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Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multiethnic population samples

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Abstract

Background. Circulating lipoproteins and their protein constituents, apolipoproteins, are risk factors for chronic kidney disease (CKD). The associations between apolipoprotein A1, apolipoprotein B and their ratio with glomerular filtration rate estimated from the new CKD Epidemiology Collaboration (CKD-EPI) equation (eGFR) are not well studied in the general population.

Methods. Associations between apolipoprotein A1, B and their ratio with the outcomes of eGFR, CKD (eGFR <60 mL/min/1.73m^2) and albuminuria were examined in the Atherosclerosis Risk in Communities study (ARIC, n = 10 292, 1996–98) and the Third National Health and Nutrition Examination Survey (NHANES III, n = 7023, 1988–91). Cross-sectional multivariable-adjusted analyses were performed using linear and logistic regression. Prospective analyses related baseline apolipoprotein levels to subsequent CKD incidence over 10 years using the ARIC Carotid MRI follow-up cohort (n = 1659).

Results. Higher apolipoprotein A1 quartiles were associated with a lower prevalence of CKD [Q4 versus Q1: odds ratio (OR) 0.73, P-trend = 0.02 in ARIC; Q4 versus Q1: OR 0.53, P-trend <0.01 in NHANES III] as well as with higher eGFR (P-trend <0.01 in ARIC and NHANES III). No consistent significant associations were found for apolipoprotein B in either study. The apolipoprotein B/A1 ratio was significantly associated with eGFR across quartiles in both studies (P-trend <0.01) and with CKD in ARIC (Q4 versus Q1: OR 1.23, P-trend = 0.01). Prospectively, there were trends for the association of apolipoproteins with incident CKD [Q4 versus Q1: incidence rate ratio (IRR) = 0.68 for apolipoprotein A1, P-trend = 0.1; Q4 versus Q1: IRR = 1.35 for apolipoprotein B, P-trend = 0.2]. Associations were not systematically stronger when comparing traditional lipids (total cholesterol, low-density lipoprotein or high-density lipoprotein) to apolipoproteins.

Conclusions. Higher serum apolipoprotein A1 was associated with lower prevalence of CKD and higher eGFR estimated by the CKD-EPI equation in two large multiethnic population-based samples. While apolipoprotein B showed no consistent associations, a higher apolipoprotein B/A1 ratio was significantly associated with lower eGFR in both studies. The direction and magnitude of the longitudinal associations between apolipoproteins and CKD incidence were overall similar to those observed cross-sectionally. No consistent differences became apparent between traditional lipids and apolipoproteins.

Keywords: apolipoprotein; ARIC; chronic kidney disease; epidemiology; NHANES

Introduction

Chronic kidney disease (CKD) affects an estimated 10% of the general adult population in the USA [1, 2]. Despite the disease burden posed by CKD, its etiological factors are still incompletely understood. Serum lipids, such as higher total cholesterol, low-density lipoprotein (LDL) and triglycerides or lower high-density lipoprotein (HDL), are well-established risk factors for the development of atherosclerotic cardiovascular disease. Evidence has also accumulated for their role as risk factors for CKD [3, 4].

While apolipoprotein A1 is the major protein constituent of HDL, apolipoprotein B is a protein constituent of intermediate-density lipoprotein (IDL), very low density lipoprotein (VLDL) and LDL particles [5, 6]. Apolipoproteins can be measured independent of fasting status. There is ongoing debate as to whether they provide prognostic information for cardiovascular disease equivalent or superior to that available from traditional lipid markers

[7–19]. In some studies, the apolipoprotein B/A1 ratio was shown to be one of the strongest risk predictors for cardiovascular events [10, 16].

Lower apolipoprotein A1 and higher apolipoprotein B were found to be associated with CKD in several retrospective and prospective studies [3, 20–24]. These general population-based studies have mostly been limited in size and few included non-Caucasian participants. To our knowledge, none assessed the relationship of apolipoproteins with continuous glomerular filtration rate estimated by the new CKD Epidemiology Collaboration (CKD-EPI) equation (eGFR).

The objectives of our analyses were to ascertain the associations between apolipoprotein A1, apolipoprotein B and the apolipoprotein B/A1 ratio with the continuous outcomes of eGFR and the urinary albumin-to-creatinine ratio (UACR) as well as the presence of CKD in two large multiethnic general population-based studies.

Materials and methods

Study participants: Third National Health and Nutrition Examination Survey

The National Center for Health Statistics of the United States Centers for Disease Control and Prevention conducted the Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994 as a cross-sectional study [25]. Its study population consisted of a representative sample of the general non-institutionalized civilian US population, using a stratified multistage probability design [25]. Very young, elderly, non-Hispanic black and Mexican American persons were deliberately oversampled for improved estimate precision in these groups. More detailed information about the study participants and methods has been published before [26].

The NHANES III analyses in this report were limited to 17 030 adult participants ≥20 years who were examined at a mobile examination center as part of the regular study protocol. Since only the first enrollment phase of NHANES III (1988–91) included apolipoprotein measurements, all examinees enrolled in the second phase were excluded. Of the remaining 8213 participants, those with missing serum apolipoprotein A1 ($n = 609$) and B ($n = 28$) as well as serum creatinine ($n = 185$) measurements were sequentially excluded. The final study population consisted of 7391 participants (90% of Phase I participants were aged over 20 years). Of the 7391 participants, 7023 had information on all covariates available and were included in the multivariable-adjusted analyses unless otherwise indicated.

Study participants: Atherosclerosis Risk in Communities study

The Atherosclerosis Risk in Communities (ARIC) study consists of population-based samples from four US communities. The detailed design of ARIC has been described [27]. In summary, 15 792 women and men were recruited between 1987 and 1989 based on probability sampling techniques. Participants underwent standardized examinations in field center clinics, including measurements of demographic, lifestyle and physical factors as well as laboratory parameters. They were re-examined at follow-up visits every 3 years. This report is based on the fourth examination of the cohort (1996 through 1998), when apolipoprotein A1 and B as well as UACR were measured. The overall ARIC cohort follow-up rate was 80% for Visit 4 [28]. All participants with missing serum creatinine and apolipoprotein measurements were excluded. Of the remaining individuals, information on all relevant covariates was available for 10 292 participants.

In 2005/06, the ARIC Carotid MRI follow-up study examined 2066 ARIC participants, aged 60–84 years. Participants were selected using a stratified plan to oversample for plaque based on carotid thickness at a prior ultrasound examination (1993–98) [29]. Of these participants, 1659 had available serum creatinine and relevant covariate measurements and were examined in the prospective analyses.

Measurements

Information was obtained on a wide variety of sociodemographic characteristics (such as age, race–ethnic group, gender, medication use) by administration of a standard questionnaire in NHANES III and ARIC participants. Race–ethnicity was reported in the categories of non-Hispanic white, non-Hispanic black, Mexican American and others for NHANES III. Race was reported in the categories of white and black for ARIC. The interview was followed by a detailed physical examination including blood specimen collection in both NHANES III and ARIC [27].

In NHANES III, diabetes mellitus was defined by a serum glycated hemoglobin >6.5% according to the 2010 guidelines of the American Diabetes Association [30] and/or self-reported use of anti-diabetic medications in conjunction with a known physician diagnosis of diabetes. In ARIC, diabetes was defined as fasting serum glucose ≥6.99 mmol/L a self-reported previous diagnosis of diabetes or use of anti-diabetic medications.

Mean blood pressure values were obtained from up to six measurements during the home interview and during the subsequent evaluation at the mobile examination center in NHANES III. Hypertension was defined by a mean systolic blood pressure >140 mmHg, mean diastolic blood pressure >90 mmHg and/or by self-reported use of anti-hypertensive medications in conjunction with a known physician diagnosis of hypertension for NHANES III. A similar definition was used for ARIC based on the mean of two blood pressure measurements.

For the NHANES III analysis, current alcohol use was defined as self-reported consumption of 12 alcoholic beverages or more during the previous 12 months. For ARIC, current alcohol intake was defined as self-reported current consumption of alcohol. Current smoking was defined as self-reported current smoking of any cigarettes for NHANES III and ARIC. Body weight and height were measured as defined by a standard protocol, and the body mass index (BMI, kg/m^2) was then calculated in both NHANES III and ARIC. Obesity was defined as BMI ≥30 kg/m^2.

Serum apolipoprotein A1 and B levels were measured regardless of the examinee's fasting status in NHANES III by three different methods: radial immunodiffusion (RID), rate immunonephelometry (INA) and the World Health Organization–International Federation of Clinical Chemistry (WHO–IFCC) method. Results using the RID and INA methods were adjusted to the WHO–IFCC method [31, 32]. The reported coefficients of variation ranged from 2.7 to 20.8% (median <5.2%) [31]. Plasma apolipoprotein A1 and B were measured in ARIC by an immunonephelometric assay with a BNII nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL). Apolipoprotein measurements were begun in September 2009 and completed by January 2010. The reliability coefficients for 397 blinded replicates were 0.88 (0.92 after removing 8 pairs of outliers) for apolipoprotein A1 and 0.89 (0.96 after removing 11 pairs of outliers) for apolipoprotein B. This immunonephelometric methodology is in contrast to radioimmunoassay and immunoturbidometry methods used for previous ARIC apolipoprotein measurements among Visit 1 and 2 participants, techniques that demonstrated lower precision than current standardized assays.

Serum triglyceride, HDL and total cholesterol levels were measured regardless of the examinee's fasting status [31, 33]. In ARIC, >95% of participants were fasting at least 8 h prior to the blood draw for the plasma lipid measurements. Due to their skewed distribution, serum triglycerides were log transformed for all analyses in both ARIC and NHANES III. Serum LDL was calculated by using the Friedewald equation [31, 34]. Serum LDL was only calculated if triglycerides were <4.52 mmol/L and if the participants were fasting for >9 h prior to blood draw for NHANES III [31].

Urinary albumin and creatinine were measured as described before [33, 35]. The UACR was calculated and microalbuminuria (MA) was then defined as UACR ≥30 mg albumin/g creatinine.

The modified kinetic Jaffe reaction using a Hitachi 737 analyzer (Boehringer Mannheim Corp., Indianapolis, IN) was employed to measure serum creatinine concentrations in NHANES III [31]. In ARIC, blood creatinine was measured with the modified kinetic Jaffe reaction from plasma samples in Visit 4 using a DACOS Chemistry Analyzer (Dart Reagent Systems; Coulter Electronics, Hialeah, FL) [34, 36]. For the ARIC Carotid MRI visit (MRI visit), blood creatinine was measured with the modified kinetic Jaffe reaction using the Olympus AU400e automated chemistry analyzer.

Standard creatinine was calculated for NHANES III using the equation: standard creatinine = 0.96 × serum creatinine – 0.184 [37]. ARIC Visit 4 creatinine measurements were calibrated for interlaboratory differences to the Cleveland Clinic formula by subtraction of 21.22 μmol/L [38] and standardized to the Roche enzymatic method by multiplication with 0.95 [37]. The MRI visit creatinine measurements did not require any standardization.

Outcome definition

In the cross-sectional analyses of NHANES III and ARIC Visit 4, the following outcome measures were evaluated: continuous eGFR, continuous UACR and the presence of CKD or MA. Moreover, incident CKD and MA were evaluated between ARIC Visit 4 and the MRI visit (average follow-up time 8.6 years).

The eGFR was calculated using the CKD-EPI equation: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] × 1.159 [if Black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1 and max indicates the maximum of Scr/κ or 1 [2].

Persons with an eGFR of <15 mL/min/1.73m^2 were treated as if their eGFR was 15 mL/min/1.73m^2 ($n = 13$ in NHANES III, $n = 19$ in ARIC and $n = 3$ at the MRI visit). Similarly, participants with an eGFR of >200 mL/min/1.73m^2 were treated as if their eGFR was 200 mL/min/1.73m^2 ($n = 1$ in NHANES III, $n = 0$ in ARIC and $n = 0$ at the MRI visit).

CKD was defined as an eGFR of <60 mL/min/1.73m^2 according to the most recent Kidney Disease Outcome Quality Initiative guidelines [39]. The definition of the term 'CKD' used in our article corresponds to CKD Stages 3–5. Incident CKD was defined as eGFR below the threshold of 60 mL/min/1.73m^2 at the MRI visit in persons free of CKD at ARIC Visit 4.

Statistical methods

All NHANES III analyses were performed using appropriate sampling weights to account for the complex sampling design according to the NHANES III analytic and reporting guidelines [25]. The application of sampling weights was not necessary for the cross-sectional ARIC Visit 4 analyses. For the longitudinal ARIC Carotid MRI follow-up study, the appropriate sampling weights were applied to account for the sampling design [40].

Serum apolipoprotein levels were evaluated in quartiles. Within each apolipoprotein quartile, the study sample was characterized by determining age-standardized mean values or proportions of the outcomes and all covariates. For NHANES III, age standardization was based on the 1980 Census population, as specified in the NHANES III analytic and reporting guidelines [25].

For the evaluation of trends across apolipoprotein quartiles, P-values were calculated by adjusted multiple linear and logistic regression: adjustment variables are detailed in the table footnotes.

Associations between apolipoprotein quartiles and eGFR or proportion of participants with CKD were first obtained from adjusted multiple linear and logistic regression analyses including age, gender and race as covariates. Subsequently, multivariable-adjusted analyses were conducted including additional covariates thought to be risk factors for CKD (length of education, obesity, diabetes, hypertension, smoking, alcohol, serum triglycerides) in the full model. P-values for trends of associations across quartiles of the exposure variables were calculated from regression models including a quartile indicator variable and adjusted for the variables listed in the table footnotes.

Collinearity was determined for triglycerides, LDL, HDL and total cholesterol as additional covariates using variance inflation factors. Multicollinearities with variance inflation factors exceeding 10 prevented the inclusion of LDL, HDL and total cholesterol into the full model.

Interactions were tested across strata of race, obesity, diabetes, hypertension, age and gender by including a multiplicative interaction term into the age-, sex- and race-adjusted regression models.

Bootstrap analysis was performed to compare effect size coefficients of the fourth quartile between apolipoprotein and traditional lipids applying 50 replications in ARIC Visit 4 and between 45 and 50 replications in NHANES III analyses.

Reported P-values are two sided. Statistical analyses were performed using STATA version 11.1, Special Edition (StataCorp LP, College Station, TX).

Results

Study population characteristics

Demographic characteristics of the study samples are displayed in Table 1. Mean eGFR was 99.9 mL/min/1.73m^2 in NHANES III and 84.1 mL/min/1.73m^2 in ARIC. CKD was present in 4.4% of NHANES III and 6.8% of ARIC Visit 4 participants, congruent with the higher average age in ARIC. Mean apolipoprotein A1 and B levels were similar in both studies.

Kidney function across apolipoprotein quartiles

The distribution of eGFR and CKD prevalence by quartiles of apolipoprotein A1, B and the apolipoprotein B/A1 ratio is shown for both NHANES III and ARIC in Table 2. Across quartiles, eGFR was significantly higher

Table 1. Demographic characteristics of the study populations[a]

	ARIC Visit 4 (1996–98)	NHANES III (1988–91)
Variable	Mean/proportion	Mean/proportion
n of study population	10 292[b]	7023[c]
Age, years	62.9 (5.7)	44.6 (0.5)
Ethnic group		
Non-Hispanic white	79.1	79.0
Non-Hispanic black	20.9	10.0
Mexican American		4.8
Other		6.2
High school education or more	81.0	74.9
Male	43.1	48.3
Triglycerides, geometric mean, mmol/L	1.42	1.30
HDL, mmol/L	1.30 (0.43)	1.33 (0.013)
LDL, mmol/L	3.17 (0.86)	3.32 (0.031)
Total cholesterol, mmol/L	5.20 (0.95)	5.32 (0.023)
Cholesterol-lowering medication use	14.3	3.8
Alcohol use, current	49.3	57.3
Smoking, current	14.5	30.2
Hypertension	47.2	24.0
Obesity (BMI ≥30 kg/m^2)	34.6	20.6
Diabetes	16.5	5.4
eGFR by CKD-EPI, mL/min/1.73m^2	84.1 (15.4)	99.9 (0.6)
CKD presence (eGFR <60 mL/min/1.73m^2)	6.8	4.4
UACR, geometric mean	4.3	7.2
MA presence (UACR ≥30 mg/24 h)	8.2	7.8
Apolipoprotein A1, g/L	1.46 (0.32)	1.44 (0.009)
Apolipoprotein B, g/L	1.00 (0.24)	1.05 (0.008)
Apolipoprotein B/A1 ratio	0.71 (0.2)	0.75 (0.01)

[a]Data presented as mean [standard deviation (SD) for ARIC and linearized standard error (SE) for NHANES III] for continuous variables and proportion for categorical variables. NHANES III results are weighted for survey sampling design and are representative of the US population.

[b]Study population size 10 128 for LDL, 10 272 for cholesterol-lowering medication use, 10 202 for UACR and MA in ARIC.

[c]Study population size 6995 for HDL, 3079 for LDL, 7022 for total cholesterol, 6716 for cholesterol-lowering medication use, 6820 for UACR and MA in NHANES III.

Table 2. Measures of kidney function by quartiles of apolipoprotein A1, B and their ratio[a]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend[b]
Apolipoprotein A1					
Cutoffs in g/L for ARIC, *n* = 10 292	<1.24	1.24–1.41	1.42–1.63	>1.63	
Cutoffs in g/L for NHANES III, *n* = 7023	<1.27	1.27–1.40	1.41–1.59	>1.59	
CKD % in ARIC	8.7	6.8	6.1	5.4	<0.001
CKD % in NHANES III[c]	5.9	5.5	4.4	3.2	<0.001
eGFR (SD) in ARIC	82.3 (15.7)	83.7 (15.3)	84.7 (15.5)	85.6 (15.0)	<0.001
eGFR (SE) in NHANES III[c]	98.3 (0.6)	99.5 (0.6)	100.0 (0.6)	101.7 (0.4)	<0.001
Apolipoprotein B					
Cutoffs in g/L for ARIC, *n* = 10 292	<0.83	0.83–0.97	0.98–1.13	>1.13	
Cutoffs in g/L for NHANES III, *n* = 7023	<0.88	0.88–1.04	1.05–1.23	>1.23	
CKD % in ARIC	5.5	6.7	7.0	7.7	0.002
CKD % in NHANES III[c]	2.9	4.0	5.0	5.2	<0.001
eGFR (SD) in ARIC	85.6 (15.7)	84.1 (15.5)	84.0 (15.1)	82.7 (15.3)	<0.001
eGFR (SE) in NHANES III[c]	101.6 (0.5)	100.3 (0.5)	99.2 (0.6)	99.2 (0.7)	0.001
Apolipoprotein B/A1 ratio					
Cutoffs for ARIC, *n* = 10 292	<0.56	0.56–0.68	0.69–0.84	>0.84	
Cutoffs for NHANES III, *n* = 7023	<0.60	0.60–0.73	0.74–0.91	>0.91	
CKD % in ARIC	5.3	6.1	7.0	8.7	<0.001
CKD % in NHANES III[c]	3.8	3.3	4.7	6.0	<0.001
eGFR (SD) in ARIC	85.8 (15.6)	84.7 (15.4)	83.7 (15.0)	82.1 (15.5)	<0.001
eGFR (SE) in NHANES III[c]	101.3 (0.5)	101.1 (0.5)	99.0 (0.5)	98.0 (0.5)	<0.001

[a]NHANES III results are weighted for survey sampling design and are representative of the US population.
[b]Obtained from age-adjusted linear or logistic regression.
[c]Standardized to age, based on 1980 census population.

with higher apolipoprotein A1 (P-trend <0.001) and lower with higher apolipoprotein B (P-trend ≤0.001) and apolipoprotein B/A1 ratio (P-trend <0.001). Likewise, CKD was significantly less prevalent with higher apolipoprotein A1 quartiles (P-trend <0.001) and more prevalent with higher apolipoprotein B (P-trend ≤0.002) and apolipoprotein B/A1 ratio quartiles (P-trend <0.001).

Multivariable-adjusted analyses of apolipoprotein associated with eGFR and CKD

In the models adjusting only for demographics (age, sex and race–ethnicity), higher apolipoprotein A1 quartiles were significantly associated with lower CKD prevalence as well as higher eGFR in both studies (P-trend ≤0.002). Higher apolipoprotein B quartiles were associated with higher CKD prevalence and lower eGFR, respectively (P-trend ≤0.001).

In the fully adjusted model which also included education, diabetes, hypertension, current smoking, current alcohol use, obesity and serum triglycerides (Table 3), the associations with apolipoprotein A1 remained statistically significant in both ARIC and NHANES. In contrast, the association with apolipoprotein B was no longer significant with hypertension and current smoking being the main confounders to account for the association.

Higher quartiles of the apolipoprotein B/A1 ratio were significantly associated with higher prevalence of CKD in ARIC (P-trend = 0.011) as well as lower eGFR in both NHANES III and ARIC in the full model (Table 3). Point estimates for CKD across quartiles were comparable in ARIC and NHANES III.

Results were similar in analyses using the full model in ARIC stratified by gender (data no shown).

Addition of HDL and total cholesterol to the covariates of the full model

After inclusion of serum HDL and total cholesterol in the full model analyses of both populations, the association of apolipoprotein A1 with kidney function remained similar and significant (P = 0.018 in ARIC and P < 0.001 in NHANES), while those of apolipoprotein B and the apolipoprotein B/A1 ratio were attenuated and did not reach statistical significance. However, the resulting collinearities prevented the consideration of HDL and total cholesterol for the final full model analyses (Supplementary Tables 1a and 1b).

Comparison of traditional lipids with apolipoproteins

When traditional lipids (HDL and LDL, the total cholesterol/HDL ratio) were compared to apolipoproteins (A1, B and the B/A1 ratio, respectively) in ARIC and NHANES, effect sizes and P-trends across quartiles indicated no consistent differences in their association with eGFR or CKD (Supplementary Tables 2a and 2b). Comparing coefficients for the fourth quartiles of HDL with those of apolipoprotein A1 in bootstrap analyses, apolipoprotein A1 was significantly stronger associated with eGFR compared to HDL in NHANES III but not in ARIC (data not shown). For LDL compared to apolipoprotein B, there were no consistent differences between the measures. When either the total cholesterol/HDL or the LDL/HDL ratio was compared to the apolipoprotein B/A1 ratio, outcomes did not change systematically across both study populations.

Table 3. Multivariable-adjusted association of CKD and mean eGFR with quartiles of apolipoprotein A1, B and their ratio[a]

	ARIC	NHANES III	ARIC	NHANES III
	CKD (eGFR <60 mL/min/1.73m^2)	CKD (eGFR <60 mL/min/1.73m^2)	eGFR mL/min/1.73m^2	eGFR mL/min/1.73m^2
	OR (95% CI)	OR (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Apolipoprotein A1				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.80 (0.64 to 0.99)	1.02 (0.55 to 1.89)	1.23 (0.43 to 2.02)	0.76 (−1.03 to 2.54)
Quartile 3	0.76 (0.60 to 0.97)	0.76 (0.50 to 1.17)	1.87 (1.04 to 2.71)	1.26 (−0.10 to 2.62)
Quartile 4	0.73 (0.56 to 0.95)	0.53 (0.31 to 0.91)	2.55 (1.65 to 3.44)	2.45 (0.91 to 3.98)
P for trend	0.015	0.008	<0.001	0.003
Apolipoprotein B				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.12 (0.89 to 1.42)	1.27 (0.74 to 2.17)	−0.70 (−1.48 to 0.09)	−0.37 (−1.82 to 1.08)
Quartile 3	1.08 (0.86 to 1.38)	1.61 (1.08 to 2.39)	−0.26 (−1.05 to 0.54)	−0.71 (−2.25 to 0.83)
Quartile 4	1.12 (0.88 to 1.42)	1.32 (0.85 to 2.06)	−1.24 (−2.06 to −0.41)	−1.55 (−3.19 to 0.09)
P for trend	0.47	0.24	0.015	0.10
Apolipoprotein B/A1 ratio				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.01 (0.79 to 1.29)	0.78 (0.50 to 1.21)	−0.28 (−1.07 to 0.51)	−0.03 (−1.35 to 1.30)
Quartile 3	1.09 (0.85 to 1.40)	1.04 (0.69 to 1.56)	−0.82 (−1.64 to 0.003)	−1.64 (−3.13 to −0.16)
Quartile 4	1.23 (0.95 to 1.57)	1.20 (0.79 to 1.82)	−1.99 (−2.86 to −1.12)	−2.36 (−3.76 to −0.97)
P for trend	0.011	0.09	<0.001	0.001

[a]All results adjusted for age, race, gender, education, hypertension, smoking (current), alcohol (current), diabetes, obesity, triglycerides; $n = 10\,292$ for ARIC, $n = 7023$ for NHANES III.

Table 4. IRR of CKD by quartiles of apolipoprotein and traditional lipids[a]

Apolipoprotein A1[b]	IRR (95% CI)	P-value	HDL[b]	IRR (95% CI)	P-value
Quartile 1	Reference		Quartile 1	Reference	
Quartile 2	0.69 (0.48–0.99)	0.046	Quartile 2	0.68 (0.47–0.99)	0.046
Quartile 3	0.68 (0.46–1.02)	0.06	Quartile 3	0.59 (0.39–0.91)	0.02
Quartile 4	0.68 (0.45–1.02)	0.06	Quartile 4	0.60 (0.39–0.93)	0.02
P for trend	0.10		P for trend	0.03	
Apolipoprotein B[c]			LDL[c]		
Quartile 1	Reference		Quartile 1	Reference	
Quartile 2	1.27 (0.85–1.89)	0.24	Quartile 2	0.86 (0.59–1.26)	0.44
Quartile 3	1.30 (0.86–1.95)	0.21	Quartile 3	0.91 (0.62–1.34)	0.63
Quartile 4	1.35 (0.90–2.02)	0.15	Quartile 4	1.15 (0.80–1.63)	0.45
P for trend	0.16		P for trend	0.43	
Apolipoprotein B/A1 ratio[d]			TC/HDL ratio[d]		
Quartile 1	Reference		Quartile 1	Reference	
Quartile 2	1.21 (0.83–1.77)	0.31	Quartile 2	1.34 (0.91–1.98)	0.14
Quartile 3	1.02 (0.68–1.53)	0.94	Quartile 3	1.17 (0.77–1.76)	0.46
Quartile 4	1.32 (0.89–1.94)	0.17	Quartile 4	1.55 (1.01–2.40)	0.047
P for trend	0.30		P for trend	0.10	

[a]All results adjusted for age, race, gender, education, hypertension, smoking (current), alcohol (current), diabetes, obesity and triglycerides.
[b]$n = 1659$ for apolipoprotein A1 subpopulation with available HDL results and for HDL subpopulation.
[c]$n = 1639$ for apolipoprotein B subpopulation with available LDL results and for LDL subpopulation.
[d]$n = 1659$ for apolipoprotein B/A1 ratio subpopulation with available total cholesterol/HDL results and for total cholesterol/HDL subpopulation.

Multivariable-adjusted analyses of apolipoprotein and albuminuria

Regression analyses of apolipoprotein A1, B and the ratio revealed significant associations with continuous UACR (natural log transformation) in ARIC, but these associations were not significant in NHANES III. With the exception of the apolipoprotein B/A1 ratio in ARIC, no significant association between apolipoprotein and MA was found in either study (Supplementary Table 3).

Longitudinal analyses of incident CKD in ARIC

Results of the longitudinal analyses are displayed in Table 4. The incidence rate ratio (IRR) of CKD was lower in the higher quartiles of apolipoprotein A1 (Q1 versus Q4:

IRR = 0.68; 95% confidence interval 0.45–1.02), but the overall trend of the association was not significant (P-trend = 0.1). For higher apolipoprotein B quartiles, the IRR was 1.35 in Q4 versus Q1 but did not reach significance (P-trend = 0.2). The apolipoprotein B/A1 ratio at ARIC Visit 4 was not significantly associated with subsequent CKD incidence. There were no associations between apolipoprotein and incident MA (data not shown).

Results of the longitudinal apolipoprotein analyses remained unchanged after addition of a covariate for prevalent coronary artery disease at ARIC Visit 4 (data not shown).

Prospective comparison of apolipoprotein A1 with HDL revealed significant associations between HDL quartiles and subsequent CKD incidence (Q1 versus Q4: IRR = 0.60, Table 4), including a significant trend (P-trend = 0.03). When LDL was compared to apolipoprotein B, effect sizes were smaller for LDL (Q1 versus Q4: IRR = 1.15). The total cholesterol/HDL ratio showed larger effect sizes compared to the apolipoprotein B/A1 ratio (Q1 versus Q4: IRR = 1.55).

Interaction analyses

Higher apolipoprotein B levels were more strongly associated with lower eGFR in blacks compared to whites in both NHANES III ($P < 0.001$) and ARIC ($P = 0.002$).

Therefore, stratified analyses by the main race–ethnic groups were performed for the associations between apolipoprotein and eGFR or CKD prevalence. The results of the stratified NHANES III analyses suggested stronger associations between both apolipoprotein B and apolipoprotein A1 with eGFR in blacks (Supplementary Tables 4a and 4b). In ARIC, the race-stratified analyses confirmed the stronger associations in blacks for apolipoprotein B and apolipoprotein A1 with eGFR, with associations approximately twice as strong compared to whites.

Discussion

Primary findings

The cross-sectional analysis of two independent general population-based studies documents significant associations between lower serum apolipoprotein A1 as well as higher apolipoprotein B/A1 ratio quartiles with lower eGFR. Additional associations were found between lower apolipoprotein A1 quartiles and higher prevalence of CKD in both studies. Apolipoprotein B showed no consistent associations. Direct comparison of apolipoproteins with traditional lipids documented no systematic difference in their association with eGFR or CKD. The samples included significant proportions of blacks, in whom the associations between apolipoproteins and eGFR were stronger compared to whites.

Longitudinal studies of baseline apolipoprotein levels and subsequent CKD incidence in the smaller ARIC Carotid MRI cohort were not statistically significant, most likely due to the limited sample size. However, point estimates indicate trends similar to the cross-sectional analyses.

In context of the current literature

Our analyses confirm the previously described associations of apolipoprotein A1 with kidney function and CKD [3, 22, 41–44]. While the ratio of apolipoprotein B/A1 is a well-studied risk factor for cardiovascular disease [7, 10, 16], this is—to the best of our knowledge—the first report on its association with kidney function in large population-based cohorts. Our study is also one of the first to relate apolipoproteins to eGFR in the general population utilizing the novel CKD-EPI equation, which was shown to be more accurate in the higher eGFR range >60 mL/min/1.73m^2 when compared to the older Modification of Diet in Renal Disease (MDRD) Study or the Cockcroft–Gault equations [2].

Biological mechanisms

Despite several years of research, the exact role of apolipoproteins in CKD remains a matter of debate. Atherosclerosis of the small- and medium-sized vessels is an important risk factor for kidney function decline with progressive age [45–48]. Apolipoprotein A1 is an integral component of serum HDL particles, whose protective association with atherosclerosis is well described. Similarly, apolipoprotein B is a component of serum IDL, VLDL and LDL particles, which may contribute to atherogenesis. It is conceivable that the association of apolipoproteins with kidney function is in part mediated by the effects of these lipoprotein particles on atherogenesis. Hypertension, obesity and diabetes are common risk factors for atherosclerosis and may also be associated with apolipoprotein levels. We therefore attempted to minimize confounding by these factors through adjustment in the statistical analyses.

Apolipoprotein B may reflect the true number of circulating LDL particles more accurately in individuals whose LDL particles contain on average less cholesterol than normal: this discrepancy is more frequent in patients with metabolic syndrome and obesity [49]. For this reason, the use of apolipoprotein B measurement has been advocated for patients with an intermediate risk for cardiovascular events [49]. If a similar argument could be made in support of apolipoproteins with respect to the risk for CKD remains unclear. In this respect, our analyses of traditional lipids compared to apolipoproteins may be informative: they suggest no clear superiority of apolipoproteins over traditional lipid measures in their association with eGFR or CKD. This may have implications since apolipoprotein measurements can be more costly than traditional lipid measurements.

The similarities in results after adjustment for a known diagnosis of coronary artery disease suggest that additional mechanisms beyond atherosclerosis of the major vessels may be involved in the association of apolipoproteins with kidney function. These could involve glomerulosclerosis, small vessel arteriosclerosis or directly toxic effects of apolipoprotein and its associated lipids on glomerular cells, such as podocytes [50–52]. Toxic effects could be mediated by several mechanisms: increased oxidative stress due to lower levels of the antioxidative, apolipoprotein A1-enriched HDL fraction, cytotoxic effects of oxidized, apolipoprotein B-rich LDL, the local

formation of lipid-laden foam cells and activation of inflammation [4]. HDL and apolipoprotein A1 have also been shown to exert anti-inflammatory effects [52, 53].

The cross-sectional analyses do not rule out altered apolipoprotein levels resulting from reduced kidney function, and indeed, apolipoprotein A1 concentrations differed slightly but significantly by quartile of eGFR (Supplementary Table 5). However, as the lowest quartile of kidney function includes individuals up to an eGFR of 75 mL/min/1.73m^2, it is unlikely that our results are driven by reduced kidney function causing low apolipoprotein A1 concentrations. In addition, our longitudinal analyses show similar results in both effect sizes and direction when compared to the cross-sectional associations.

Univariate analyses in both NHANES III and ARIC showed higher mean apolipoprotein A1 and lower apolipoprotein B values in the black subpopulations compared to their white counterparts (data not shown). This finding is in line with other studies, where apolipoprotein values were compared between black and other ethnic populations [16, 53]. The stronger association between apolipoproteins and kidney function in blacks compared to whites raises the important question about the underlying mechanisms. Genetic factors could play an important role in this regard [54].

Strengths and limitations

Major strengths of our analyses include the large size and multiethnic composition of the general population-based ARIC and NHANES III study samples. Furthermore, data from the longitudinal ARIC Carotid-MRI study allowed us to examine disease incidence. Estimating eGFR using the recently developed CKD-EPI equation should describe kidney function more accurately in the eGFR range >60 mL/min/1.73m^2 than previous equations. Direct comparison of the reproducible and significant association between apolipoprotein A1 and eGFR estimated from the MDRD equation instead of the CKD-EPI equation revealed tighter confidence intervals and smaller P-values in ARIC, supporting our use of the newer CKD-EPI equation (data not shown).

Importantly, our analyses are the first to assess the association between apolipoprotein B/A1 ratio and kidney function in two independent large population samples.

A limitation of all observational studies is the inability to establish causal relationships. Nevertheless, the observed strength and consistency of associations across different population groups in different studies lend considerable support to our findings.

Our observational analyses could further be limited by effects of confounding factors. For example, low socioeconomic status and associated lifestyle factors have been implicated in the development of CKD [55, 56]. Low apolipoprotein A1 and elevated apolipoprotein B levels are more common in people of low socioeconomic status [57, 58]. We attempted to adjust for socioeconomic status by including a variable for attained length of education.

Another potential confounder could be the role of medication intake: use of anti-hypertensive and anti-diabetic medications has the potential to lower the risk for CKD development and could serve as surrogate marker for access to medical care and overall socioeconomic status. These potential confounders were addressed by adjusting for the use of anti-hypertensive, anti-diabetic and anti-lipidemic medications. Only anti-hypertensive and anti-diabetic medication use were kept in the final multivariable-adjusted model after cholesterol-lowering medication use did not modify the point estimate results by >10% in both NHANES III and ARIC.

Different assays were used to measure apolipoproteins in ARIC and NHANES and absolute values may therefore not be directly comparable between studies. However, all methods used in NHANES were adjusted to the WHO–FCC method. Details of the methods and coefficients of variation can be found in the NHANES manual [31].

Conclusions

Significant associations between higher serum apolipoprotein A1 quartiles and lower prevalence of CKD as well as higher eGFR were found in cross-sectional multivariable-adjusted regression analyses of two large general population samples: NHANES III and ARIC. While apolipoprotein B showed only inconsistent associations, a higher apolipoprotein B/A1 ratio was significantly associated with lower eGFR in both studies. The direction and magnitude of the longitudinal associations between apolipoproteins and CKD incidence were overall similar to those observed cross-sectionally. There were no consistent differences between traditional lipids and apolipoproteins in their association with eGFR or CKD.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.

(See related article by Arnadottir. The question of primary lipid nephrotoxicity. *Nephrol Dial Transplant* 2012; 27: 2614–2615.)

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Contribution of calcium, phosphorus and 25-hydroxyvitamin D to the excessive severity of secondary hyperparathyroidism in African-Americans with CKD

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Abstract

Background. Parathyroid hormone (PTH) levels in African-American (AA) chronic kidney disease (CKD) patients exceed those in patients of other races; mechanisms are unknown.

Methods. We performed a cross-sectional analysis of initial laboratory data collected on 2028 CKD patients (505 AA) from US practices using a laboratory CKD service. Serum calcium (Ca), phosphorus (P), 25-hydroxyvitamin D (25-D) and plasma PTH levels were compared between the two groups.

Results. Mean PTH for AA exceeded PTH for non-AA in Stages 2–5 ($P < 0.001$, all four stages). 25-D levels were higher for non-AA in Stages 1–3 ($P < 0.001$). Serum Ca and P did not differ between groups at any stage. Full adjustment for these variables using multivariable generalized linear modeling did not remove the effect of AA race: AA PTH values exceeded non-AA values in CKD Stages 2–5 ($P < 0.02$, all four stages). Serum Ca, P and 25-D were all inversely correlated with PTH levels irrespective of race, but all factors combined accounted for ~42% of the variance in PTH.

Conclusions. PTH rises with progressive CKD stage far more in AA than in non-AA patients, and only a moderate component of the rise in PTH is explained by changes in serum Ca, P and 25-D in either group. These findings