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Apolipoprotein A-IV Serum Concentrations Are Elevated in Patients with Mild and Moderate Renal Failure

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Abstract. Cell culture studies and investigations in mice that overexpress either human or mouse apolipoprotein A-IV (apoA-IV) revealed anti-atherogenic properties of apoA-IV. An association between low apoA-IV concentrations and coronary artery disease in humans was demonstrated; therefore, apoA-IV may also play an antiatherogenic role in humans. Because apoA-IV is markedly elevated in dialysis patients, patients with the earliest and modest stages of renal impairment were studied to assess the association of apoA-IV with GFR and atherosclerotic complications. GFR was measured by the use of iohexol in 227 non-nephrotic patients with different degrees of renal impairment. ApoA-IV increased significantly with decreasing GFR and was already elevated in earliest stages of renal disease (GFR $>$ 90 ml/min per 1.73 m^2). Multiple linear regression analysis identified renal function parameters (GFR, creatinine, and urea) as the most important determinants of apoA-IV levels in serum of these patients. Twenty-six patients had already experienced 36 atherosclerotic events. Logistic regression analysis identified three variables associated with atherosclerotic complications: age, apoA-IV, and gender. Each 1 mg/dl increase of apoA-IV decreased the odds ratio for an atherosclerotic complication by 8% (P = 0.011). The data clearly show that the anti-atherogenic apoA-IV starts to increase during the earliest phases of renal insufficiency, which makes apoA-IV an early marker of renal impairment.

The glycoprotein apolipoprotein A-IV (apoA-IV) is almost exclusively produced in intestinal human enterocytes and secreted into the lymph (1). It is a structural protein of chylomicrons; the mean plasma levels are approximately 15 mg/dl (2). In the fasting state, the majority of apoA-IV circulates in plasma as part of a lipid-poor, small HDL-like particle that does not contain apoA-I (3,4).

The physiologic function of apoA-IV is controversial. It was postulated to be involved in fat absorption (5) and regulation of food intake (6), but both findings were not confirmed in genetically modified mice (7,8). *In vitro* studies reported convincing evidence that apoA-IV participates in several steps of the reverse cholesterol transport pathway, which removes cholesterol from peripheral cells and directs it to liver and steroidogenic organs for metabolization (9–11). ApoA-IV activates lecithin:cholesterol acyltransferase (12,13) and modulates the activation of lipoprotein lipase (14) as well as the cholesterylester transfer protein–mediated transfer of cholesteryl esters from HDL to LDL (15), which suggests that apoA-IV may represent an anti-atherogenic factor. This is supported by studies in both humans and mice. Fat-fed mice that overexpress either human (16) or mouse apoA-IV (17) developed significantly fewer atherosclerotic lesions in the aorta than control mice. This was even observed when apoA-IV was overexpressed in apoE-deficient mice—that is, in a highly atherogenic background (16). In line with these data, we recently demonstrated for the first time in two independent populations that patients with angiographically verified coronary artery disease (CAD) have markedly lower apoA-IV concentrations when compared with controls (18).

A few studies have investigated apoA-IV in renal patients. Nestel *et al.* (19) as well as Seishima and Muto (20) described markedly elevated apoA-IV concentrations in small groups of patients receiving hemodialysis and continuous ambulatory

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peritoneal dialysis. This was confirmed by Dieplinger *et al.* (21), who observed significant differences in the plasma distribution of apoA-IV with an accumulation of apoA-IV in HDL when compared with controls. They suggested that this altered distribution reflects impaired reversed cholesterol transport in these patients (22). In a large multicenter study that included 534 patients receiving hemodialysis and 168 patients receiving continuous ambulatory peritoneal dialysis, we observed about twofold elevated apoA-IV concentrations when compared with controls (23). As soon as end-stage renal disease was reached, apoA-IV concentrations did not differ between the two dialysis treatment modalities or between patients with and without diabetes (23).

To our knowledge, however, apoA-IV has not been investigated in mild and moderate renal failure. It is not known in which stage of renal impairment apoA-IV starts to increase and whether it is associated with atherosclerotic complications in this patient population. Therefore, we investigated a group of 227 patients with primary renal disease (24); those with a nephrotic syndrome were excluded. True GFR was determined by using iohexol clearance.

Materials and Methods

Patients

Patients were recruited during 1997 from eight nephrology departments in Germany (Göttingen, Greifswald, Heidelberg, Homburg/Saar, and Munich), Austria (Feldkirch and Innsbruck), and South Tyrol (Bozen), with nearly two-thirds of the patients from two departments (Heidelberg and Innsbruck) (24). We included white patients aged 19 to 65 yr who had visited the outpatient department at least once during the preceding year. Exclusion criteria were serum creatinine >6 mg/dl, diabetes mellitus, malignancy, liver, thyroid or infectious disease at the time of recruitment, nephrotic syndrome (defined as daily proteinuria >3.5 g/1.73 m^2), organ transplantation, allergy to ionic contrast media, and pregnancy. Three hundred forty patients fulfilled the criteria. Of these, 28 could not be reached, and 85 refused to participate in the study. The remaining 227 patients were included. Their characteristics are provided in Table 1. The study was approved by the institutional ethic committees, and subjects provided written informed consent.

To avoid interobserver differences, all renal patients were recruited by one doctor (EK) who visited all the participating centers. Patient history, including atherosclerosis events, was recorded by interview and confirmed with patient records. The atherosclerosis events were defined as myocardial infarction, aortocoronary bypass, percutaneous transluminal coronary angioplasty, angiographically verified stenosis of the coronary arteries, stroke, or a symptomatic stenosis of the peripheral arterial vessels (carotis, aortoiliac, or femoral arteries). Each patient underwent a physical examination. The primary cause of renal disease was glomerulonephritis in 97 patients (confirmed by biopsy in 90 patients), polycystic kidney disease in 37 patients, chronic pyelonephritis in 24 patients, other types of renal disease in 43 patients, and unknown in 26 patients.

Patients were compared with 227 age- and gender-matched white controls of the same ethnic origin without renal impairment or liver disease who were recruited in 1997 from one of the PROCAM study centers (25).

Laboratory Procedures

Serum and ethylenediaminetetraacetate plasma were taken after a 12-h overnight fast. After low-speed centrifugation, samples were frozen and kept at −80°C before analysis (26). Depending on the serum creatinine level, two to three blood samples for the determination of GFR by the iohexol method (27) were obtained after infusion of iohexol during the same visit in the outpatient department. We calculated the GFR in 18 patients with mostly advanced impairment of renal function by using the formula of Cockcroft and Gault (28). Patients received careful instructions regarding the collection of 24-h urine samples, which we planned to use to determine proteinuria.

Measurements of apoA-IV, lipoprotein(a) (Lp(a)), lipids, serum albumin, GFR, C-reactive protein, and apolipoprotein(a) (apo(a)) phenotyping were performed in a central laboratory to avoid interlaboratory differences in measurements. At this time, the laboratory staff involved in the study was unaware of the patients' renal function or

Table 1. Characteristics of patients with renal disease and age- and gender-matched controls[a]

Characteristic	Controls (n = 227)	Patients with Renal Disease (n = 227)
Age (yr)	45.8 ± 12.3	45.7 ± 12.6
Gender (F/M)	73/154	73/154
Body mass index	26.4 ± 3.6	25.2 ± 3.8[b]
GFR (ml/min per 1.73 m^2)		70 ± 42 [38, 63, 96]
Creatinine (mg/dl)	0.99 ± 0.18	2.02 ± 1.16[b]
Urea (mg/dl)	29 ± 7	60 ± 34[b]
Proteinuria (g/24 h per 1.73 m^2)		0.9 ± 0.9 [0.2, 0.6, 1.5]
Serum albumin (g/dl)	4.88 ± 0.49	4.57 ± 0.41[b]
Hematocrit		0.41 ± 0.06
C-reactive protein (mg/dL)		0.37 ± 0.76 [0.07, 0.16, 0.41]
Systolic BP (mmHg)	129 ± 13	137 ± 21[b]
Diastolic BP (mmHg)	81 ± 9	87 ± 14[b]
Drug-treated hypertension (%)	10.6	78.9[b]
Smoker/ex-smoker/nonsmoker (n)	61/58/108	49/57/121

[a] Data are mean ± SD and [25th percentile, median, 75th percentile] where appropriate.
[b] $P < 0.001$ for comparison with controls.

history; the status of the measured samples as from patient or control was also unknown to the staff.

Plasma apoA-IV concentrations were determined with an enzyme-linked immunosorbent assay that uses affinity-purified rabbit anti-human apoA-IV polyclonal antiserum as the capture antibody and the same antibody coupled to horseradish peroxidase as detection antibody (26,29). Plasma with known content of apoA-IV (standardized with purified apoA-IV after phenylalanine quantification by high-pressure liquid chromatography) served as calibration standard. Intra-assay and interassay coefficients of variation of this assay were 4.5 and 6.6%, respectively (26). Samples from the patients and controls were analyzed as duplicates within one series in a blinded fashion and after a similar time of sample storage at −70°C. Lp(a) quantification and apo(a) phenotyping were performed as recently described in detail (24). Serum albumin (brom-cresol green method), total and HDL cholesterol, and triglycerides were measured with kits from Roche (Basel, Switzerland). Measurements were made on microtiter plates as described previously (26). LDL cholesterol was calculated according to the Friedewald formula. C-reactive protein was measured on a Behring BNA nephelometer with reagents purchased from Behring Diagnostics (N Latex CRP Mono; Behring Diagnostics, Marburg, Germany). The lower detection limit of this test was 0.02 mg/dl.

Statistical Analyses

Statistical analyses were performed with SPSS for Windows version 10.0 (SPSS, Chicago, IL). Univariate comparisons of continuous variables between controls and renal patients were performed by unpaired *t* test or the nonparametric Wilcoxon rank-sum test in case of non-normally distributed variables. Dichotomized variables were compared by Pearson's χ^2 test. ANOVA was used to compare continuous variables between controls and renal patients subgrouped by the three tertiles of GFR. Non-normally distributed variables were logarithmically transformed before inclusion into the analysis.

The Spearman correlation test was used to correlate apoA-IV with other continuous variables. Adjustment of apoA-IV serum concentrations for age and proteinuria in patients was performed by linear regression analysis. Multiple regression analysis was used to investigate the associations of different variables with apoA-IV serum concentrations. Logistic regression analysis was performed to identify predictors for previous atherosclerotic events in patients with renal disease.

Results

Influence of Renal Function on ApoA-IV Concentrations

Renal patients differed from healthy controls by significantly higher serum levels of total cholesterol, triglycerides, Lp(a), and apoA-IV and significantly lower concentrations of apoA-I and apoB, but not by HDL and LDL cholesterol (Table 2). One of the most pronounced differences was the 70% higher mean apoA-IV concentration in patients than in controls (24.6 ± 8.6 *versus* 14.6 ± 4.2 mg/dl, $P < 0.001$).

Serum concentrations of apoA-IV had strong and significant inverse correlations with parameters of renal function so that apoA-IV concentrations increased with decreasing renal function (serum creatinine $r = 0.73$, serum urea $r = 0.66$, GFR $r = -0.62$, daily proteinuria $r = 0.37$, all $P < 0.001$) (Figure 1). The correlations with age ($r = 0.20$, $P < 0.01$), total cholesterol ($r = 0.13$, $P < 0.05$), apoA-I ($r = 0.14$, $P < 0.05$), and Lp(a) ($r = 0.14$, $P < 0.05$) were much weaker. After adjustment for age and proteinuria, the correlation of apoA-IV with renal function but not correlations with variables of lipoprotein metabolism remained significant (serum creatinine $r = 0.56$, serum urea $r = 0.56$, GFR $r = -0.54$, all $P < 0.001$).

We calculated the apoA-IV concentrations in three strata of renal function to investigate at which phase of renal impairment apoA-IV concentrations start to increase (Table 3). We therefore grouped renal patients according to the tertiles of GFR (*i.e.*, >90, 45 to 90, and <45 ml/min per 1.73 m^2). ApoA-IV concentrations increased significantly with decreasing renal function ($P < 0.001$ by ANOVA). ApoA-IV was already increased in the group of patients with primary renal disease, but GFR values were still in the normal range (>90 ml/min per 1.73 m^2) when compared with healthy controls (17.7 ± 6.2 *versus* 14.6 ± 4.2 mg/dl, $P < 0.001$). These associations remained significant when apoA-IV concentrations in patients were adjusted for age and proteinuria. We also determined whether the primary cause of renal disease influences apoA-IV concentrations. Patients with polycystic kidney

Table 2. Serum concentrations of lipids, lipoproteins, and apolipoproteins in controls and patients with renal disease[a]

Characteristic	Controls ($n = 227$)	Patients with Renal Disease ($n = 227$)
Total cholesterol (mg/dl)	206 ± 41	215 ± 45[b]
HDL cholesterol (mg/dl)	43.6 ± 11.5	43.7 ± 14.2
LDL cholesterol (mg/dl)	134 ± 37	136 ± 40
Triglycerides (mg/dl), mean ± SD	141 ± 96	173 ± 101[c]
[25th percentile, median, 75th percentile]	[84, 114, 170]	[101, 144, 223]
Apolipoprotein A-I (mg/dl)	157 ± 22	120 ± 21[c]
Apolipoprotein A-IV (mg/dl)	14.6 ± 4.2	24.6 ± 8.6[c]
Apolipoprotein B (mg/dl)	123 ± 30	107 ± 27[c]
Lipoprotein(a) (mg/dl), mean ± SD	20.7 ± 32.8	29.5 ± 32.0[c]
[25th percentile, median, 75th percentile]	[2.2, 6.9, 19.4]	[4.9, 17.9, 42.5]

[a] Data are mean ± SD and [25th percentile, median, 75th percentile] where appropriate.
[b] $P < 0.05$ for comparison with control subjects.
[c] $P < 0.001$ for comparison with control subjects.

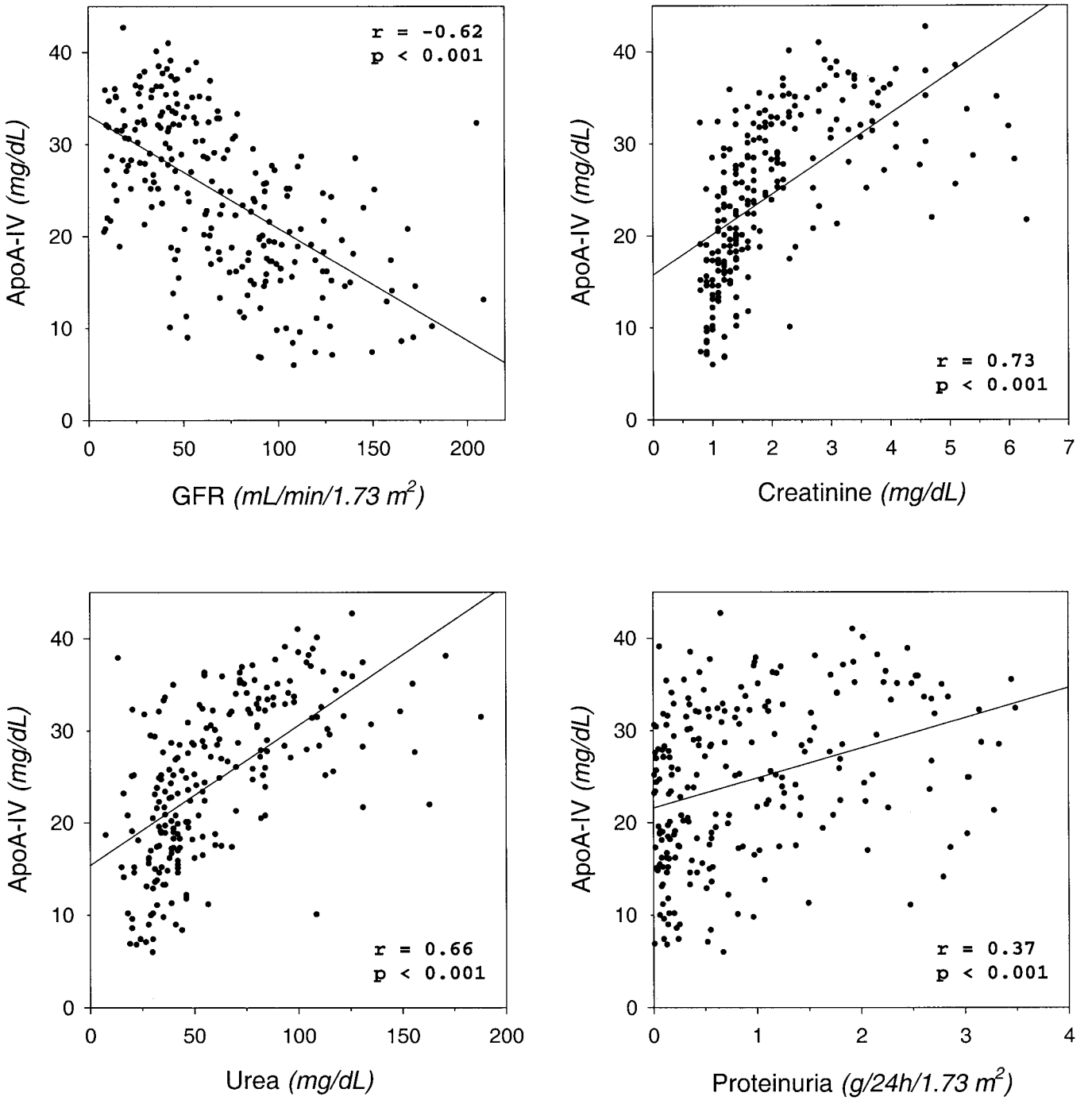

Figure 1. Correlation of apolipoprotein A-IV (apoA-IV) serum concentrations with parameters of renal function (serum creatinine, serum urea, GFR, and daily proteinuria).

disease showed a trend to slightly higher apoA-IV concentrations when compared with those with glomerulonephritis (25.6 ± 8.8 *versus* 23.0 ± 8.1 mg/dl, $P = 0.11$). However, when we adjusted apoA-IV concentrations for differences in GFR and proteinuria, these two patient groups did no longer differ by apoA-IV levels (24.5 ± 6.7 *versus* 23.5 ± 7.1 mg/dl, $P = 0.48$).

In a next step, we used multiple regression analysis to assess which variables were significantly associated with apoA-IV concentrations in renal patients. Because GFR, serum creatinine, and serum urea are strongly correlated, we calculated three different models that showed very similar results (the model considering GFR is presented in Table 4). ApoA-IV showed the strongest associations with the parameters of renal function (GFR, serum creatinine, or serum urea), which explained approximately 35% of the apoA-IV concentrations. Further, but much smaller, contributions to the apoA-IV levels came from proteinuria and apoA-I (Table 4).

Table 3. Mean ± SD apolipoprotein A-IV (apoA-IV) serum concentrations in controls and patients with renal disease

Characteristic	ApoA-IV (mg/dl), Crude Values	ApoA-IV (mg/dl), Adjusted for Age and Proteinuria
Controls ($n = 227$)	14.6 ± 4.2	
GFR >90 ml/min per 1.73 m^2 ($n = 72$)	17.7 ± 6.2	18.4 ± 6.1
GFR 45–90 ml/min per 1.73 m^2 ($n = 76$)	25.1 ± 7.9	24.7 ± 7.3
GFR <45 ml/min per 1.73 m^2 ($n = 79$)	30.5 ± 6.2	30.1 ± 6.2
P value from ANOVA	<0.001[a]	<0.001[a]

[a] *Post hoc* comparisons between all possible group pairs showed *P* values <0.001 (after correction according to the method of Bonferroni).

ApoA-IV and Atherosclerotic Complications

Finally, we analyzed the association between apoA-IV concentrations and a history of atherosclerotic complications in renal patients. Twenty-six patients experienced 36 atherosclerotic events, including 17 coronary events (mostly myocardial infarctions and aortocoronary bypasses), nine strokes, and 10 events that affected the peripheral arterial system. In univariate analysis, patients with atherosclerotic complications showed a trend to lower apoA-IV concentrations when compared with the patients without complications (24.9 ± 8.7 *versus* 22.3 ± 7.7 mg/dl, $P = 0.15$). This difference was statistically significant in the stratum with the worst GFR (31.1 ± 5.8 *versus* 27.0 ± 7.5 mg/dl, $P = 0.04$). We also performed a logistic regression analysis for the entire patient group, including the GFR in the analysis. The most parsimonious model identified three variables associated with atherosclerotic complications: age, apoA-IV, and gender (Table 5). Each 1 mg/dl increase of apoA-IV decreased the odds ratio for an atherosclerotic complication by 8% ($P = 0.011$). The low molecular weight apo(a) phenotype and GFR showed a borderline association with atherosclerotic complications (Table 5). Other variables (*e.g.* smoking, hypertension, lipoprotein variables) did not significantly discriminate between affected and unaffected patients.

Table 4. Association of variables with apoA-IV serum concentrations in patients with mild and moderate renal failure[a]

Parameter	Coefficient	SE	*P*	Change in R^2
GFR	−0.114	0.011	<0.001	0.354
ln proteinuria	1.265	0.334	<0.001	0.044
Apolipoprotein A-I	0.050	0.020	0.012	0.017

[a] Association was determined by multiple regression analysis. Results are presented for a model including GFR. Models considering creatinine or urea revealed very similar results. Variables and interaction terms that did not significantly contribute to the multiple regression model were as follows: total cholesterol, HDL and LDL cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), serum albumin, smoking, body mass index, age, gender, and the interaction terms GFR × proteinuria, creatinine × proteinuria and urea × proteinuria. ln proteinuria means that the variable is logarithmically transformed. Coefficient and SE for GFR are provided on a natural scale for better interpretation. Use of logarithmically transformed values resulted in similar contributions to the models.

Discussion

Influence of Renal Function on ApoA-IV Concentrations

The study presented here demonstrates that renal function strongly effects apoA-IV serum concentrations. Earlier studies had revealed that patients with end-stage renal disease have a pronounced increase of apoA-IV concentrations (19–21,23). However, it has so far been unknown that even renal disease with GFR values in the normal range is accompanied by a significant increase in apoA-IV concentrations. It therefore seems that apoA-IV is an early marker of renal impairment, indicating that its elevation might be caused by a diminished renal catabolism. This hypothesis is supported by two observations. First, studies in rats showed that apoA-IV is catabolized by kidney and liver. Histologic analysis found apoA-IV to be localized within proximal tubular cells (30). Because of its molecular weight of approximately 46 kD, apoA-IV can be filtered in the glomeruli at least in its lipoprotein-unbound (free), and hence predominant, form (3,4). An uptake by proximal tubular cells could then be followed by degradation. Whether the catabolic pathway in humans is the same as in rats remains to be determined, however. Second, because apoA-IV is already elevated in the earliest stages of renal disease when GFR is still normal—or at most, slightly subnormal—it is likely that the elevation is not simply caused by an impaired GFR. Disturbance of renal functions not reflected by whole kidney GFR is conceivable. Immunohistochemical studies will help clarify this point.

An alternative, but less likely, explanation for the elevated apoA-IV levels is that apoA-IV is not fully functionally active in renal disease. Uremia could have an influence on, for example, the enzyme-activating and antioxidative properties of apoA-IV. An elevation of apoA-IV protein concentration might be viewed as a compensatory response to functional impairment of apoA-IV.

The influence of renal function on apoA-IV concentrations might be the reason why a study by Sun *et al.* (31) in middle-aged and elderly men and women identified age and diabetes mellitus as major determinants of apoA-IV concentrations. The

correlation with age might mainly be explained by age-dependent changes in renal function. In contrast to the data by Sun *et al.* (31), we did not observe any significant correlation with age in our control group recruited from the PROCAM study ($r = 0.057$, $P = 0.39$). This can be explained by the fact that we excluded controls with renal impairment defined by a serum creatinine >1.5 mg/dl, macroalbuminuria, or both. Similarly, we assume that the reported elevation of apoA-IV in patients with diabetes (31) is explained by the fact that renal function is impaired in many patients with diabetes mellitus. Diabetes mellitus was an exclusion criterion in our study. We did also not observe any differences in apoA-IV levels in an earlier study of dialysis patients when 189 patients with diabetes mellitus were compared with 513 patients without diabetes (23). Other studies in patients with diabetes mellitus, however, reported an elevation of apoA-IV but failed to assess renal function (32,33). This clearly indicates the need for thorough controlling of apoA-IV concentrations for renal function in case control studies. If renal function is not considered, the interpretation of results can be misleading when differences in renal function exist between cases and controls.

ApoA-IV and Atherosclerotic Complications

We recently reported for the first time significantly lower apoA-IV levels in 114 white men with angiographically defined CAD compared with 114 age-adjusted male controls (10.2 ± 3.8 mg/dl *versus* 15.1 ± 4.0 mg/dl, $P < 0.001$). This inverse relationship between apoA-IV levels and the presence of CAD was confirmed in an independent sample of 68 Asian Indian men with angiographically documented CAD and 68 age-matched controls. In line with this finding, we observed lower apoA-IV concentrations in renal patients who had already experienced an atherosclerotic event when compared with those without an event. In the logistic regression analysis, apoA-IV emerged as a significant and independent predictor for the presence of atherosclerotic events (Table 5). The cross-sectional study design, however, may underestimate the association of atherosclerosis risk with low apoA-IV levels because only survivors of events could be studied. Of course, larger and prospective investigations will be necessary to definitively prove this association and to obtain data investigating a possible causality. Nevertheless, there is strong mechanistic *a priori* evidence that makes this association highly likely: cell culture studies showed the involvement of apoA-IV in several steps of the reverse cholesterol transport (4,9–14) and document its antioxidative properties (34); overexpression of human and mouse apoA-IV in mice inhibited the development of atherosclerosis (16) and reduced oxidation parameters *in vivo* (17,35); and finally, first results demonstrated lower apoA-IV concentrations in men with angiographically proven CAD (18).

The results of this and another study (18) are in contrast to the results of an investigation in patients with non–insulin-dependent diabetes mellitus that described significantly higher apoA-IV concentrations in patients with macrovascular complications compared with those without macrovascular complications (33). As previously discussed (18), the explanation for this discrepancy might be the increased prevalence of microalbuminuria and the concomitant renal impairment in patients with diabetes with macrovascular complications. The authors excluded patients with renal failure, but they did not provide detailed information about the exclusion criteria. However, approximately 40% of the patients had microalbuminuria (33), pointing at least to a renal involvement expected to significantly affect apoA-IV concentrations. We clearly showed in this study that even renal disease with GFR values in the normal or subnormal range is accompanied by a significant increase in apoA-IV concentrations. Because patients with diabetes with macrovascular complications are more likely to have renal involvement than patients with diabetes without vascular disease, high levels of apoA-IV in patients with diabetes with macrovascular complications may simply reflect their impaired renal function.

Paradox of High ApoA-IV Concentrations in Uremia, a State of High Cardiovascular Risk

One might ask why patients with renal disease have such an excessive risk for atherosclerotic complications (36) when they have such high apoA-IV concentrations. If apoA-IV has indeed antiatherogenic properties, these patients should be more protected than nonrenal patients. This argument is intriguing from a univariate point of view. We should keep in mind, however, that these patients have numerous other atherosclerosis risk factors yielding an unfavorable overall profile (36). Besides the changes in traditional atherosclerosis risk factors, we and others demonstrated marked changes for Lp(a) and homocysteine

Table 5. Logistic regression analysis investigating the predictive value of apolipoprotein A-IV serum concentrations and other variables for atherosclerotic events[a]

Parameter	Coefficient	SEM	χ^2	Odds Ratio (95% Confidence Interval)	*P*
Age	0.080	0.027	9.1	1.08 (1.03–1.14)	0.003
Apolipoprotein A-IV	−0.085	0.033	6.5	0.92 (0.86–0.98)	0.011
Gender	1.434	0.655	4.8	4.20 (1.16–15.15)	0.028

[a] Variables not in the model: low molecular weight apo(a) phenotype ($P = 0.11$) and ln-transformed GFR ($P = 0.16$).

(for reviews, see [37,38]), even at very early stages of renal disease when GFR is normal or minimally reduced at best (24,39,40).

Several studies demonstrated that homocysteine as well as Lp(a) and especially Lp(a) of low molecular weight apo(a) phenotypes are important risk factors for atherosclerosis in these patients (41–49). Whether apoA-IV counteracts this burden is not yet determined, but it would be in line with our observation of lower apoA-IV levels in renal patients with a history of atherosclerotic events. A recent discussion focused on the issue whether renal insufficiency *per se* is a marker for already established generalized atherosclerosis or whether it is a proatherogenic state (50). This discussion was mainly based on the prospective results from the Framingham Study in subjects with little comorbidity that failed to identify renal insufficiency as an independent risk factor for subsequent cardiovascular disease when the data were adjusted for traditional cardiovascular risk factors and presence of cardiovascular disease (51). One may speculate that in renal insufficiency, apoA-IV and possibly other protecting factors offset potentially atherogenic circulating mediators associated with renal insufficiency, so that the proatherogenic character of renal failure is obscured.

ApoA-IV: A Surrogate for ApoA-I?

It is an interesting observation that patients with renal disease in our study had normal HDL cholesterol values but markedly decreased apoA-I levels. Past studies that investigated patients with more advanced renal failure described decreased HDL cholesterol concentrations (23,52–54). In contrast, the patients we studied had a mean GFR of approximately 70 ml/min per 1.73 m^2. We propose that the decrease in HDL cholesterol is preceded by an apoA-I depletion or a lipid particle accumulation of HDL cholesterol consistent with an impaired reverse cholesterol transport pathway. Because apoA-I and apoA-IV show substantial functional overlap (*e.g.*, lecithin:cholesterol acyltransferase activation), it remains to be determined whether an increase of apoA-IV is a homeostatic attempt to compensate the decrease of the apoA-I. In-depth studies of reverse cholesterol transport in the early stages of renal disease are obviously indicated.

In summary, our data clearly show that apoA-IV starts to increase during the earliest phases of renal insufficiency, which makes apoA-IV an early marker of renal impairment. On the other hand, low apoA-IV concentrations seem to be associated with atherosclerotic complications in patients with mild to moderate renal failure.

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