Abnormal HDL Apolipoprotein A-I and A-II Kinetics in Hemodialysis Patients: A Stable Isotope Study

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Abstract. Low levels of HDL cholesterol and its major apo-

protein constituents apoA-I and apoA-II are common in pa-

tients who have ESRD and are undergoing hemodialysis (HD),

but the metabolic basis for the low HDL is poorly understood.

This study aimed to investigate in vivo metabolism of apoA-I

and apoA-II in five normotriglyceridemic ESRD-HD patients

and compared it with five control subjects using endogenous

stable isotope labeling methods coupled with a multicompart-

mental modeling. HDL cholesterol, apoA-I, and apoA-II levels

were markedly decreased in the ESRD-HD patients by 39, 30,

and 44%, respectively, in comparison with the control subjects.

Fractional catabolic rate of apoA-I was found to be signifi-

cantly increased by 59% to 0.360 ± 0.084/d in ESRD-HD

patients as compared with control subjects of 0.227 ± 0.076/d

(P = 0.028), whereas the production rates remained un-

changed. Conversely, the apoA-II production rate significantly
decreased by 31% to 1.50 ± 0.61 mg/kg per d in the ESRD-HD

patients in comparison with control subjects of 2.17 ± 0.40

mg/kg per d (P = 0.047) with apoA-II fractional catabolic rate

unchanged. These results revealed that the decreased levels

of apoA-I are due solely to the increased rate of catabolism,

whereas the reduced apoA-II levels are due primarily to the
decreased rate of production in ESRD-HD patients. This dif-
yferential regulation of apoA-I and apoA-II further supports
the concept that apoA-I and apoA-II have distinct metabolic
pathways.

Patients who have ESRD and undergo hemodialysis (HD) are

at increased risk for coronary artery disease (CAD) (1,2),

which is due at least in part to lipid abnormalities, typically
called uremic dyslipidemia (3). One of the major lipid abnor-

malities of uremic dyslipidemia is a decreased level of HDL

cholesterol (HDL-C) (4–6). In general, low HDL-C is often

associated with elevated triglyceride (TG) levels, and this

inverse relation is also observed in ESRD-HD patients (7),
suggesting a possibility that hypertriglyceridemia but not ure-

mia per se may be an underlying mechanism for the decreased

levels of HDL. However, TG levels in ESRD-HD patients in

Japan (5–7) are generally lower than counterparts in Western
countries (4,8), and HDL-C in ESRD-HD patients is still lower

than in control subjects with comparable TG levels (7), indi-
cating that the decreased HDL-C is not due simply to hyper-

triglyceridemia in ESRD-HD patients.

Plasma concentrations of HDL-C and apoA-I, the major

protein constituent of HDL, have been shown to be inversely

associated with the incidence of CAD (9–11). Although the

mechanism by which HDL may exert a direct protective effect

against development of atherosclerosis is not yet well under-

stood, HDL has been postulated to facilitate the efflux of

cholesterol from peripheral tissues and transport it back to the

liver in a process called reverse cholesterol transport (12).

HDL metabolism is regulated by several enzymes, including
hepatic triglyceride lipase (HTGL), lecithin:cholesterol acyl-

transferase (LCAT), and cholesteryl esters transfer protein

(CETP). Previous studies reported decreased HTGL activity
(13,14) and decreased LCAT activity (14,15) but inconsistent

results in CETP activity (16,17) in ESRD-HD patients. Thus, it

is important to assess whether and, if so, how these altered

enzyme activities modulate synthesis and catabolism of HDL

in vivo.

Unfortunately, little is known about the metabolic basis for

the decreased HDL in ESRD-HD patients. To our knowledge,

no HDL apolipoprotein kinetic studies in ESRD-HD patients

have been reported to date. One kinetic study was reported by
Fuh et al. (18) in which only apoA-I metabolism was studied

in predialysis patients by using a conventional radiotracer

technique. Because the majority of ESRD patients eventually

need maintenance dialysis and the number of ESRD-HD pa-

tients has been increasing, a better understanding of the met-

abolic basis for the decreased levels of HDL in ESRD-HD

patients is an urgent task and should provide a substantial

clinical benefit. We therefore conducted an in vivo metabolism

study of apoA-I and apoA-II in normotriglyceridemic

ESRD-HD patients using endogenous stable isotope labeling

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methods coupled with a multicompartamental modeling for data analysis.

Materials and Methods

Study Subjects

Five ESRD-HD patients (three men and two women) and five control subjects (all men) were recruited for this study. Eligibility criteria of ESRD-HD patients included age between 40 and 70 yr, body mass index <25 kg/m², fasting plasma triglyceride concentration <150 mg/dl, and no evidence of diabetes. The cause of ESRD was chronic glomerulonephritis in four patients and polycystic kidney disease in one patient (patient 5). The average duration of maintenance hemodialysis was 7.9 yr. None of the study subjects, including the ESRD-HD patients, had any history of familial hyperlipidemia or were on medications that affect lipid metabolism. The study was approved by the Ethics Committee of Jikei University School of Medicine. All study subjects gave their written informed consent to take part in this study.

HDL Kinetic Study

The study subjects were admitted to Jikei University Hospital (Shinbashii Hospital or Aoto Hospital) before the kinetic study. The stable-isotope turnover study was begun at 5 a.m. after 12-h fasting. Then, the subjects were fed hourly for 15 h, and each meal consisted of 1/15th of their required calories. In all ESRD patients, the study was performed 1 d after hemodialysis. Two plastic indwelling catheters were placed intravenously on contralateral arm veins; one catheter was used for the tracer infusion, and the other was used for the frequent blood sampling during the study. Three times deutrium-labeled L-leucine (L-leucine-methyl-D3; Cambridge Isotope Laboratories, Woburn, MA) was administered as a priming bolus of 1.0 mg/kg at 8 a.m., immediately followed by a constant infusion of 1 mg/kg per h for 12 h. Blood samples (15 ml) were drawn into tubes containing EDTA at a final concentration of 1 g/L before the tracer injection; after 10 min, then 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 18, 24, 36, and 48 h and an additional sampling at 72 h in all control subjects. Blood was kept on ice, and the plasma was immediately separated by centrifugation (3000 × g, 20 min at 4°C). NaF and aprotinin were added to the plasma at final concentrations of 0.5 g/L and 200,000 KIU/L, respectively.

Isolation of Lipoproteins and Apolipoproteins

HDL was isolated by an ultracentrifugation from 4 ml of plasma and proceeded for the analysis by a gas chromatography–mass spectrometry (GC-MS) as previously reported (19). Briefly, isolated HDL (density 1.063 to 1.21 g/ml) was dialyzed against 10 mM ammonium bicarbonate, lyophilized, then delipidated. ApoA-I was isolated by preparative gradient SDS-PAGE (5 to 15%) (20), and apoA-II was isolated by preparative isoelectric focusing (pH 4 to 6) (21).

Determination of Tracer/Tracee Ratio by GC-MS

Samples were prepared for GC-MS analysis as reported previously (19–21). Briefly, apolipoprotein bands were cut from gels and dried overnight (90°C) and then were hydrolyzed in 6 N HCl (amino acid analysis grade; Wako Pure Chemical Industries, Osaka, Japan) at 110°C for 24 h. The protein hydrolysates were lyophilized in a Speed-Vac evaporator (Savant Instrument, Farmingdale, NY). Free amino acids were purified from plasma or protein hydrolysates by cation exchange chromatography (AG-50W-X8; Bio-Rad Laboratories, Richmond, CA) and then derivatized to the N-heptafluorobutyl isoamyl esters and analyzed by GC-MS on a 6890 gas chromatograph connected to a 5973 quadrupole mass spectrometer (Hewlett Packard, Palo Alto, CA) in the chemical ionization mode, using methane as the reagent gas. Selective ion monitoring at 365 m/z (M + 2 isotopomer) for unlabeled leucine and 366 m/z (M + 3 isotopomer) for labeled leucine was used to determine the tracer/tracee (T/T) ratio by regression analysis of standards of known T/T ratios (0 to 10%) as reported previously (22,23). Each sample was analyzed at least two times.

Kinetic Modeling

A multicompartamental model (Figure 1) was developed to determine apoA-I and apoA-II kinetic parameters using an interactive computer program (SAAMII version 1.1; SAAM Institute, Seattle, WA) (24). In brief, compartment 1 represents the plasma amino acid pool, and plasma leucine T/T data are fitted by a three-exponential equation using SAAM II numerical module. The equations below describe the exponential function and consist of two parts, the first part representing T/T during the primed-constant infusion and the second part representing the T/T decay during the washout phase after the termination of infusion at 12 h.

\[
\text{Plasma leucine } T/T = \text{swit} \times \text{infusion} + \text{washout}
\]

\[
\text{Infusion } = A_0 + A_1 \times \exp(-a_1 \times t) + A_2 \times \exp(-a_2 \times t) + A_3 \times \exp(-a_3 \times t)
\]

\[
\text{Infusion } 12 = A_0 + A_1 \times \exp(-a_1 \times 12) + A_2 \times \exp(-a_2 \times 12) + A_3 \times \exp(-a_3 \times 12)
\]

\[
\text{Washout } = (1 - \text{swit}) \times \text{infusion } 12 \times (B_1 \times \exp(-a_1 \times (t - 12)) + (1 - B_1) \times B_2 \times \exp(-a_2 \times (t - 12)) + (1 - B_1) \times (1 - B_2) \times \exp(-a_3 \times (t - 12)))
\]

At 12 h, “swit” is changed from 1 to 0 using a change condition function in SAAMII. Therefore, during the infusion period, “Plasma leucine T/T” equal to “infusion,” then to “washout” after 12 h, SAAMII can determine the best estimate of the parameters (Ai, Bi, and ai) to fit actual plasma T/T data, which are then implanted into the equation window in the multicompartamental model and used as a forcing function. The plasma leucine T/T curve of the mean of five control subjects is shown in Figure 2. Fitting curve precisely traces the observed T/T points, and fractional SD of most parameters resides within 20%. Compartment 2 accounts for a delay of HDL assembly and subsequent secretion. A single compartment (compartment 3) is
allocated for the HDL apoA-I or apoA-II pool. Originally, an extravascular pool was set up to allow the movement of HDL between the plasma and extravascular pool. However, the exchange pathway hit 0 after iteration and did not improve the overall fitting in all study subjects. We therefore decided to eliminate this pathway. Plasma concentrations of apoA-I and apoA-II were measured during the study period to find that percentage changes of apoA-I and apoA-II were within 5.6 and 4.4% in control subjects and 1.7 and 3.0% in ESRD-HD patients, respectively, none of which was statistically significant. Therefore, we assumed that steady-state conditions were maintained throughout the study period, under which fractional catabolic rate (FCR; /d) was equal to fractional synthetic rate (FSR).

Apolipoprotein concentration in plasma *(1

Analytical Methods
The plasma total cholesterol and TG levels were determined by the automated enzymatic technique using a Toshiba TBA-80FR autoanalyzer (Toshiba, Tokyo, Japan). HDL-C was measured after heparin-manganese precipitation of plasma LDL-C was calculated using the Friedewald formula. Plasma apoA-I and apoA-II concentrations were quantified using immunoturbidimetric assays (34). CETP mass was measured by a sandwich ELISA using two monoclonal antibodies, JHC1 and JHC2, as reported previously (35). LCAT activity in plasma was determined by a method using dimyristoyl phosphatidylcholine-cholesterol liposome as substrate (36). HTGL activity in post-heparin plasma collected 10 min after intravenous injection of heparin (30 U/kg body wt) was measured as the rate of radiolabeled fatty acids liberation from [14C]triolein emulsion in gum arabic (13).

Figure 2. Tracer/tracer curve (T/T) ratio curve for plasma leucine in control subjects. Plasma leucine T/T curve is used as a forcing function in the multicompartmental model for apoA-I and apoA-II (Figure 1). All data points are given as the means of five control subjects and fitted by the three exponential model using SAAMII numerical module (see Materials and Methods for details).

The plasma total cholesterol and TG levels were determined by the automated enzymatic technique using a Toshiba TBA-80FR autoanalyzer (Toshiba, Tokyo, Japan). HDL-C was measured after heparin-manganese precipitation of plasma LDL-C was calculated using the Friedewald formula. Plasma apoA-I and apoA-II concentrations were quantified using immunoturbidimetric assays (34). CETP mass was measured by a sandwich ELISA using two monoclonal antibodies, JHC1 and JHC2, as reported previously (35). LCAT activity in plasma was determined by a method using dimyristoyl phosphatidylcholine-cholesterol liposome as substrate (36). HTGL activity in post-heparin plasma collected 10 min after intravenous injection of heparin (30 U/kg body wt) was measured as the rate of radiolabeled fatty acids liberation from [14C]triolein emulsion in gum arabic (13).

Statistical Analyses
Comparisons between groups were performed using Mann-Whitney rank sum test. P < 0.05 was considered to be statistically significant. All statistical procedures were performed using SPSS software (version 9.1; SPSS, Chicago, IL).

Results
The plasma and lipoproteins lipid and apolipoprotein profiles are summarized in Table 1. The average total cholesterol was significantly lower in the ESRD-HD patients (153 ± 11 mg/dl) than in control subjects (175 ± 8 mg/dl; P = 0.016 versus ESRD-HD patients), primarily as a result of a markedly decreased HDL-C level (31.2 ± 5.3 mg/dl in ESRD-HD patients versus 51.1 ± 4.6 mg/dl in control subjects; P = 0.009). In line with previous findings in the literature, LDL-C levels in HD patients did not differ from those in control subjects. In parallel to the decreased HDL-C, both apoA-I and apoA-II levels in ESRD-HD patients significantly decreased by 30 and 44%, respectively, compared with control subjects. It should be noted that the magnitude of decrease in apoA-II was somewhat greater than that in apoA-I. As a result, the apoA-I/apoA-II ratio was nonsignificantly increased by 40% in the ESRD-HD patients in comparison with the control subjects (6.74 ± 2.50 versus 4.83 ± 0.35; P = 0.17), thus indicating that the metabolism of HDL with apoA-I and apoA-II may be more profoundly modulated than those with apoA-I but without apoA-II in ESRD-HD patients. CETP masses were comparable between ESRD-HD patients and control subjects, and, although not significant, LCAT activities were decreased by 30% in ESRD-HD patients as compared with control subjects, a finding consistent with previous studies (14,15). Likewise, HTGL activities in three ESRD-HD patients were significantly decreased by 33% in comparison with the control subjects in our previous study (13).

The T/T ratio curves for apoA-I and apoA-II are shown in Figure 3. In both subject groups and proteins, the calculated curves generated by the multicompartmental model using SAAMII yielded reasonable fittings. The mean T/T ratio of apoA-I in the ESRD-HD patients reached a higher level and thereafter decreased more rapidly than that in the control subjects (Figure 3, top). In contrast, the T/T ratio of apoA-II in the ESRD-HD patients increased to reach a somewhat higher level, but the disappearance slope was almost identical to that in the control subjects (Figure 3, bottom). Higher T/T peaks in both apoA-I and apoA-II likely reflect higher plasma T/T ratios during the infusion period in ESRD-HD patients (9.32 ± 1.92%) than in control subjects (7.98 ± 1.77%).
The kinetic parameters are summarized in Table 2. As expected by the T/T curve (Figure 3), the mean apoA-I FCR significantly increased by 59% to 0.360 ± 0.084/day in ESRD-HD patients as compared with control subjects of 0.227 ± 0.076/day (p = 0.028). PR of apoA-I were not different between groups, although the average PR in ESRD-HD groups was 36% higher than that in the control group (p = 0.117). As a result, the decreased apoA-I levels in ESRD-HD patients were primarily due to the increased rate of catabolism. We found a different metabolic alteration of apoA-II in the ESRD-HD patients. The apoA-II FCR were found to be similar between the two groups (0.196 ± 0.059/day in the ESRD-HD patients versus 0.186 ± 0.031/day in the control subjects), which is consistent with similar disappearance curves in Figure 3. In contrast, the apoA-II PR decreased significantly by 31% to 1.50 ± 0.61 mg/kg per day in ESRD-HD patients as compared with control subjects of 2.17 ± 0.40 mg/kg per day (p = 0.047). Therefore, the decreased apoA-II levels in ESRD-HD patients were attributable to the decreased rates of production.

**Discussion**

In the present study, we demonstrate for the first time the metabolic basis for the two major HDL protein constituents,
apoA-I and apoA-II, in ESRD-HD patients. The decreased apoA-I and apoA-II levels are entirely due to the increased rate of catabolism for the former and the decreased rate of production for the latter, respectively. We (37) and others (38,39) have previously shown the rate of catabolism to be the determinant of the plasma apoA-I level, whereas the rate of production is the determinant of the plasma apoA-II levels in normolipidemic humans. Therefore, apoA-I FCR and apoA-II PR as the primary regulators for their steady-state concentrations are applicable to hypoalphalipoproteinemia associated with ESRD-HD patients. Different metabolic regulation between apoA-I and apoA-II provided further evidence that HDL subtypes have different metabolic pathways depending on the presence or absence of apoA-II on HDL particles (37,40). These subclasses have different metabolic pathways depending on the presence or absence of apoA-II on HDL particles (37,40–42). Although this study is not able to identify the primary cause of the increased catabolism of apoA-I, several mechanisms might contribute to these findings. First, although statistically not significant, we found that LCAT activities were decreased by 30% in ESRD-HD patients as compared with control subjects, which suggests an inflammation in the ESRD-HD patients. Inflammation has been shown to be associated with reduced levels of HDL (46). Under inflammatory conditions, serum amyloid A, an acute-phase reactant, is synthesized by the liver and displaces apoA-I from HDL, resulting in an accelerated apoA-I catabolism (47,48). Although we did not directly measure serum amyloid A concentrations, this can be a third reason. Beside LCAT, HTGL has been considered to be a factor modulating HDL. In this study, preliminary results of HTGL activities in three ESRD-HD patients were found to be decreased as compared with control subjects in our previous study (13). The decreased HTGL activity is supported by the study by Shoji et al. (14). Rashid et al. (49) reported that HTGL accelerates apoA-I catabolic rate in rabbit models. Therefore, the decreased HTGL activity can be a reason for delayed apoA-I catabolism, but our kinetic data show otherwise. Overall, it is indicated that alterations in other metabolic factors surpass the effect of the decreased HTGL activity in our ESRD-HD patients.

Of note is a nonsignificant increase in apoA-I PR in the ESRD-HD patients (36% increase versus control subjects). The exact mechanism remains unclear at present; collective data of in vivo albumin (25,26,50) and fibrinogen kinetics (25) demonstrated that these protein synthesis were increased in ESRD-HD patients. They speculated that increased protein synthesis might represent a compensatory response to decreased osmotic pressure caused by PV expansion. In this regard, increased apoA-I synthesis could be explained by the same mechanism. Why was apoA-II production markedly decreased in ESRD-HD patients in contrast to other proteins mentioned above? We could not identify the exact mechanism, either, because factors that regulate apoA-II PR per se have been poorly understood. This could be due to a different tissue response to uremia, as apoA-I is synthesized in the liver and/or has a high affinity for cell-surface receptors including scavenger receptor class B type I. Plasma C-reactive protein levels were mildly elevated (0.3 to 0.8 mg/dl) in four ESRD-HD patients, suggesting an inflammation in the ESRD-HD patients. Inflammation has been shown to be associated with reduced levels of HDL (46). Under inflammatory conditions, serum amyloid A, an acute-phase reactant, is synthesized by the liver and displaces apoA-I from HDL, resulting in an accelerated apoA-I catabolism (47,48). Although we did not directly measure serum amyloid A concentrations, this can be a third reason. Beside LCAT, HTGL has been considered to be a factor modulating HDL. In this study, preliminary results of HTGL activities in three ESRD-HD patients were found to be decreased as compared with control subjects in our previous study (13). The decreased HTGL activity is supported by the study by Shoji et al. (14). Rashid et al. (49) reported that HTGL accelerates apoA-I catabolic rate in rabbit models. Therefore, the decreased HTGL activity can be a reason for delayed apoA-I catabolism, but our kinetic data show otherwise. Overall, it is indicated that alterations in other metabolic factors surpass the effect of the decreased HTGL activity in our ESRD-HD patients.

Table 2. Kinetic parameters of ApoA-I and ApoA-II in ESRD-HD patients

<table>
<thead>
<tr>
<th>Subjects</th>
<th>ApoA-I</th>
<th></th>
<th></th>
<th>ApoA-II</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration (mg/dl)</td>
<td>FCR (/d)</td>
<td>PR (mg/kg per d)</td>
<td>Concentration (mg/dl)</td>
<td>FCR (/d)</td>
<td>PR (mg/kg per d)</td>
</tr>
<tr>
<td>ESRD-HD patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>98</td>
<td>0.358</td>
<td>19.35</td>
<td>15.9</td>
<td>0.176</td>
<td>1.54</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
<td>0.302</td>
<td>14.30</td>
<td>7.7</td>
<td>0.253</td>
<td>1.03</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>0.297</td>
<td>13.97</td>
<td>18.9</td>
<td>0.166</td>
<td>1.64</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>0.342</td>
<td>15.39</td>
<td>14.1</td>
<td>0.124</td>
<td>0.88</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>0.503</td>
<td>22.72</td>
<td>17.8</td>
<td>0.261</td>
<td>2.42</td>
</tr>
<tr>
<td>mean ± SD</td>
<td>91 ± 5</td>
<td>0.360 ± 0.084</td>
<td>17.15 ± 3.78</td>
<td>14.9 ± 4.4</td>
<td>0.196 ± 0.059</td>
<td>1.50 ± 0.61</td>
</tr>
<tr>
<td>Control subjects (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>129 ± 11</td>
<td>0.227 ± 0.076</td>
<td>12.59 ± 3.78</td>
<td>26.7 ± 1.9</td>
<td>0.186 ± 0.031</td>
<td>2.17 ± 0.40</td>
</tr>
</tbody>
</table>

a FCR, fractional catabolic rate; PR, production rate.
b P < 0.05.
c P < 0.01 compared with control subjects.
intestine, whereas apoA-II derives exclusively from the liver. Indeed, apoA-I and apoA-II show a different transcriptional response in an animal model (51). As reported previously, decreased apoA-II synthesis observed in this study is consistent with the concept that apoA-II synthesis is a primary determinant for the plasma apoA-II levels. It may be that apoA-II synthesis in ESRD-HD is still low with the compensatory action. This issue certainly deserves future studies.

The present observation contrasts with the previous observation by Fuh et al. (18), who found a delayed catabolism as well as a decreased rate of production of apoA-I in predialysis patients with chronic renal failure (CRF). Although the exact reason for this discrepancy is not clear, several differences do exist between the two studies. First, the patients in their study were not treated by HD, whereas our patients all underwent HD. Although most studies observed similar HDL-C levels between predialysis and ESRD-HD patients (4,5,8), HD may further exacerbate the already-existing abnormal HDL metabolism in CRF patients. On the basis of previous kinetic findings, decreased apoA-I always associates with increased rate of catabolism, which compares favorably to the present study but not their study. Second, there are some differences in lipid profile between the two studies. In this study, we carefully selected ESRD-HD patients who had decreased levels of HDL-C but normal TG levels to minimize potential confounding effect of hypertriglyceridemia on HDL metabolism. In contrast, CRF patients in their study obviously included hypertriglyceridemic patients. This finding, together with the fact that the apoA-I level in this study showed a greater reduction (−29.4%) than their counterpart (−19.5%), could lead to different alterations on HDL metabolism. A third reason could be different labeling methods used. They used conventional exogenous labeling with a radiotracer, whereas we used endogenous labeling with stable isotope amino acids. In their study, it is not clear whether the radiolabeled apoA-I is an autologous or a homologous protein, and, if the latter is the case, injected apoA-I is not the subject’s own apoA-I, which would in turn behave differently from endogenous apoA-I. In addition, because they used exogenous labeling, the tracer apoA-I may undergo a modification during the labeling procedure, which again causes a potential error in their study. Overall, a kinetic study using endogenous labeling techniques needs to be performed in predialysis patients to conclude their abnormality of HDL. Nonetheless, we believe that our data provide new and concrete information on apoA-I and apoA-II metabolism in ESRD-HD patients.

HDL are heterogeneous in apolipoprotein composition and comprise two major HDL subclasses: particles that contain apoA-I but not apoA-II (LpA-I) and those that contain both apoA-I and apoA-II (LpA-I:A-II) (52). We have previously shown that apoA-I on LpA-I is catabolized faster than apoA-I on LpA-I:A-I-II (41). Furthermore, we found the LpA-I levels to be inversely correlated with the rate of apoA-I catabolism, whereas the LpA-I:A-I-II levels closely correlated with the rate of apoA-II production in normolipidemic subjects (37). These results thus indicate that apoA-I and apoA-II (i.e., LpA-I and LpA-I:A-I-II) have distinct metabolic pathways. Taken together, we propose that HDL metabolism in ESRD-HD patients is altered as follows. The decreased apoA-II production in ESRD-HD patients limits the ability of apoA-I to associate with apoA-II, thus altering HDL composition as LpA-I predominant. LpA-I is, in turn, catabolized at a faster rate than normal LpA-I, as evidenced by the increased rate of catabolism. The increased proportion of LpA-I relative to LpA-I:A-I-II is indeed consistent with previous observations by us (6) and others (53).

There are several limitations in the present study. Although not significant, age and gender were not strictly matched between control subjects and ESRD-HD patients. In general, catabolic rates of apoA-I and apoA-II are somewhat faster in men than in women (37). This finding, together with the fact that the ESRD-HD patients included two women, indicates that difference in apoA-I FCR would have been greater if some control subjects had been women. The effect of age is considered to be minimal relative to gender. Second, the sample size of the study subjects may not be large enough to draw a solid conclusion. This is certainly an inherent limitation of in vivo kinetic study, which involves full collaboration of study subjects as well as labor- and time-intensive procedures to determine kinetic parameters. In this study, we carefully selected ESRD-HD patients who had normal plasma TG concentrations to minimize the potential confounding effects of hypertriglyceridemia on HDL metabolism. Therefore, we believe that the present study reasonably represents the underlying metabolic defects of HDL in normotriglyceridemic ESRD-HD patients. Although further accelerated apoA-I FCR are likely to be expected, a caution should be exercised to apply our results to hypertriglyceridemic ESRD-HD patients, and this requires further study. Third, steady-state condition, which is a prerequisite for the kinetic study, may not be maintained in ESRD-HD patients who lack normal kidney function, but we found that apolipoprotein concentrations did not vary significantly during the study period, thus indicating that perturbation of lipoprotein metabolism is minimal during the study period. Finally, we did not directly measure PV by the tracer dilution method but instead used a formula to correct PV by using Hct to calculate PR. Although the resulted PV expansion in our ESRD-HD patients is comparable to a recent result obtained by the tracer dilution method (25), PR should be interpreted with caution.

In summary, the present study established that decreased levels of apoA-I are due solely to increased rates of catabolism, whereas reduced apoA-II levels are due to decreased rates of production in normotriglyceridemic ESRD-HD patients. This differential modulation of two major apolipoproteins within HDL should provide a basis to help develop a better strategy to ameliorate abnormal HDL metabolism and therefore prevent cardiovascular events in these high-risk patients.

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