HPLC analysis [9, 10]. Stabilized samples yielded the same results as fresh plasma for at least 6 months.

2.3. HPLC method

Lipoprotein profiles were determined by a high-performance liquid chromatographic (HPLC) method using an anion-exchange column filled with nonporous polymer-based gel (diameter of $2.5\ \mu\text{m}$) coupled with diethylaminoethyl ligands [9, 10]. First, the thawed serum samples were set to an automated sampler (AS-8020, Tosoh, Tokyo, Japan) applied to the column. The sample volume was set to $4.5\ \mu\text{l}$ for reproducible data. According to the ion strength of the eluent, the bound lipoproteins were eluted in a stepwise fashion from the column. Eluate was mixed with enzyme solution for cholesterol measurement at 37°C in a reactor. We were able to detect five lipoprotein fractions (chylomicron, very low-density lipoprotein [VLDL], IDL, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) and quantitate the total cholesterol concentrations in these fractions.

Unlike the gel filtration HPLC method, an anion-exchange HPLC method can separate the IDL fraction as a sharp peak. We had already reported that the lipoprotein fractions determined by this method correlated well with those determined by ultracentrifugation [9]. The inter- and intra-assay CVs of cholesterol concentrations of all lipoprotein fractions were $< 12\%$, and those of the elution time were $< 1.2\%$ [9, 10].

2.4. Other laboratory measurements

We measured total cholesterol (TC), triglyceride (TG), phospholipid (PL), and creatinine concentrations enzymatically with a Hitachi-7450 automated analyzer (Hitachi, Tokyo, Japan). Apolipoprotein (Apo) AI, ApoAII, ApoB, ApoCII, ApoCIII, and ApoE concentrations were determined with a turbidity immunoassay, using commercial kits (ApoAI, AII, B, CII, CIII, E Auto N [Daiichi], Sekisui Medical, Tokyo, Japan). Albumin concentration was measured by the dye-binding bromcresol purple method (Pureauto S ALB, Sekisui Medical, Tokyo, Japan). Lecithin-cholesterol acyltransferase (LCAT) activity was expressed as the reduction rate of serum free cholesterol concentration during a 37°C incubation with endogenous lipoproteins as a substrate (NESCAUTO LCAT kit-S, Alfresa Pharma, Osaka, Japan). High-sensitivity C-reactive protein (hs-CRP) and serum amyloid A (SAA) concentrations were determined by latex immunoturbidimetry (CRP-Latex X2 'SEIKEN' NX, Denka Seiken, Tokyo, Japan and LZ TEST 'EIKEN' SAA, Eiken Kagaku, Tokyo, Japan).

2.5. Statistical analysis

Statistical analyses were performed using Microsoft Excel 2007 (Microsoft Japan, Tokyo, Japan) with Statcel, an add-in software for Excel (OMS, Tokorozawa, Japan). The data are presented as mean value \pm SD unless otherwise stated. To apply a suitable method to the each analysis, we examined whether the data showed a Gaussian distribution. Student's *t*-test or Welch's *t*-test was used to compare the variables between the CAPD and control groups.

The Wilcoxon–Mann–Whitney U -test was applied to the data that did not follow a Gaussian distribution. To compare the variables among the subgroups of CAPD patients, either one-factor ANOVA or the Kruskal–Wallis test was used.

Differences among the subgroups were tested by Fisher’s PLSD. For all the analyses, a p -value < 0.05 was considered significant.

3. Results

3.1. Clinical characteristics of the study subjects

The BMI of the CAPD group was similar to the BMI of the gender-matched controls (Table 1). The mean systolic blood pressure was 16 mm Hg higher in the CAPD group than in the control group. All patients took anti-hypertensive treatments (Table 1). Most subjects were treated with renin-angiotensin-aldosterone (RAA) blockers (80%) or calcium-channel blockers (CCB) (80%), or both (65%). Creatinine concentration was markedly higher in the CAPD group than in the control group. These tendencies were evident in those who had received CAPD treatment for a long time (subgroups II and III). Because of renal dysfunction, the use of statins was limited ($n = 4$). In contrast, albumin concentration was 25% lower in the CAPD group than in the control group. No significant differences were found among the CAPD subgroups.

3.2. Serum lipid and apolipoprotein concentrations

All patients in the CAPD group had significantly higher TG and ApoCIII concentrations compared with controls, but their ApoAII concentrations were significantly lower than those in the control group (Table 2). In the subgroup analysis, subgroup I had more variables showing abnormalities than did the other subgroups. The patients in subgroup III had no significant lipid or apolipoprotein concentrations except for ApoCIII levels.

3.3. Lipoprotein concentrations determined by anion-exchange HPLC method

We previously reported that five lipoprotein classes were separated clearly by anion-exchange HPLC [9]. For all patients in the CAPD group, cholesterol concentrations in all TG-rich lipoprotein types increased significantly (Table 3). In particular, the IDL cholesterol in all patients in the CAPD group was nearly double that in the control group. Among TG-rich lipoproteins (chylomicron, VLDL, and IDL), only IDL cholesterol was elevated in all 3 CAPD subgroups (Table 3). LDL-C did not differ between CAPD and control groups.

In contrast to TG-rich lipoproteins, HDL cholesterol was reduced by 19% among all patients in the CAPD group vs. those in the control group. However, it should be noted that HDL cholesterol was significantly reduced only in patients in CAPD subgroup I. Moreover, HDL cholesterol concentration was 37% higher in subgroups II and III than in the subgroup I.

3.4. Effects of the duration of CAPD treatment on inflammatory and lipoprotein-related makers

Inflammatory markers and LCAT activity exhibited close association with the number of months patients remained on CAPD treatment. In subgroups I and II, hs-CRP and SAA concentrations were significantly higher than those in the control group. In subgroup III, however, hs-CRP was as low as levels observed in the control group. SAA was even lower in subgroup III than in the control group (Table 4). Some anti-hypertensive agents have a favorable effect on inflammation, but the frequency of anti-hypertensive agent use and their treatment doses were not different among the three subgroups.

LCAT activity in subgroup I was as high as levels observed in the control group. However, LCAT activity was significantly lower in subgroups II and III than in the control group (Table 4).

4. Discussion

The present study indicates that CAPD patients have chronic inflammation and dyslipidemia and that the cholesterol level of TG-rich lipoproteins, particularly IDL cholesterol, is elevated regardless of the duration of CAPD treatment. We found that hs-CRP and SAA concentrations were higher in the patients in subgroups I and II (who had initiated CAPD within the past 3 y) than in the control group. On the other hand, SAA concentration was significantly lower in subgroup III (treated for > 3 y) than in the control group (Table 4). In the HPLC analysis, all TG-rich lipoproteins showed significant elevation in subgroup I (treated for < 1 y). In subgroup III, however, only IDL cholesterol was increased significantly among the TG-rich lipoproteins (Table 3).

Inflammatory markers tend to be elevated in CAPD patients, probably because CAPD procedures mechanically irritate the peritoneum during dialysis. Antunes et al. reported that CAPD patients had higher levels of interleukin-6, tumor necrosis factor- α and CRP, indicating the presence of chronic inflammation [11]. Lin et al. examined the effects of icodextrin dialysis solution on inflammatory markers over a 1-y period in 32 CAPD patients [12]. They found that the hs-CRP concentration decreased significantly in the icodextrin group, whereas it did not change in CAPD patients treated with dextrose dialysis solution. These results strongly suggest that high levels of inflammatory markers are reversible. In our study, inflammatory markers were not elevated in subgroup III. Patients who had moderate to severe inflammation were likely to give up CAPD treatment due to peritoneal damage related to chronic

inflammation. If we successfully suppress inflammation, we could extend the period of CAPD treatment.

With regard to dyslipidemia, elevated IDL cholesterol is characteristic in CAPD patients. In our study, IDL cholesterol concentration was 140, 72, and 76 % higher in subgroups I, II, and III, respectively, than in the control group (Table 3). These increases in IDL cholesterol were 3- to 6-fold greater in CAPD patients than in hemodialysis patients (25%, $p < 0.05$ vs. the control group) whom we examined using the same HPLC system [10]. In the hemodialysis patients, IDL cholesterol (IDL-C, $d = 1.006-1.063$) is the best predictor of aortic stiffness [13]. CAPD patients had significantly higher carotid intima media thickness and lower flow-mediated dilatation compared with controls [14]. Therefore, atherosclerotic disorders might progress more rapidly in CAPD than in hemodialysis patients.

One possible reason for the high IDL cholesterol in CAPD patients is that ApoCIII concentration is elevated in these patients (Table 2). Increased ApoCIII is typical of renal dyslipidemia and may result from a disturbance in insulin metabolism in chronic renal disease [15]. ApoCIII inhibits the activity of lipoprotein lipase, a key enzyme for the catabolism of TG-rich lipoproteins [16]. Therefore, it is likely that hydrolysis of TG-rich lipoproteins is impaired in CAPD patients. In addition, in vitro experiments suggest that ApoCIII can promote atherosclerosis by its direct proatherogenic actions [16]. Another possible reason for high IDL cholesterol is that TG-rich lipoproteins are overproduced due to glucose overload derived from the dialysis solution. In Japan, hypertonic dialysis solution is more common than icodextrin solution for CAPD [4]. In this study, all

patients used hypertonic dialysis solution. During the CAPD procedures, glucose in this solution moves from the peritoneal cavity into blood, and excess glucose enters the liver. As a result, TG synthesis is enhanced, leading to increased secretion of TG-rich lipoproteins. A recent study showed that icodextrin dialysis solution, which does not diffuse from the peritoneal cavity into the blood, alleviates inflammation [12] and dyslipidemia [17]. Thus, it is worth attempting to change the dialysis solution from hypertonic to icodextrin solution to reduce IDL cholesterol concentration in CAPD patients.

Our subgroup analysis suggests that suppression of inflammation is important in maintaining HDL cholesterol, a marker for the amount of HDL particles. In general, both inflammation and low LCAT activity were associated with low HDL cholesterol [18, 19]. Although subgroup I exhibited normal LCAT activity (Table 4), their mean HDL cholesterol was 35% lower than levels seen in the control group (Table 3), which might be related to significant elevations of hs-CRP and SAA, reflecting chronic inflammation (Table 4). On the other hand, subgroup III exhibited low LCAT activity, but almost same levels in inflammatory makers, may increase HDL cholesterol compared to subgroup I. ApoAI, the main protein component of HDL, is known as one of the negative acute-phase proteins [20]. When lipopolysaccharides (LPS) were injected into mice, hepatic mRNA expression of apoAI was reduced by 40% within 24 h. On the other hand, hepatic mRNA levels of SAA were increased 2000-fold from the baseline level [21]. SAA has high affinity for HDL particles and displaces apoAI and phospholipids on HDL particles [22, 23]. If inflammation is successfully suppressed in CAPD patients, HDL cholesterol is expected to increase due to

increased synthesis and decreased dissociation of apoAI. In fact, subgroup III exhibited normal or even lower inflammatory markers (Table 4), and their HDL cholesterol concentration was 37% higher than levels observed in subgroup I (Table 3). However, we should be cautious about low LCAT activity in subgroup III. In our previous study, low LCAT activity was associated with impaired maturation of lipid-poor HDL into spherical HDL in hemodialysis patients, even if they had normal HDL cholesterol concentrations [24]. Therefore, we need to further examine the function of HDL in CAPD patients in future studies.

There are some limitations in our study. First, this is a cross-sectional case-control study. We did not examine longitudinal changes in various parameters using the samples from the same patients at different time points. Second, it is possible that some patients with severe inflammation might have given up long-term CAPD treatment, and they might therefore be excluded from subgroup III. Third, the number of CAPD patients was relatively small. CAPD is a bridging treatment before the induction of hemodialysis. Thus, we could not enroll many CAPD patients in this study. A prospective longitudinal study is required to confirm how the profiles of inflammation and dyslipidemia change during the course of long-term CAPD treatment.

In summary, the present study indicates that CAPD patients have chronic inflammation and dyslipidemia, and that only IDL cholesterol remains at a high level regardless of the number of months on CAPD treatment. We speculate that IDL cholesterol may accelerate atherosclerosis even if CAPD patients could avoid peritoneal damage due to chronic inflammation. Strict management of dyslipidemia is desirable for improving long-term mortality in

CAPD patients.

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Table 1: Clinical characteristics of CAPD and control groups.

	CAPD Patients				Healthy Subjects
	Subgroup I (n = 7)	Subgroup II (n = 7)	Subgroup III (n = 6)	Total (n = 20)	(Control group) (n = 20)
Age (year)	66.1 ± 6.7	58.0 ± 9.8	53.5 ± 9.8	59.5 ± 9.9	56.8 ± 10.1
Male / Female	4 / 3	5 / 2	3 / 3	12 / 8	12 / 8
BH (m)	1.62 ± 0.06	1.66 ± 0.10	1.60 ± 0.08	1.63 ± 0.08	1.64 ± 0.08
BW (kg)	66.2 ± 17.3	64.5 ± 20.2	54.2 ± 8.9	62.0 ± 16.5	60.4 ± 12.4
BMI (kg/m ²)	25.0 ± 5.2	23.1 ± 5.1	21.4 ± 3.9	23.3 ± 4.8	22.1 ± 2.6
SBP (mmHg)	130 ± 20	141 ± 29 *	142 ± 19 *	138 ± 23 *	122 ± 14
DBP (mmHg)	73 ± 20	87 ± 23	84 ± 11	81 ± 19	79 ± 12
ARB/ACEI/CCB/Others	4 / 0 / 6 / 10	5 / 2 / 5 / 8	5 / 2 / 5 / 9	14 / 4 / 16 / 27	—
Duration of CAPD (month)	4.2 ± 3.5	21.0 ± 6.6 ###	38.5 ± 2.3 ###, †††	20.4 ± 14.8	—
Creatinine (mg/L)	59.4 ± 16.1 ***	93.4 ± 31.7 ***, #	104.7 ± 32.3 ***, ##	84.9 ± 33 ***	7.5 ± 1.4
Albumin (g/L)	31.5 ± 6.0 ***	29.5 ± 6.4 ***	35.4 ± 3.6 ***	32.0 ± 5.8 ***	42.9 ± 3.7

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. healthy subjects

$p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. Subgroup I; ††† $p < 0.001$ vs. Subgroup II

BH , body height; BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker

Table 2: Lipids and lipoprotein concentrations in CAPD and control groups.

	CAPD Patients				Healthy Subjects
	Subgroup I	Subgroup II	Subgroup III	Total	(Control group)
	(n = 7)	(n = 7)	(n = 6)	(n = 20)	(n = 20)
TC (mmol/L)	5.03 ± 0.56	4.89 ± 1.30	5.07 ± 0.95	4.99 ± 0.93	5.16 ± 0.48
TG (mmol/L)	2.21 ± 0.92 **	1.53 ± 0.62	1.64 ± 0.85	1.80 ± 0.82 **	1.13 ± 0.59
PL (mmol/L)	2.55 ± 0.28	2.50 ± 0.55	2.72 ± 0.55	2.58 ± 0.46	2.74 ± 0.25
ApoAI (mg/L)	1168 ± 204 *	1302 ± 282	1325 ± 320	1262 ± 265	1414 ± 224
ApoAII (mg/L)	224 ± 48 **	246 ± 29 *	268 ± 45	245 ± 43 **	286 ± 37
ApoB (mg/L)	1050 ± 159 *	825 ± 195	890 ± 138	923 ± 187	887 ± 155
ApoCII (mg/L)	40 ± 18	40 ± 20	40 ± 17	40 ± 17	34 ± 15
ApoCIII (mg/L)	127 ± 46 **	120 ± 46 *	130 ± 33 ***	125 ± 40 ***	87 ± 15
ApoE (mg/L)	48 ± 11	44 ± 8	44 ± 9	45 ± 9	41 ± 11
ApoB/ApoAI ratio	0.92 ± 0.22 **	0.65 ± 0.16	0.70 ± 0.18	0.76 ± 0.22	0.65 ± 0.19
ApoCIII/ApoCII ratio	3.40 ± 0.90	3.29 ± 0.81	3.44 ± 0.67	3.37 ± 0.77	2.85 ± 0.82

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. healthy subjects

TC, total cholesterol; TG, triglyceride; PL, phospholipid

Table 3: Cholesterol concentrations in five lipoprotein fractions determined by HPLC analysis in CAPD and control groups.

	CAPD Patients				Healthy Subjects
	Subgroup I	Subgroup II	Subgroup III	Total	(Control group)
	(n = 7)	(n = 7)	(n = 6)	(n = 20)	(n = 20)
Chylomicron (mmol/L)	0.10 ± 0.03 **	0.11 ± 0.05 *	0.08 ± 0.03	0.10 ± 0.04 **	0.07 ± 0.03
VLDL (mmol/L)	0.50 ± 0.33 **	0.34 ± 0.23	0.33 ± 0.24	0.40 ± 0.27 *	0.22 ± 0.17
IDL (mmol/L)	0.60 ± 0.30 ***	0.43 ± 0.15 ***	0.44 ± 0.23 **	0.49 ± 0.24 ***	0.25 ± 0.07
LDL (mmol/L)	3.00 ± 0.50	2.93 ± 1.02	3.05 ± 0.45	2.99 ± 0.68	3.17 ± 0.56
HDL (mmol/L)	1.04 ± 0.27 **	1.43 ± 0.52	1.42 ± 0.61	1.29 ± 0.49 *	1.60 ± 0.40
Total (mmol/L)	5.24 ± 0.74	5.23 ± 1.48	5.32 ± 1.04	5.26 ± 1.07	5.30 ± 0.50

* p < 0.05, ** p < 0.01, *** p < 0.001 vs. healthy subjects

Lipoprotein fractions were separated by the HPLC method using an anion-exchange column as described in Materials and Methods. Cholesterol concentration in each fraction was obtained by multiplying serum cholesterol concentration by the respective area ratio.

VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 4: Inflammatory markers and LCAT activity in CAPD and control groups.

	CAPD Patients				Healthy Subjects
	Subgroup I	Subgroup II	Subgroup III	Total	(Control group)
	(n = 7)	(n = 7)	(n = 6)	(n = 20)	(n = 20)
hs-CRP (mg/L)	3.07 ± 3.18 *	1.07 ± 0.81 *	0.56 ± 0.44	1.62 ± 2.16 *	0.75 ± 1.15
SAA (mg/L)	14.7 ± 13.1 *	17.5 ± 14.4 *	2.3 ± 1.9 *	11.9 ± 12.8	4.5 ± 2.4
LCAT (Δ FC μ mol/L/h at 37°C)	89.4 ± 18.3	70.9 ± 16.5 **	63.8 ± 22.7 **	75.2 ± 21.2 **	93.2 ± 17.2

* p < 0.05, ** p < 0.01, *** p < 0.001 vs. healthy subjects

hs-CRP, high-sensitivity C-reactive protein; SAA, serum amyloid A; LCAT, lecithin-cholesterol acyltransferase