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CLINICAL INVESTIGATION

Serum apolipoprotein profile of patients with chronic renal failure

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Serum apolipoprotein profile of patients with chronic renal failure. Serum concentrations of apolipoproteins A-I, A-II, B, C-I, C-II, C-III and E were determined by electroimmunoassay in 56 patients with chronic renal failure (CRF) in the predialytic phase. The results were compared with those obtained in asymptomatic normolipidemic subjects, patients with type IV hyperlipoproteinemia, and patients with type II diabetes mellitus. CRF patients had reduced concentrations of ApoA-I and ApoA-II, normal levels of ApoB and ApoC-I, and increased concentrations of ApoC-II and, in particular, of ApoC-III. There was a significant reduction in the levels of ApoE, especially in male patients. In comparison with type IV, hyperlipoproteinemic patients, CRF patients had lower concentrations of ApoA-I, ApoA-II, ApoB, ApoC-I and, particularly, ApoE; there was no difference in ApoC-III levels reflecting the hypertriglyceridemia common to both disorders. Similar but less marked differences were also found in comparison with type II diabetics. The findings suggest that in CRF, the accumulation of ApoC-III-enriched lipoprotein particles accompanied by a moderate hypertriglyceridemia may be caused more probably by an impaired catabolism than overproduction of triglyceride–rich lipoproteins. CRF patients with vascular disease tended to have higher serum concentrations of triglycerides, cholesterol and ApoB and lower ApoA-I/ApoC-III and ApoA-I/ApoB ratios than patients without vascular disease.

The recognized importance of plasma apolipoproteins for the structural integrity and functional specificity of lipoprotein particles has led to the concept of apolipoprotein profiling as a new means of recognizing and classifying dyslipoproteinemic states [1, 2]. The usefulness of apolipoprotein profiling has been further enhanced by recent studies indicating that apolipoproteins may be better predictors of coronary artery disease than lipids [3–7].

In addition to a high frequency of hypertriglyceridemia, chronic renal failure (CRF) is associated with other risk factors for the development of vascular disease including hypertension, hyperuricemia and hyperparathyroidism [8–10]. It is still uncertain whether the uremic patients are more prone to develop atherosclerotic disease [11], but a more rapid progression of already existing disease is often observed [12]. The role of the usually moderate hypertriglyceridemia in this disease process is difficult to assess. In nonuremic patients, triglyceride elevation is most frequently associated with increased levels of triglyceride–rich, very low density lipoproteins (VLDL) which represent a mixture of particles differing in density, size, charge distributions and apolipoprotein composition [13–17]. In normolipidemic subjects, these particles contain various combinations of apolipoproteins B, C and E with the major lipoprotein species (LP-B:C:E) characterized by the presence of all three apolipoproteins [18, 19].

In contrast to numerous studies on the plasma lipid profile in CRF [20–23], there are only a few reports on the direct measurement of some apolipoproteins in uremic patients [24–30]. We have already shown that patients with various types of familial hypo- and hyperlipoproteinemias exhibit characteristic apolipoprotein profiles that may be used either as valuable diagnostic and monitoring tools, or as clues about the chemical nature of accumulating lipoprotein particles as defined by their apolipoprotein composition [1, 2, 31]. To establish whether CRF is also characterized by a specific apolipoprotein profile, we have determined the levels of apolipoproteins A-I, A-II, B, C-I, C-II, C-III, and E in a well defined group of patients with chronic renal failure before dialysis, and evaluated their possible relation to clinical vascular disease. The apolipoprotein profile of patients with CRF was also compared with apolipoprotein profiles of two other types of moderate hypertriglyceridemia, that is, type IV hyperlipoproteinemia and type II diabetes mellitus.

Methods

Patients

Fifty–six Swedish patients with chronic renal failure were investigated. Thirty–three male patients had a mean age of 44.8 ± 14.6 years and twenty–three female patients had a mean age of 51.0 ± 11.9 years. The renal diagnosis was chronic glomerulonephritis in seventeen patients, chronic interstitial nephritis in twenty–four patients, polycystic kidney disease in twelve patients, and other or unknown diagnosis in three patients. All patients had advanced renal failure with mild or moderate uremic symptoms. The patients were on an ad libitum diet and the individual food intake was not monitored. The mean body mass index (BMI) was 25.1 ± 4.7 kg/m^2 and the mean glomerular filtration rate was 8.1 ± 3.6 ml/min/1.73 m^2 BSA.

Forty–eight patients were treated with beta blocking agents for hypertension. Since treatment with beta blocking agents has been reported to affect lipoprotein levels, patients on beta

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blocking treatment ($N = 46$) and patients without beta blocking treatment ($N = 8$) were separated, but no significant difference could be found in any variable between the two groups of patients. Patients with diabetes mellitus, thyroid disorders or treatment with other drugs known to influence lipid metabolism were excluded from the study. The patients were treated with diuretics, antihypertensive drugs and sodium bicarbonate as appropriate. No patient received steroid or immunosuppressive treatment.

Control subjects

Two groups of control subjects were recruited among healthy, asymptomatic men and women. One group, referred to as "American controls," consisted of 74 white men and 82 white women with a mean age of 38.6 ± 16.5 years. They were classified as normolipidemics according to the recommended criteria of the Lipid Research Clinics of the National Institutes of Health, Bethesda, Maryland [32] and were employees of the Oklahoma Medical Research Foundation.

The second control group, referred to as "Swedish controls," consisted of nine men and eight women with a mean age of 37.5 ± 8.2 years. They were all employees of the Department of Medicine, University of Göteborg, Sweden. There were no differences in serum lipids, lipoprotein, cholesterol or apolipoprotein values between the two control groups. Therefore the two groups were pooled when evaluating differences with the patient population.

Reference populations

Two American hypertriglyceridemic populations were recruited for comparison with the uremic patients. One group consisted of thirteen non-obese normotensive men aged 57.8 ± 5.4 years with type IV hyperlipoproteinemia, but otherwise healthy, asymptomatic and consuming a regular American diet. Their mean serum triglyceride value of 4.1 ± 1.6 mmol/liter was not significantly different from that of the uremic male patients.

The second group consisted of 58 men and 107 women aged 55.3 ± 12.7 years with type II diabetes mellitus with a mean duration of disease of 6.8 ± 6.8 years. The mean body mass index (BMI) was 31.6 ± 6.3 kg/m^2 and 61% of the patients were hypertensive (blood pressure >140/90 mm Hg). Thirty–five percent of the patients were treated with insulin, 43% with oral hypoglycemic agents and 22% with diet only. The mean fasting blood glucose was 201 ± 70 mg/dl and the mean HbA_1 value was 11.5 ± 3.6%. Although elevated, the mean serum triglyceride value of 2.4 mmol/liter was lower than that of the uremic patients.

Methods

Lipid and apolipoprotein analyses

Blood samples were drawn by antecubital venipuncture after an overnight fast of at least 12 hours. In patients and Swedish controls, serum cholesterol was determined according to Cramér and Isaksson [33], and serum triglyceride was estimated by the method of Carlson [34]. HDL-cholesterol was determined in the supernate after precipitation with heparin-$MnCl_2$ [35]. VLDL-cholesterol was assayed in the supernate after ultracentrifugation at density 1.006 g/ml, and LDL-cholesterol was estimated as the difference between the cholesterol content of the infranate at density 1.006 g/ml and HDL cholesterol. Total cholesterol, triglyceride and cholesterol contents of VLDL, LDL and HDL of American controls were measured according to the procedures used by the Lipid Research Clinics Program [32]. Apolipoprotein analyses were carried out by electroimmunoassays according to previously described procedures for ApoA-I and ApoA-II [36], ApoB [37], ApoC-I [38], ApoC-II [38], ApoC-III [39] and ApoE [40]. The heparin precipitated (HP = VLDL + LDL) and heparin non-precipitated (HS = HDL) lipoproteins for measurement of ApoC-III-HS/ApoC-III-HP ratio [41] were isolated by a modification [42] of the heparin-$MnCl_2$ method [43] in that a Mn^{++} concentration of 0.092 M was used instead of 0.046 M as originally described.

Serum samples collected in Göteborg from patients and Swedish controls were shipped by air freight from Göteborg to Oklahoma City for the determination of apolipoproteins. The analyses of apolipoproteins were carried out three to four days after the blood collection. All serum samples contained Thiomerosal (0.1 mg/ml) as a preservative.

Cardiovascular disease

The case records of all patients were reviewed for clinical evidence of vascular disease within five years of sampling for apolipoprotein determination. Clinical vascular disease was judged to be present in cases of myocardial infarction, severe coronary atherosclerosis (coronary angiography, exercise ECG, autopsy), disabling angina pectoris, cerebral vascular lesion (stroke or symptoms of cerebral ischemia) or peripheral arterial insufficiency requiring surgery. Suspected vascular disease was judged to be present in cases with moderate effort angina pectoris, cardiac arrythmias not explained by electrolyte disturbances or drug treatment and sudden death. The distribution of main vascular complications among the patients was as follows:

	Male	Female
Myocardial infarction	4	2
Severe coronary atherosclerosis, without myocardial infarction	1	2
Disabling angina pectoris	1	—
Cerebral vascular lesion	1	3
Peripheral arterial insufficiency	2	—
Moderate angina pectoris	4	3
Atrial fibrillation	—	1
Sudden death	2	—

Nine male and six female patients had well documented clinical vascular disease while six male and four female patients were suspected of having vascular disease. Taken together 45% of the male and 43% of the female patients had definite or suspected vascular disease.

Statistical methods

Means, standard deviation and standard errors of the means were calculated by conventional methods. Wilcoxon's two sample tests was used for testing the significance of differences between means, and the correlation coefficients were calculated by Spearmans rank correlation method.

Results

Serum triglycerides and cholesterol were significantly higher in patients than either the American or Swedish controls (Table

Table 1. Serum cholesterol, triglycerides and cholesterol distribution in VLDL, LDL and HDL in patients with chronic renal failure and American and Swedish control subjects (values are given as mean ± SD)

Subjects	Serum		VLDL	LDL	HDL
	Triglyceride	Cholesterol		Cholesterol	
	mmol/liter			*mmol/liter*	
All patients	3.22 ± 2.05[d]	6.28 ± 1.40[d]	1.38 ± 1.43[d]	3.43 ± 1.27	1.14 ± 0.34[b]
	(*N* = 56)	(*N* = 56)	(*N* = 30)	(*N* = 30)	(*N* = 35)
American controls	0.98 ± 0.37	4.83 ± 0.90	0.31 ± 0.15	3.19 ± 0.80	1.40 ± 0.35
	(*N* = 149)	(*N* = 149)	(*N* = 109)	(*N* = 108)	(*N* = 116)
Swedish controls	0.93 ± 0.28	5.07 ± 0.67	0.42 ± 0.19	3.20 ± 0.69	1.43 ± 0.48
	(*N* = 17)	(*N* = 17)	(*N* = 5)	(*N* = 5)	(*N* = 13)
Male patients	3.43 ± 2.18[d]	6.18 ± 1.51[d]	1.51 ± 1.52[d]	3.22 ± 1.25	1.19 ± 0.36
	(*N* = 33)	(*N* = 33)	(*N* = 21)	(*N* = 21)	(*N* = 23)
Male American controls	1.06 ± 0.40	4.83 ± 0.89	0.32 ± 0.16	3.31 ± 0.88	1.21 ± 0.23
	(*N* = 69)	(*N* = 69)	(*N* = 48)	(*N* = 48)	(*N* = 49)
Female patients	2.90 ± 1.85[d]	6.44 ± 1.22[d]	1.10 ± 1.14[d]	4.06 ± 1.61[a]	1.14 ± 0.31[c]
	(*N* = 23)	(*N* = 23)	(*N* = 9)	(*N* = 9)	(*N* = 12)
Female American controls	0.93 ± 0.35	4.83 ± 0.92	0.29 ± 0.13	3.10 ± 0.71	1.55 ± 0.36
	(*N* = 80)	(*N* = 80)	(*N* = 61)	(*N* = 60)	(*N* = 67)

Significance of difference between patients and American controls:
[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$
[d] $P < 0.0001$

Table 2. Serum apolipoproteins in patients with chronic renal failure and American and Swedish controls (Values are given as mean ± SD)

Subjects	Serum apolipoproteins *mg/dl*						
	A-I	A-II	B	C-I	C-II	C-III	E
All patients	90.0 ± 24.2[c]	43.3 ± 8.7[c]	109.3 ± 44.8	9.3 ± 2.9	4.4 ± 2.0[a]	18.5 ± 6.3[c]	8.5 ± 4.4[b]
	(*N* = 35)	(*N* = 18)	(*N* = 56)	(*N* = 33)	(*N* = 14)	(*N* = 55)	(*N* = 43)
American controls	136.0 ± 27.5	69.0 ± 14.1	99.0 ± 26.8	9.0 ± 2.6	3.2 ± 0.9	8.3 ± 2.4	10.9 ± 3.9
	(*N* = 155)	(*N* = 128)	(*N* = 155)	(*N* = 37)	(*N* = 61)	(*N* = 156)	(*N* = 153)
Swedish controls	144.5 ± 40.1	63.7 ± 13.6	97.0 ± 20.3	8.1 ± 2.0	3.2 ± 0.6	9.1 ± 2.7	11.1 ± 2.6
	(*N* = 17)	(*N* = 16)	(*N* = 16)	(*N* = 5)	(*N* = 10)	(*N* = 16)	(*N* = 16)
Male patients	80.2 ± 20.8[c]	44.9 ± 7.9[c]	105.5 ± 49.9	9.4 ± 3.2	4.4 ± 2.3	18.6 ± 7.2[c]	7.1 ± 4.6[b]
	(*N* = 19)	(*N* = 11)	(*N* = 33)	(*N* = 22)	(*N* = 9)	(*N* = 32)	(*N* = 23)
Male American controls	124.0 ± 22.6	62.6 ± 11.5	106.3 ± 28.8	8.1 ± 2.4	3.2 ± 0.9	8.1 ± 2.7	10.2 ± 3.3
	(*N* = 74)	(*N* = 55)	(*N* = 73)	(*N* = 24)	(*N* = 28)	(*N* = 74)	(*N* = 73)
Female patients	101.6 ± 23.4[c]	40.8 ± 9.9[c]	114.8 ± 36.6[a]	9.0 ± 2.3[a]	4.5 ± 1.6	18.3 ± 5,0[c]	10.0 ± 3.8
	(*N* = 16)	(*N* = 7)	(*N* = 23)	(*N* = 11)	(*N* = 5)	(*N* = 23)	(*N* = 20)
Female American controls	146.3 ± 27.6	74.0 ± 16.3	93.2 ± 23.7	10.5 ± 2.5	3.2 ± 1.0	8.4 ± 2.0	11.6 ± 4.3
	(*N* = 81)	(*N* = 73)	(*N* = 82)	(*N* = 13)	(*N* = 33)	(*N* = 82)	(*N* = 80)

Significance of difference between patients and American controls:
[a] $P < 0.05$
[b] $P < 0.001$
[c] $P < 0.0001$

1). The triglyceride levels were markedly increased with 66% of the patients having triglyceride values above 2.2 mmol/liter. The elevated levels of triglycerides and cholesterol were reflected in the elevation of the VLDL cholesterol both in male and female patients. The female patients also had an increase of LDL and a decrease of HDL cholesterol.

Apolipoprotein A-I and A-II were significantly lower in patients than in either Swedish or American controls (Table 2). Similary to control subjects, the concentration of ApoA-I in male patients was lower than in female patients. ApoB levels were slightly increased in female patients but not in males. Female but not male patients also had slightly lower levels of ApoC-I. Apolipoprotein C-II was slightly elevated in all patients, reaching statistical significance only when compared to all American controls. In contrast, both male and female patients had a highly significant elevation of ApoC-III levels in comparison with both control groups. A statistically significant decrease in the concentration of ApoE in the patient population was primarily due to a significant decrease of this apolipoprotein in the male patients.

The ApoA-I/ApoC-III and ApoB/ApoC-III ratios (Table 3) were the most significant discriminators between the patients and the controls for both sexes. There was also a significant reduction of the ApoA-I/ApoB ratio in the patients.

The most striking difference between the uremic patients and the type IV patients with a similar degree of hypertriglyceridemia was a pronounced decrease of ApoE levels in the uremic population (Table 4). The uremic male patients had significantly lower levels of ApoA-I, ApoA-II, ApoB and ApoC-II than patients with type IV disease. Although the mean triglyceride

Table 3. Ratios of serum apolipoproteins in patients with chronic renal failure and American and Swedish controls

Subjects	ApoA-I/ ApoB	ApoA-I/ ApoC-III	ApoB/ ApoC-III	ApoC-III-HS/ApoC-III-HP
All patients	0.79 ± 0.4[a] (*N* = 35)	6.15 ± 3.3[a] (*N* = 35)	6.46 ± 3.0[a] (*N* = 55)	0.55 ± 0.4[a] (*N* = 19)
American controls	1.46 ± 0.5 (*N* = 154)	17.3 ± 4.7 (*N* = 155)	12.6 ± 4.0 (*N* = 155)	2.07 ± 1.1 (*N* = 116)
Swedish controls	1.45 ± 0.6 (*N* = 15)	15.8 ± 6.2 (*N* = 15)	11.1 ± 2.6 (*N* = 16)	1.83 ± 0.8 (*N* = 11)
Male patients	0.73 ± 0.4[a] (*N* = 19)	5.83 ± 3.4[a] (*N* = 19)	6.27 ± 3.1[a] (*N* = 32)	0.34 ± 0.2[a] (*N* = 10)
Male American controls	1.25 ± 0.4 (*N* = 73)	16.5 ± 4.8 (*N* = 74)	13.9 ± 4.1 (*N* = 73)	1.85 ± 1.3 (*N* = 50)
Female patients	0.86 ± 0.3[a] (*N* = 16)	6.53 ± 3.2[a] (*N* = 16)	6.73 ± 3.1[a] (*N* = 23)	0.78 ± 0.4[a] (*N* = 9)
Female American controls	1.64 ± 0.5 (*N* = 81)	18.0 ± 4.5 (*N* = 81)	11.6 ± 3.8 (*N* = 82)	2.23 ± 0.8 (*N* = 66)

ApoC-III-HS/ApoC-III-HP is the ratio of ApoC-III in heparin supernates (HS, heparin non-precipitable lipoproteins) and heparin precipitates (HP, heparin precipitable lipoproteins). Values are given as mean ± SD.

[a] Significance of difference between patients and American controls $P < 0.01$

level was slightly lower in the uremic patients, the mean ApoC-III value tended to be higher than in the type IV patients. There was no difference in the apolipoprotein ratios between the uremic patients and patients with type IV hyperlipoproteinemia.

Despite lower cholesterol values, patients with type II diabetes mellitus had significantly higher concentrations of apolipoproteins A-I, B and E than patients with CRF (Table 5). On the other hand, uremic patients had significantly higher levels of ApoC-III relative to serum triglyceride concentrations than diabetics.

The distribution of ApoC-III in HDL vs LDL and VLDL, reflected in the apo C-III-HS/apo C-III-HP ratio (Table 3), showed a marked increase of ApoC-III in the lower density classes, which was more pronounced in the uremics than in patients with type IV disease or diabetes.

The mean ApoA-I/ApoC-III and ApoB/ApoC-III ratios were considerably higher in the diabetics than in patients with CRF (16.7 vs. 6.2 and 15.1 vs. 6.5).

Correlations among variables

Triglycerides were highly significantly correlated with VLDL-cholesterol, ApoC-II, ApoC-III and ApoC-III in heparin–precipitated lipoproteins, and less strongly but significantly with ApoB, ApoC-I, ApoE and total cholesterol levels; there was a significant negative correlation between triglycerides and HDL-cholesterol. ApoB levels were significantly correlated with ApoE levels. ApoA-I was significantly correlated with ApoA-II but not with HDL-cholesterol or any other lipid or apolipoprotein.

Vascular disease

The selection of patients depended on their availability for the study with a special interest towards patients with hypertriglyceridemia in renal failure. For this reason, the present patient group cannot be used to determine the incidence of vascular disease in a uremic population. Patients with definite vascular disease had a higher level of serum cholesterol (7.1 vs. 5.8 mmol/liter, $P < 0.05$) and ApoB (138 vs. 97 mg/100 ml, $P < 0.05$) and a lower ratio of (7.2 vs. 15.0, $P < 0.05$) ApoA-I/ApoC-III in VLDL + LDL (heparin precipitate) in comparison with patients without evidence of vascular disease (Table 6). The ApoC-III values were not significantly higher in the vascular disease patients (21.0 vs. 17.9, $P = 0.07$). There were no significant differences in other variables between the two groups of patients. Patients with both the ApoA-I/ApoC-III ratio below normal −2 SD (that is, <7) and ApoB levels above normal +2 SD (that is, 150 mg/100 ml) were studied for presence of vascular disease, and in this group eight out of ten patients had definite or suspected vascular disease. Thus, patients with elevated ApoB level and low ApoA-I/ApoC-III ratios seemed to be prone to develop vascular disease in renal failure.

Discussion

The well established high incidence of hypertriglyceridemia [20–24] in male and female patients with CRF has again been demonstrated in this study. Triglyceride levels were well correlated with the levels of VLDL-cholesterol and, among apolipoproteins, with the concentrations of ApoC-II and ApoC-III. The female patients had higher concentrations of LDL-cholesterol than male patients possibly due to a more efficient conversion of their VLDL to LDL. This interpretation is also supported by the fact that female patients had lower levels of VLDL-cholesterol and higher values for ApoC-III-HS/ApoC-III-HP ratios than male patients.

The most characteristic feature of the apolipoprotein profile in uremic patients, in comparison with that of control subjects, was the marked elevation of ApoC-III levels. Increased concentrations of serum-ApoC-III reflected an absolute and relative elevation of this apolipoprotein in heparin–precipitable lipoproteins (VLDL + LDL). There was no comparable change in the mean levels of apolipoproteins B, C-I, C-II and E, the other major apolipoproteins of heparin–precipitable lipoproteins. Furthermore, the male patients had normal concentrations of ApoB while a slight increase was found in the female patients. The ApoE levels were significantly lower than controls in male but not in female patients. However, female patients also tended to have lower concentrations of ApoE than the corresponding controls. Earlier studies of apolipoproteins in CRF have not covered the whole spectrum of apolipoproteins and have almost exclusively been performed in patients on hemodialysis [25–29, 44–46) which might explain some discrepancies with our findings, especially with respect to ApoE levels. ApoB has been reported to be either subnormal [27, 29] or slightly elevated [44, 47]. The findings of Staprans, Feltz and Zacherle [44] of a reduced ApoC-II to ApoC-III ratio could not be confirmed in our study. The significantly reduced levels of ApoA-I and ApoA-II were well correlated in patients with CRF, indicating a decrease in the concentration of lipoprotein particles containing both ApoA-I and ApoA-II. Similar results have been reported by Savdie et al [46]. In other studies, levels of ApoA-I have been found to be similar or slightly reduced [27–29, 45, 47] in comparison to those of control subjects. The selection of patients and control subjects may be responsible, at least in part, for these slightly divergent results.

Table 4. Serum lipids and apolipoproteins in male patients with chronic renal failure and male subjects with type IV hyperlipoproteinemia (values are given as mean ± SD)

Subjects	Serum lipids *mmol/liter*		Serum apolipoproteins *mg/dl*					
	Triglyceride	Cholesterol	A-I	A-II	B	C-II	C-III	E
Chronic renal failure	3.43 ± 2.18 (N = 33)	6.18 ± 1.51 (N = 33)	80.2 ± 20.8[c] (N = 19)	44.8 ± 7.9[c] (N = 11)	105.5 ± 49.9[b] (N = 33)	4.4 ± 2.3[a] (N = 9)	18.6 ± 7.2 (N = 32)	7.1 ± 4.6[d] (N = 23)
Type IV hyperlipoproteinemia	4.09 ± 1.60 (N = 12)	6.03 ± 0.94 (N = 12)	116.7 ± 22.0 (N = 12)	61.6 ± 9.0 (N = 12)	136.8 ± 28.0 (N = 12)	7.0 ± 2.0 (N = 12)	17.1 ± 4.8 (N = 12)	20.5 ± 6.7 (N = 12)

Significance of difference:
[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$
[d] $P < 0.0001$

Table 5. Serum lipids and apolipoproteins in patients with chronic renal failure and type II diabetes mellitus (values are given as mean ± SD)

Subjects	Serum		Serum apolipoproteins			
	Triglyceride	Cholesterol	A-I	B	C-III	E
Chronic renal failure	3.22 ± 2.05[c] (N = 56)	6.28 ± 1.40[c] (N = 56)	90.0 ± 24.2[c] (N = 35)	109.3 ± 44.8[b] (N = 18)	18.5 ± 6.3[c] (N = 55)	8.5 ± 4.4[a] (N = 43)
Type II diabetes mellitus	2.37 ± 2.16 (N = 138)	5.34 ± 1.18 (N = 138)	127.4 ± 34.1 (N = 165)	129.8 ± 39.2 (N = 165)	11.9 ± 7.5 (N =165)	11.4 ± 7.5 (N = 165)

Significance of difference:
[a] $P < 0.05$
[b] $P < 0.001$
[c] $P < 0.0001$

Table 6. Serum lipids and apolipoproteins in chronic renal failure patients without clinical evidence of vascular disease and in patients with clinical evidence of vascular disease (values are given as mean ± SD)

Subjects	Serum		Serum apolipoproteins (mg/dl)					
	Triglyceride	Cholesterol	A-I	A-II	B	C-II	C-III	E
No vascular disease	3.06 ± 2.24 (N = 31)	5.97 ± 1.30 (N = 31)	90.3 ± 23.4 (N = 19)	40.8 ± 4.6 (N = 11)	97.4 ± 33.2 (N = 31)	4.4 ± 2.2 (N = 9)	17.9 ± 6.6 (N = 30)	8.3 ± 4.9 (N = 26)
Vascular disease	3.92 ± 2.09 (N = 15)	7.06 ± 1.44* (N = 15)	86.4 ± 25.3 (N = 10)	42.1 ± 10.4 (N = 5)	137.9 ± 51.0* (N = 15)	4.2 ± 2.0 (N = 4)	21.0 ± 6.2 (N = 15)	9.3 ± 2.8 (N = 10)

Significance of difference:
[a] $P < 0.05$

The unique characteristics of the apolipoprotein profile of the CRF patients are further underlined by the comparison with the reference populations with hypertriglyceridemia as a common denominator which, to our knowledge, has not been demonstrated earlier. These patients also had an elevation of ApoC-III as a consequence of hypertriglyceridemia, but they differed from CRF patients by having marked elevation of ApoE and a moderate increase of ApoB. Furthermore, despite higher HDL-cholesterol values, the ApoA-I, and A-II levels were even more reduced in the uremic patients than in patients with type IV hyperlipoproteinemia or type II diabetes.

These results show that CRF patients have a characteristic apolipoprotein profile in comparison with both the normal subjects and patients with other forms of hypertriglyceridemia. Whereas ApoC-III values cannot be used as a differentiating criterion, the apoliproteins A-I, A-II, B and E are more suitable than serum cholesterol or triglycerides for that purpose. These differences also suggest that the underlying metabolic deffects in CRF are not the same as in other forms of hypertriglyceridemia.

Although apolipoprotein profiles of patients with primary or secondary hyperlipoproteinemias cannot be utilized as absolute diagnostic criteria, they may offer very useful clues about the nature of accumulating lipoprotein particles [1, 2]. In patients with CRF, the significant correlation between ApoC-III and serum triglyceride and VLDL-cholesterol and a disproportionate increase in the levels of ApoC-III, in comparison with the levels of ApoC-I and ApoC-II, suggest the accumulation of triglyceride–rich particles with ApoC-III as one of their major protein constituents. A positive and highly significant correlation between ApoB and ApoE levels, in the absence of any significant changes in the absolute concentration of these two apolipoproteins, suggests the possible presence of lipoprotein particles characterized by ApoB and ApoE as the main components of their protein moiety. Preliminary results of our ongoing studies on the identification of discrete lipoprotein particles in patients with CRF indicate the occurrence of both types of these lipoproteins. The ApoB and ApoE containing particles may be similar to the late pre-beta lipoproteins (LP-β) detected by agarose electrophoresis at high frequency in patients with CRF [48] and to the cholesterol ester–rich beta, very low density lipoproteins (β-VLDL) found in patients with type III hyperlipoproteinemia [49].

The surprising finding of low ApoE values is not readily explained. Blume et al [50] have recently suggested that the kidney might be a source for the production of apolipoprotein E and the possibility that a reduced renal parenchyma contributes less to the serum pool of ApoE than in normal subjects should be further explored.

A number of studies have indicated that both an impaired removal and an increased production of triglyceride–rich lipoprotein particles contribute to the hypertriglyceridemia of chronic renal failure [22, 26, 46, 51, 52]. Our earlier studies indicate, however, that a defective removal mechanism may be a more significant contributing factor than an increased production of triglyceride–rich lipoproteins [22]. This view is supported by studies demonstrating reduced plasma postheparin–lipolytic activities and a decreased triglyceride clearance in CRF [23, 53–57]. Moreover, findings such as reduced fractional turnover rates of VLDL triglyceride [45, 51] and absolute and/or relative increases of triglyceride in VLDL, LDL and HDL [21, 26] the identification of ApoB-48 in VLDL, increased levels of ApoA-IV in VLDL and LDL, and ApoC and ApoE in LDL [26] are also suggesting an incomplete degradation and/or uptake of triglyceride–rich lipoproteins and consequent accumulation of remnant particles. Recently Gonen et al [58] have reported that LDL from dialysis patients have abnormal composition and are less readily taken up and degraded by fibroblasts than normal LDL.

Our finding of low ApoE concentrations in CRF might indicate the formation of triglyceride–rich lipoprotein particles with abnormal apolipoprotein characteristics. A relative deficiency of ApoE could make these remnant particles a less attractive substrate for further degradation and, as a consequence, with result in their accumulation in the plasma.

The triglyceride elevation found in familial hypertriglyceridemia [58, 59] and diabetes mellitus [60, 61] has been attributed to the overproduction of triglyceride–enriched VLDL. These patients are not only characterized by elevated levels of ApoC-III but also by increased concentrations of ApoB and ApoE [62]. Since these two latter apolipoproteins are not elevated in most patients with CRF it is less likely that overproduction of triglyceride–rich VLDL plays an important role in the development of uramic dyslipoproteinemia. Further insight may be gained by measuring the apolipoprotein distribution in lipoprotein particles.

One of the main reasons for studying uremic hyperlipoproteinemia has been its possible relationship to and role in the development of atherosclerosis. It was therefore of considerable interest to establish whether patients with CRF and clinical evidence of atherosclerosis exhibited any particular traits in their apolipoprotein profile. Results showed that patients with vascular disease tend to have higher concentrations of plasma cholesterol and ApoB and lower values for ApoA-I/ApoC-III and ApoA-I/ApoB ratios than patients without vascular disease; patients with documented vascular disease also had higher concentrations of serum triglyceride and ApoC-III, but these increases did not reach statistical significance. In an analysis of cardiovascular risk factors in dialysis patients, Hahn et al [9] observed that patients with cardiovascular disease had higher serum triglyceride values and lower HDL-cholesterol, but no change in serum cholesterol when compared to patients without disease. These initial results suggest the usefulness of lipid and apolipoprotein profiles as potential predictors for coronary artery disease in patients with CRF, but additional cross–sectional and prospective studies are warranted in order to fully realize this potential.

In summary, the main characteristics of apolipoprotein profile in patients with CRF are significantly decreased concentrations of apolipoproteins A-I, A-II and E and a significantly increased concentration of ApoC-III. In contrast to the apolipoprotein profile of uremic patients, patients with primary hypertriglyceridemia (phenotype IV) have significantly higher levels of ApoB and ApoE, while patients with insulin independent diabetes mellitus have significantly higher concentrations of ApoA-I and ApoB and a lower concentration of ApoC-III. These results indicate different underlying defects in these three types of moderate hypertriglyceridemia and suggest that a catabolic impairment leading to the accumulation of remnant lipoprotein particles may be the main derangement of lipid transport in CRF. A characteristic apolipoprotein profile reflecting the degree and extent of accumulating remnant particles appears to be a potential predictor of coronary artery disease in patients with CRF.

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