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Apolipoprotein B is a risk factor for end-stage renal disease

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ABSTRACT

Background. Apolipoprotein B (ApoB), a constituent of lipid particles, is known to increase the risk of cardiovascular diseases. However, the association between ApoB and end-stage renal disease (ESRD) remains to be resolved. Our objective was to determine whether the ApoB concentration has an association with the risk of ESRD.

Methods. Serum ApoB, ApoA1, conventional lipid parameters and lipid subfractions were analyzed in 9403 subjects. The hazard ratio (HR) for the risk of ESRD was calculated using tertiles of ApoB concentration.

Results. ESRD developed in 110 patients (1.2%) during 10 years of follow-up. Several lipid parameters were compared for their association with the risk of ESRD, of which ApoB was best and its relationship was also independent of other clinical parameters. Individuals in the second and third ApoB tertiles had a higher risk of ESRD than those in the first tertile, with HRs of 1.5 [95% confidence interval (CI) 0.89–2.61] and 2.6 (1.56–4.20), respectively. A high ApoB:ApoA1 ratio was associated with a higher risk of ESRD, but ApoA1 had no independent association. Even after adjusting the competing risk for all-cause death, high ApoB concentrations had an association with the risk of ESRD.

Conclusions. High ApoB concentration is associated with a higher risk of ESRD, despite adjustment for other lipid and clinical parameters. Accordingly, the monitoring of ApoB may be helpful for the prediction of ESRD.

Keywords: apolipoprotein A1, apolipoprotein B, cholesterol, end-stage renal disease, lipid subfraction

INTRODUCTION

Dyslipidemia is an established risk factor for atherosclerotic disease because it promotes inflammation within the intima, which can lead to cardiovascular disease, stroke and atherosclerotic kidney disease [1]. Kidney and cardiovascular diseases share the risk of dyslipidemia that exacerbates both diseases by damaging endothelial cells and inducing inflammation [2]. These interacting mechanisms also explain that

dyslipidemia is associated with high all-cause and cardiovascular mortality in chronic kidney disease (CKD) [3]. Accordingly, the Kidney Disease: Improving Global Outcomes guidelines recommend the evaluation of a lipid profile, including serum low-density and high-density lipoprotein (LDL and HDL) cholesterol, and triglyceride when kidney disease is diagnosed [4]. However, a number of studies have failed to

demonstrate relationships between these conventional lipid parameters and renal outcomes [5–8].

Apolipoprotein B (ApoB) is an important structural component of intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL) and LDL particles (i.e. non-HDL cholesterols). Consistent with this, several studies have identified a relationship between ApoB concentration and the risk of atherosclerotic cardiovascular disease [9–11]. The recently published American Heart Association guidelines state that >130 mg/dL of serum ApoB corresponds to ≥150 mg/dL of LDL cholesterol, thus ApoB may have potential as a marker of high cardiovascular risk [12]. Few studies have used ApoB to predict renal outcomes, and those that did were inconclusive. However, these studies did not account for the LDL subfractions, which might act as a confounding factor in a relationship [6, 13–15]. Therefore, in this study we determined whether ApoB concentration has an association with the risk of end-stage renal disease (ESRD) after considering the effects of both conventional lipid parameters and LDL subfractions.

MATERIALS AND METHODS

Study subjects

The study protocol complied with the Declaration of Helsinki, as revised in 2013, and was approved by the institutional review board of the Seoul National University Hospital (no. H-1807-013-955). A total of 14 123 patients attending a tertiary referral center (Seoul National University Hospital) were retrospectively reviewed between 2009 and 2016. Adult patients (≥18 years of age) for whom lipid parameters and the LDL subfraction were profiled were included. We excluded patients who had previously started renal replacement therapy (hemodialysis, peritoneal dialysis or kidney transplantation; $n = 591$) and those with missing clinical or laboratory data ($n = 4128$). Consequently, data from 9403 patients were analyzed in this study. Under the terms of the ethics approval, the requirement for informed consent was waived.

Study variables

Baseline clinical parameters including age, sex, body mass index, smoking status and comorbidities such as diabetes mellitus, hypertension, coronary artery disease, stroke, peripheral vascular disease, atrial fibrillation/flutter, valvular heart disease and CKD were reviewed. The blood parameters reviewed included white blood cells, hemoglobin and serum protein, albumin and creatinine concentrations. The lipid parameters measured were total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, LDL subfractions (Lipoprint, Quantimetrix, Redondo Beach, CA, USA), and ApoB and ApoA1 (using the immunoturbidimetric method, Toshiba, Tokyo, Japan). Blood was drawn after a 12-h fast. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [16]. Random urine albumin:creatinine and protein:creatinine ratios were available for 5856 patients. The medications being used included statins, ezetimibe, fenofibrate, omega-3 fatty acids, anti-platelet drugs, anticoagulants, oral antidiabetic drugs, insulin and antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers and diuretics).

Study outcomes

The primary study outcome was the event of ESRD (maintenance dialysis or kidney transplantation). Information regarding ESRD was obtained from the Korean Society of Nephrology database. All-cause mortality data were obtained from the National Database of Statistics Korea. Patients were followed up until their death or August 2018.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA) and R version 3.5.1 (R Foundation, Vienna, Austria, http://cran.r-project.org). Continuous variables are expressed as means and standard deviations if normally distributed and as medians and interquartile ranges if not normally distributed. Normality was determined using the Kolmogorov–Smirnov test. Categorical variables are expressed as proportions and the chi-square test was used for their comparison, or Fisher's exact test if this was not applicable. Student's *t*-test was used to analyze continuous variables and the Mann–Whitney U test was used if the variables were not normally distributed. Analysis of variance was used when normality was satisfied for comparisons between multiple groups and the Kruskal–Wallis test was used if the data were not normally distributed. Survival curves were drawn using the Kaplan–Meier method and the log-rank test was initially used to compare survival curves between groups. The hazard ratios (HRs) for renal outcome were estimated using the Cox regression model before and after backward conditional stepwise analysis, with adjustment for multiple covariates. The competing risk analysis was conducted using a cause-specific proportional hazards model after adjustment of multiple variables (CFC package of the R software). All P-values were two sided and were considered to indicate statistically significant differences when <0.05.

RESULTS

Evaluation of baseline characteristics according to ApoB concentration

Table 1 shows the baseline characteristics of the patients. The mean age of the patients was 65 ± 11 years and 64.7% were men. When the baseline characteristics were compared using tertiles of ApoB concentration, the individuals in the higher tertiles were more likely to be obese, smokers and have high eGFR compared with the lowest tertile. Individuals in the lower tertiles were more likely to have diabetes, hypertension and coronary artery disease than those in the highest tertile. The lipid profiles differed among the three groups, with individuals in the higher tertiles having a higher concentration of total cholesterol or LDL subfractions than those in the lowest tertile.

Lipid parameters associated with a higher risk of ESRD

During a median follow-up period of 5 years (IQR 3–7; maximum 10), ESRD developed in 110 patients (1.2%). Table 2 shows the HRs of lipid parameters for the risk of ESRD. In univariate analyses, serum ApoB, ApoA1, triglyceride and HDL and IDL cholesterol concentrations were associated with

Table 1. Baseline characteristics of the study subjects

| Variables | Total (n = 9403) | Tertile of ApoB | | | P-value |
		First tertile (n = 3135)	Second tertile (n = 3134)	Third tertile (n = 3134)	
Age (years) mean ± SD	64.8 ± 10.9	65.8 ± 10.7	64.9 ± 10.8‡	63.5 ± 11.1‡	<0.001
Female (%)	35.3	31.7	33.8	40.4‡	<0.001
Body mass index (kg/m²) mean ± SD	24.2 ± 3.3	23.8 ± 3.2	24.2 ± 3.4‡	24.5 ± 3.4‡	<0.001
Current smoker (%)	14.5	12.0	13.7*	17.8‡	<0.001
Comorbidity (%)					
Diabetes	10.6	12.3	10.5*	8.9‡	<0.001
Hypertension	15.2	17.7	15.6*	12.4‡	<0.001
Coronary artery disease	64.0	68.4	65.0†	58.7‡	<0.001
Stroke	1.6	1.7	1.7	1.3	0.311
Peripheral vascular disease	1.3	1.5	1.6	0.8*	0.015
Atrial fibrillation/flutter	2.7	2.7	2.7	2.7	0.940
Valvular heart disease	3.7	3.0	3.9	4.2†	0.009
Chronic kidney disease	14.0	13.8	13.9	14.1	0.795
Blood laboratory finding mean ± SD					
White blood cells (×10³/μL)	6.9 ± 2.6	6.7 ± 2.4	6.9 ± 2.5†	7.2 ± 2.8‡	<0.001
Hemoglobin (g/dL)	13.3 ± 1.8	13.1 ± 1.8	13.3 ± 1.8‡	13.4 ± 1.8‡	<0.001
Protein (g/dL)	7.0 ± 0.7	7.0 ± 0.7	7.0 ± 0.7	7.0 ± 0.7	0.010
Albumin (g/dL)	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.5‡	0.006
eGFR (mL/min/1.73 m²)	80.8 ± 19.0	80.2 ± 18.5	80.7 ± 18.9	81.5 ± 19.5†	<0.001
Urine laboratory finding, mean ± SD					
ACR (mg/mg)	0.1 ± 0.5	0.1 ± 0.5	0.1 ± 0.3	0.2 ± 0.6†	0.001
PCR (mg/mg)	0.3 ± 0.9	0.3 ± 0.9	0.3 ± 0.7	0.4 ± 1.2‡	<0.001
Hematuria (%)	11.9	11.4	11.1	13.1	0.080
Medications (%)					
Statin	19.2	17.2	17.4	22.9‡	<0.001
Ezetimibe	1.9	1.6	1.7	2.6†	0.010
Fenofibrate	0.2	0.2	0.3	0.2	0.866
Omega-3 fatty acid	6.0	5.4	6.1	6.5	0.166
Aspirin	20.6	19.6	19.7	22.6†	0.003
Other anti-platelets	5.1	5.7	4.3*	5.4	0.034
Anti-coagulants	3.0	2.5	3.1	3.5*	0.082
Oral antidiabetic drugs	4.6	3.8	4.6	5.4†	0.012
Insulin	1.3	1.2	1.2	1.5	0.469
ACEI or ARB	10.9	9.0	10.9*	12.7‡	<0.001
β-blocker	12.5	11.9	11.6	14.2†	0.002
Calcium channel blocker	10.2	9.4	9.1	12.1‡	<0.001
Diuretics	5.9	4.8	5.7	7.1‡	0.001
Lipid profile, median (IQR)					
Total cholesterol (mg/dL)	152 (130–178)	125 (114–137)	151 (139–163)‡	188 (172–209)‡	<0.001
Triglyceride (mg/dL)	105 (78–146)	89 (68–118)	105 (79–144)‡	127 (94–172)‡	<0.001
HDL cholesterol (mg/dL)	37 (31–44)	36 (30–43)	36 (30–44)	37 (31–45)‡	<0.001
LDL cholesterol (mg/dL)	86 (68–109)	63 (54–72)	86 (77–96)‡	120 (104–138)‡	<0.001
VLDL cholesterol (mg/dL)	23 (18–29)	20 (16–24)	23 (19–28)‡	27 (22–35)‡	<0.001
IDL A cholesterol (mg/dL)	12 (9–15)	9 (7–11)	11 (9–14)‡	15 (12–18)‡	<0.001
IDL B cholesterol (mg/dL)	10 (8–13)	8 (7–10)	10 (8–12)‡	13 (11–16)‡	<0.001
IDL C cholesterol (mg/dL)	15 (12–19)	13 (10–16)	15 (12–19)‡	19 (15–22)‡	<0.001
LDL subfraction score	1.6 (1.4–1.8)	1.4 (1.3–1.6)	1.6 (1.4–1.8)‡	1.8 (1.5–2.2)‡	<0.001
ApoB (mg/dL)	77.0 (65.0–93.0)	61.0 (55.0–65.0)	77.0 (74.0–82.0)‡	100.0 (92.0–111.0)‡	<0.001
ApoA1 (mg/dL)	109 (98–121)	108 (98–120)	108 (98–120)	110 (99–123)‡	<0.001
ApoB/A1	0.7 (0.6–0.9)	0.6 (0.5–0.6)	0.7 (0.6–0.8)‡	0.9 (0.8–1.1)‡	<0.001

ACR, random urine albumin:creatinine ratio; PCR, random urine protein:creatinine ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
*P < 0.05; †P < 0.01; ‡P < 0.001 (compared with the lowest tertile).

the risk of ESRD. The LDL subfraction score correlated with the development of ESRD. When backward stepwise regression was applied, after adjustment for age, sex, body mass index, smoking status, diabetes mellitus, hypertension and coronary artery disease, lipid parameters (ApoB and total, HDL and IDL cholesterols) remained significant predictors of ESRD. Specifically, 1 mg/dL increase in ApoB conferred an approximate 3% increase in the risk of ESRD.

Table 2. Use of lipid parameters in the prediction of ESRD risk

Parameters	Univariate		Multivariate[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ApoB (per 1 mg/dL)	1.02 (1.007–1.023)	<0.001	1.03 (1.009–1.043)	0.002
ApoA1 (per 1 mg/dL)	0.98 (0.964–0.986)	<0.001	–	–
Total cholesterol (per 1 mg/dL)	1.00 (0.997–1.007)	0.571	0.97 (0.960–0.985)	<0.001
Triglyceride (per 1 mg/dL)	1.00 (1.000–1.003)	0.008	–	–
HDL cholesterol (per 1 mg/dL)	0.94 (0.922–0.960)	<0.001	0.97 (0.945–0.993)	0.011
VLDL cholesterol (per 1 mg/dL)	1.01 (0.999–1.025)	0.062	–	–
IDL A (per 1 mg/dL)	1.07 (1.038–1.094)	<0.001	1.05 (0.999–1.105)	0.054
IDL B (per 1 mg/dL)	1.12 (1.092–1.139)	<0.001	1.14 (1.089–1.190)	<0.001
IDL C (per 1 mg/dL)	1.05 (1.026–1.082)	<0.001	1.04 (1.000–1.078)	0.049
LDL subfraction score (per 1)	1.06 (0.991–1.124)	0.094	–	–

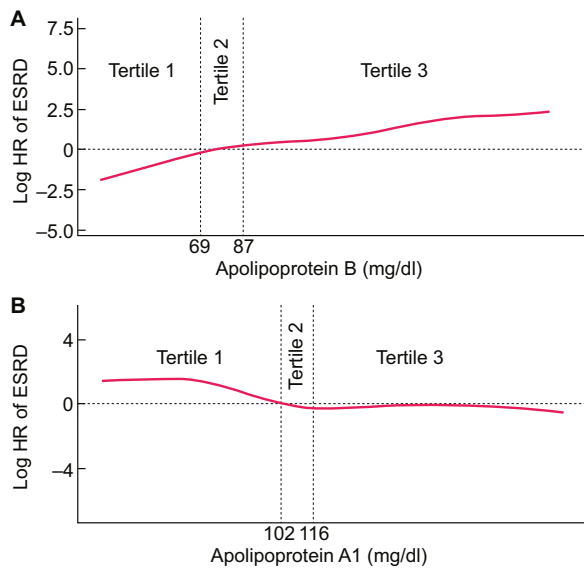[a]Adjusted for age, sex, body mass index, smoking status, diabetic mellitus, hypertension and coronary artery disease.

FIGURE 1: Spline-based HR curves for the predicted risk of ESRD, classified according to serum (**A**) ApoB and (**B**) ApoA1 concentrations.

Effect of ApoB concentration on the risk of ESRD

Spine-based HR curves of serum ApoB or ApoA1 for the risk of ESRD are presented in Figure 1. As a result, patients with high ApoB and low ApoA1 concentrations seemed to be at risk of ESRD. Subsequently patients were divided into tertiles according to their Apo concentrations. Figure 2 shows the Kaplan–Meier curves representing cumulative ESRD events classified according to Apo tertile. The higher and lower tertiles of ApoB and ApoA1, respectively, were associated with a higher crude risk of ESRD (Figure 2A and B) and therefore the ApoB:ApoA1 ratio was positively associated with a higher risk of ESRD (Figure 2C). Unadjusted Cox regression analysis of the relationships between ApoB, ApoA1 and ESRD yielded similar results (Table 3). When clinical and laboratory parameters were sequentially adjusted for, the association of ApoA1 with ESRD disappeared; ApoB was independent of these clinical and laboratory parameters. In addition, ApoB:ApoA1 remained significant in an association with the risk of ESRD after adjustment for multiple parameters. Figure 3 demonstrates that the positive relationship between ApoB concentration and the risk of ESRD remained consistent irrespective of age, sex, diabetes mellitus and eGFR.
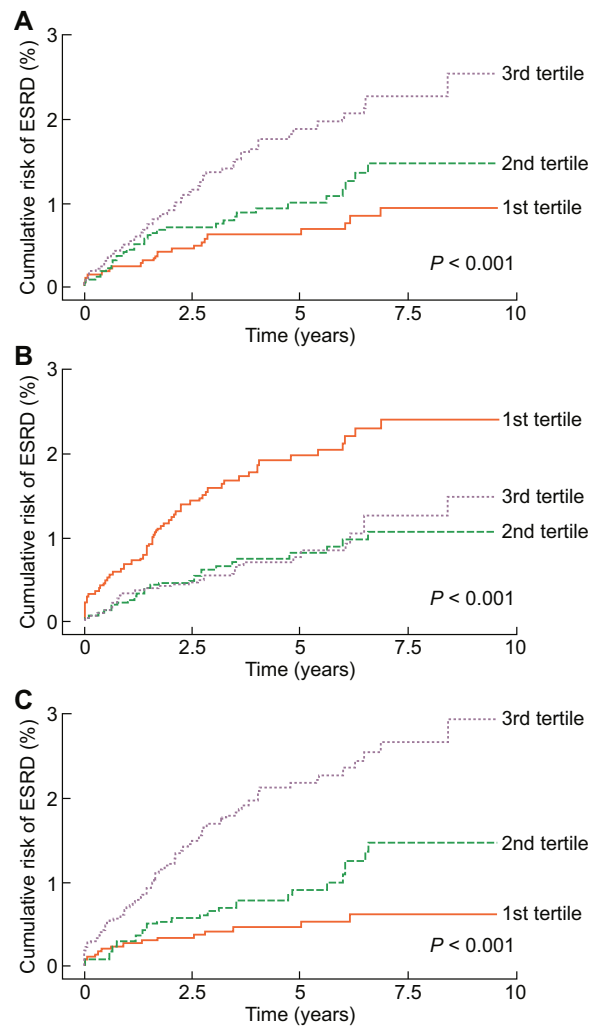

FIGURE 2: Risk of ESRD, according to tertiles of (**A**) ApoB, (**B**) ApoA1 and (**C**) ApoB:ApoA1 ratio.

Because urinary data were available for only 5856 patients (62.3%), we additionally adjusted for random urine albumin:creatinine and protein:creatinine ratios in the model as a sensitivity analysis (Table 3). The higher tertiles had a higher risk of ESRD than the lowest tertile with the following HR

Table 3. Risk of ESRD according to the ApoB and ApoA1 levels, using backward stepwise multivariate model

Parameter	Tertiles	Univariate		Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
ApoB	T1	1 (Reference)	<0.001*	1 (Reference)	<0.001*	1 (Reference)	0.006*	1 (Reference)	<0.001*
	T2	1.52 (0.887–2.610)	0.127	1.58 (0.918–2.702)	0.096	1.85 (1.005–3.400)	0.023	2.13 (1.225–3.689)	0.007
	T3	2.56 (1.563–4.202)	<0.001	2.86 (1.741–4.703)	<0.001	2.31 (1.376–3.863)	0.002	2.82 (1.683–4.734)	<0.001
ApoA1	T1	1 (Reference)	0.001*	1 (Reference)	<0.001*	–		–	
	T2	0.42 (0.262–0.667)	<0.001	0.44 (0.274–0.700)	0.001	–		–	
	T3	0.49 (0.283–0.712)	0.001	0.46 (0.289–0.728)	0.001	–		–	
ApoB: ApoA1	T1	1 (Reference)	<0.001*	1 (Reference)	<0.001*	1 (Reference)	0.095*	1 (Reference)	0.023*
	T2	2.01 (1.083–3.742)	0.027	2.10 (1.127–3.895)	0.019	1.75 (0.937–3.280)	0.079	1.95 (1.030–3.672)	0.040
	T3	4.41 (2.515–7.729)	<0.001	4.66 (2.660–8.180)	<0.001	1.90 (1.057–3.409)	0.032	2.29 (1.270–4.145)	0.006

Model 1: adjusted for age, sex, body mass index and smoking status.
Model 2: adjusted for Model 1 variables plus comorbidity and laboratory findings.
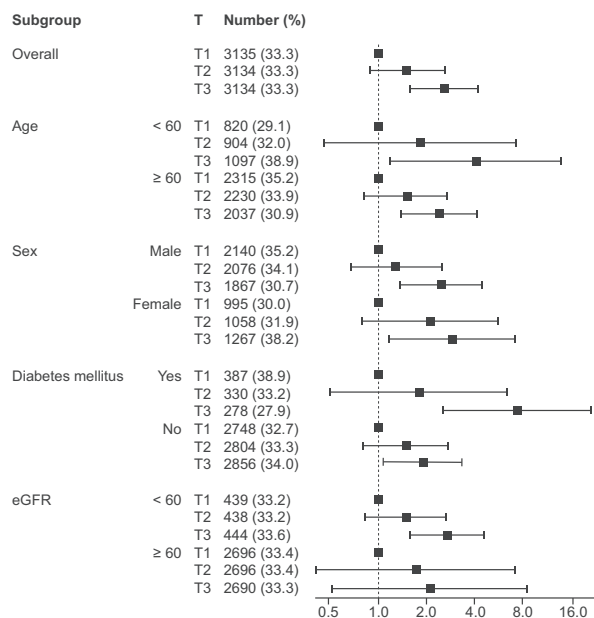Model 3: adjusted for Model 2 variables plus medications.
*P-value for trend.

FIGURE 3: Subgroup analysis for the risk of ESRD, according to tertiles of ApoB concentration.
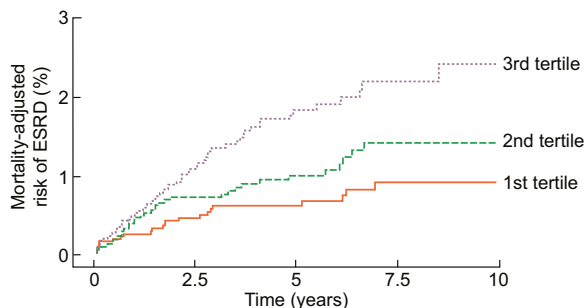

FIGURE 4: Death-adjusted risk of ESRD, according to tertiles of ApoB concentration.

and P-values: HR 2.13 [95% confidence interval (CI) 1.225–3.689] and P = 0.007 for the second tertile and HR 2.82 (1.683–4.734) and P < 0.001 for the third tertile.

Effect of ApoB concentration on the mortality-adjusted risk of ESRD

During the follow-up period, 1162 patients (12.4%) died. A competing risk analysis was performed because the association between ApoB and ESRD could have been affected by the high death rate [17, 18]. Although the risk of death was adjusted for, a high ApoB concentration remained a risk factor for ESRD (Figure 4). When multiple covariates were adjusted for, the HRs for the second and third tertiles were 1.43 (95% CI 0.833–2.470), P = 0.193 and 1.86 (1.105–3.132), P = 0.019, respectively, compared with the first tertile.

DISCUSSION

Dyslipidemia is associated with substantial morbidity and mortality and ApoB can be used to help clarify the risk [12]. Despite the high prevalence of high serum ApoB concentrations [19], the association of ApoB with the risk of renal outcomes has not been fully established. This study aimed to determine whether ApoB concentration is associated with the risk of ESRD after taking interactions with other lipid parameters, including LDL subfractions, and the competing risk of death into account.

Various parameters indicative of dyslipidemia have been evaluated for their predictive value for the progression of renal disease to ESRD [20], although the relationships identified between conventional lipid parameters and renal outcomes have been both positive [8, 21] and negative [5–7, 22]. Failure to identify correlations has been attributed to the confounding effect of uremia on lipid metabolism. However, these studies evaluated conventional lipid parameters, such as total cholesterol, triglyceride and HDL and LDL cholesterols, but not other parameters, including serum ApoB and LDL subfractions.

Recently Apo have been of clinical interest for their potential use in relation to outcomes in CKD. Two large prospective cohort studies and other observational studies have assessed their suitability with regard to the survival of pre-dialysis CKD patients [14, 23–25]. The Atherosclerosis Risk in Communities Study has provided evidence that ApoB:ApoA1 and non-HDL:HDL cholesterol ratios are associated with the risk of cardiovascular disease in CKD. In addition, the Chronic Renal Insufficiency Cohort (CRIC) study has shown that high ApoB and low ApoA1 concentrations are correlated with higher risks

of atherosclerotic cardiovascular disease. Thus a high ApoB concentration is known to be associated with the risks of atherosclerotic cardiovascular morbidity and mortality in CKD.

To date, few studies have identified the value of Apo in relation to renal outcomes [26–28]. Genetic polymorphisms of ApoE and ApoL1 have been shown to be associated with the progression of renal impairment [26, 28], and high ApoA4 concentration has been shown to be associated with the early progression of kidney disease, although ApoA4 is thought to be a reverse cholesterol transporter or antioxidant [27]. Despite these findings, Apo are not measured routinely in the clinic and are not mentioned in the guideline in CKD patients since few clinical or mechanistic studies have been conducted on the proteins to date. The CRIC study of CKD patients has identified a relationship between ApoB and renal outcomes, although this was not independent of other clinical and laboratory parameters [6]. The different results between ours and the CRIC study may be attributable to a different target population (outpatient versus CKD), study outcome (ESRD alone versus composite renal outcome) and investigated parameters. Furthermore, the CRIC study did not adjust LDL subfractions in the relationships.

The serum ApoB concentration reflects the amount of atherogenic lipid burden, as the subendothelial retention of ApoB-containing lipoproteins is a key insult in the development of atherosclerosis [29]. The ionic interaction between the negatively charged sulfate group on the extracellular matrix proteoglycans and the basic amino acids within ApoB promotes this deposition of lipid particles in the subendothelium [30]. These lipid deposits accelerate oxidation and inflammation, both of which result in endothelial dysfunction and the formation of atherosclerotic plaques [31]. The inflammation is also perpetuated by autoimmunity targeting the ApoB100 isoform [32]. In a similar way, glomerular endothelial cells and kidney vessels can become sites of oxidation and inflammation secondary to high ApoB concentrations, resulting in progression of CKD [33–35].

This study revealed that the ApoA1 concentration is not independently related to ESRD. ApoA1, the main protein constituent of HDL cholesterol, was originally thought to have a number of antiatherosclerotic influences [36]. However, when compared with concrete status of ApoB as a risk factor of atherosclerotic disease, the role of ApoA1 appears to be more limited [37], as the status of HDL for the prediction of atherosclerosis has recently been challenged [38]. Consistent with this doubt, an experimental study has shown that the plasma ApoA1 concentration does not reflect the real concentration within the endothelium [39]. Furthermore, another study found that HDL cholesterols lose their anti-inflammatory properties, and may in fact be converted into pro-inflammatory agents during chronic inflammatory disorders such as CKD [40]. These findings may explain the lack of association identified between ApoA1 and ESRD in this study.

Although the data obtained are informative, there were some limitations to the study. Neither causal relationships nor the underlying mechanisms linking ApoB and the risk of ESRD could be determined, although potential mechanisms are discussed above. In addition, other unmeasured lipid parameters, such as other subclasses of Apo, could have had a confounding effect on the association identified. The lifestyles and diets of the patients were not reviewed, which could have affected the concentrations of lipid parameters, including ApoB.

This study has demonstrated the association between ApoB and the risk of ESRD, adding to the related associations with cardiovascular morbidity and mortality identified in previous studies. Furthermore, the association was independent of the conventional lipid parameters and LDL subfraction. Future studies should aim to determine an appropriate strategy of ApoB monitoring, aiming to reduce the risk of ESRD.

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CONFLICT OF INTEREST STATEMENT

None declared.

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