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Associations between serum apolipoproteins, urinary albumin excretion rate, estimated glomerular filtration rate, and diabetic retinopathy in individuals with type 2 diabetes

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Abstract

The published data regarding the role of serum apolipoprotein (apo) A-I, apoB, and the apoB/A-I ratio in the risk of diabetic retinopathy remain inconsistent, and there is limited information about the effect of renal status on their associations in individuals with type 2 diabetes. The aim of this study was to investigate whether serum apoA-I, apoB, and the apoB/A-I ratio are associated with the presence of diabetic retinopathy in type 2 diabetes and to explore whether the relationships between these apolipoproteins and diabetic retinopathy are modified by urinary albumin excretion rate (UACR) and estimated glomerular filtration rate (eGFR).

In total, 1215 individuals with type 2 diabetes were included in this cross-sectional study. Serum levels of apoA-I and apoB and the apoB/apoA-I ratio were measured. A logistic regression model was performed to explore associations of apolipoproteins with retinopathy.

Individuals with diabetic retinopathy had significantly lower levels of serum apoA-I and higher apoB/apoA-I ratio than those without diabetic retinopathy. In the multivariable analyses, the associations between apoA-I and diabetic retinopathy and between the apoB/apoA-I ratio and diabetic retinopathy were statistically significant after adjustment for the traditional risk factors (odds ratio [OR] per standard deviation [SD] increase in the log-transformed value; 0.55, 95% confidence interval (CI); 0.32 to 0.97, $P = .038$; OR per SD increase in the log-transformed value; 2.83, 95% CI; 1.18 to 6.76, $P = .019$; respectively). Additional adjustments for UACR or eGFR removed the significant associations.

In individuals with type 2 diabetes, serum apoA-I and the apoB/apoA-I ratio are associated with presence of diabetic retinopathy, which might be attributable to the correlated changes in UACR and eGFR.

Abbreviations: apo = apolipoprotein, BP = blood pressure, CI = confidence intervals, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NPDR = non-proliferative diabetic retinopathy, OR = odds ratio, PDR = proliferative diabetic retinopathy, SD = standard deviation, UACR = urinary albumin excretion rate.

Keywords: albuminuria, apolipoprotein A-I, apolipoproteins B, diabetic retinopathy, glomerular filtration rate

1. Introduction

Diabetic retinopathy is 1 common complication, which causes visual impairment and blindness in individuals with diabetes mellitus (DM).[1] Diabetic retinopathy might be related with increased risk of cardiovascular disease and mortality in individuals with type 2 DM.[2] Chronic hyperglycemia, hypertension, and the duration of diabetes are well-established risk factors for diabetic retinopathy; however, the risk of diabetic retinopathy could not be completely explained just by these factors, and other factors might be implicated in the pathogenesis of diabetic retinopathy.[1]

The associations of apolipoprotein (apo) A-I, apoB, and the apoB/apoA-I ratio with angiopathy have been explored. ApoA-I is present in high-density lipoprotein, which is involved in reverse cholesterol transport.[3] ApoB is the structural protein of low-density lipoprotein, very low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein(a).[3] Mounting evidence has demonstrated that these apolipoproteins are strongly linked to cardiovascular disease risk,[4,5] but their potential role in the risk of diabetic retinopathy remains less consistent. In the literature, some studies supported the close relations of apoA-I, apoB, and the apoB/apoA-I ratio with the risk of diabetic retinopathy,[6–9]

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while others did not.[10] In addition, the renal status of study subjects, which might be related to apolipoprotein abnormalities, was unspecified or not considered in most studies and there is limited information about its effect on the associations between apolipoprotein and retinopathy in individuals with type 2 DM.

Therefore, we tested the hypothesis that apoA-I, apoB and the apoB/A-I ratio are associated with the presence of diabetic retinopathy in Korean individuals with type 2 DM. We further explored whether the relationships between these apolipoproteins and diabetic retinopathy are modified by urinary albumin excretion rate and estimated glomerular filtration rate.

2. Subjects and methods

2.1. Study population

The current cross-sectional study was performed with 1,215 individuals with type 2 DM randomly chosen using a random number table from patients who visited the diabetes clinic of Chonnam National University Hospital in Korea. The study was conducted between May 2017 and September 2018. The diagnosis of type 2 DM was based on the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus".[11] Hypertension was settled by to the intake of antihypertensive agents or blood pressure (BP) ≥140/90 mmHg. The clinical data, which include smoking status, diabetes duration, and other health factors, were gathered from standardized inquiries. Individuals who had a history of chronic liver disease, pancreatitis, advanced renal dysfunction (serum creatinine more than 177 μmol/L), infection, alcoholism, malignancy, or glucocorticoid use were excluded from the study. The study was approved by an ethics committee of Chonnam National University Hospital, with informed consent obtained from all study subjects.

2.2. Methods

After 12 hours fasting, venous blood samples were collected. We measured serum lipid concentrations (total cholesterol, triglycerides, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) by using an AU5400 analyzer (Olympus, Tokyo, Japan). We analyzed serum concentrations of apoA-I and apoB immunoturbidimetrically (Beckman Coulter Inc., FL). Inter- and intra-assay coefficients of variation for apoB and apoA-I ranged from 1% to 3%, relying on the matrix of control samples and apolipoprotein concentrations. The measure of urinary albumin excretion was done using urinary albumin-to-creatinine ratio (UACR) in random urine samples. Urinary albumin concentrations were determined by an immunoturbidimetric commercial kit (Randox, Antrim, UK). Serum creatinine levels were determined by the Jaffe method, calibrated to isotope dilution mass spectrometry. The calculation of estimated glomerular filtration rate (eGFR) was done using the Chronic Kidney Disease Epidemiology Collaboration Eq. ([12]). Following dilation of the pupils, fundoscopy was carried out by ophthalmologists to assess diabetic retinopathy. The study subjects were divided into 3 groups: no diabetic retinopathy, non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). Both these last groups were considered as diabetic retinopathy.

2.3. Statistical analysis

Sample size was determined to detect a small effect size (d) of 0.2 with an alpha of 0.05 and 80% power. By using G*Power 3.1.9.2,[13] the sample size was calculated for a 1:2 ratio of retinopathy/no retinopathy using 2-tailed test. The estimated sample size was 886.

Values were represented as the means ± standard deviation for quantitative variables and frequencies (percentages) for qualitative variables unless otherwise stated. Normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Data with skewed distributions were logarithmically transformed before analysis, and the values are given as a geometric mean (95% confidence intervals [CI]). For continuous parameters, a Mann–Whitney *U* test or Student *t* test was performed, while for categorical parameters, the chi-squared test was performed. For comparisons of the transformed data, parametric analysis was conducted, and similar *P* values were obtained when data with skewed distributions were compared by using a Mann–Whitney *U* test. A multiple linear regression model was used to compare mean apolipoprotein concentrations according to the degree of diabetic retinopathy after adjusting for the confounders. In order to analyze the association of apolipoproteins with retinopathy, multivariable analysis using the logistic regression model was conducted with the identified independent parameters and the previously reported parameters having independent relations. The Hosmer–Lemeshow test was conducted to assess the goodness-of-fit of the model, and $P > .05$ was considered as a good model. Predictive properties of logistic regression model were assessed by calculating the area under the receiver operating characteristic curve (AUROC). Model 1 was adjusted for sex and age. Model 2 was adjusted for the same parameters as model 1 plus body mass index, hypertension, diabetes duration, A1C, use of lipid-lowering agents, and anti-diabetic therapy. Model 3a was adjusted for every Model 2 parameter plus UACR. Model 3b was adjusted for every Model 2 parameter plus eGFR. Using SPSS software version 20.0 (SPSS, Chicago, IL), statistical analyses were carried out. A *P* value $< .05$ was regarded as statistically significant.

3. Results

Individuals with type 2 DM are described in Table 1. Individuals with diabetic retinopathy were older and had higher systolic BP, longer duration of diabetes, lower body mass index, higher A1C levels, lower HDL-C levels, lower eGFR, and higher UACR than those without diabetic retinopathy (Table 1). Individuals with diabetic retinopathy were associated with a higher prevalence of hypertension and insulin use and had lower levels of serum apoA-I and higher apoB-to-apoA-I ratio than those without diabetic retinopathy.

According to the severity of diabetic retinopathy, the average value of serum apolipoprotein levels is represented in Table 2. After adjustment for sex, age, body mass index, hypertension, diabetes duration, A1C, and use of lipid-lowering drugs, oral antihyperglycemic agents, and insulin in Model 2, the mean apoA-1 levels significantly differed according to the severity of diabetic retinopathy (no diabetic retinopathy, 1.26 g/L, 95% CI 1.24–1.29; NPDR, 1.22 g/L, 95% CI 1.18–1.26; PDR, 1.19 g/L, 95% CI 1.15–1.24; *P* for trend = .030). Likewise, the apoB/apoA-I ratio was significantly different according to the severity of diabetic retinopathy (no diabetic retinopathy, 0.71, 95% CI 0.69–0.73; NPDR, 0.75, 95% CI 0.71–0.78; PDR, 0.78, 95% CI 0.74–0.83; *P* for trend = .021).

In order to evaluate the effects of apolipoprotein levels on diabetic retinopathy, we conducted logistic regression analyses

Table 1

Characteristics of individuals with type 2 diabetes.

	Without diabetic retinopathy	With diabetic retinopathy	*P* value
Number	743	472	
Age, yr	57.8 ± 14.1	63.0 ± 11.3	<.001
Men, %	398 (53.6)	240 (50.8)	.355
Diabetes duration, yr	4.1 (3.8–4.4)	11.3 (10.3–12.4)	<.001
Current smoking, n (%)	140 (18.8)	95 (20.1)	.581
Hypertension, n (%)	395 (53.2)	311 (65.9)	<.001
Body mass index, kg/m^2	24.8 ± 4.1	23.9 ± 4.5	<.001
Waist circumference, cm	86.8 ± 10.2	86.4 ± 11.0	.584
Systolic blood pressure, mmHg	126.0 ± 16.8	128.6 ± 16.3	.009
Diastolic blood pressure, mmHg	78.1 ± 10.9	77.1 ± 11.1	.128
A1C, %	8.7 ± 2.5	9.0 ± 2.2	.012
A1C, mmol/mol	71 ± 27	75 ± 24	.012
Triglyceride, mmol/L	1.54 (1.48–1.60)	1.46 (1.39–1.53)	.124
Total cholesterol, mmol/L	4.73 ± 1.44	4.59 ± 1.22	.068
LDL-C, mmol/L	2.84 ± 1.03	2.78 ± 1.01	.351
HDL-C, mmol/L	1.17 ± 0.35	1.12 ± 0.37	.015
Non-HDL-C, mmol/L	3.55 ± 1.28	3.43 ± 1.52	.125
Ratio of triglyceride to HDL-C	3.34 (3.18–3.51)	3.36 (3.16–3.56)	.719
ApoB, g/L	0.87 (0.85–0.90)	0.86 (0.84–0.89)	.521
ApoA-I, g/L	1.26 (1.24–1.29)	1.20 (1.17–1.23)	.002
ApoB/apoA-I ratio	0.72 (0.70–0.74)	0.75 (0.73–0.78)	.033
UACR, mg/gCr	18.8 (16.6–21.2)	60.7 (52.3–70.3)	<.001
UACR ≥30 mg/gCr, n (%)	251 (33.8)	300 (63.6)	<.001
eGFR (mL/min/1.73 m^2)	89.5 (87.5–91.4)	74.0 (71.9–76.0)	<.001
eGFR <60 mL/min/1.73 m^2, n (%)	66 (8.9)	123 (26.1)	<.001
Use of oral antihyperglycemic drugs, n (%)	555 (74.7)	353 (74.8)	.972
Use of insulin, n (%)	107 (14.4)	178 (37.7)	<.001
Use of lipid-lowering drugs, n (%)	237 (31.9)	173 (36.7)	.088

Results are given as the mean ± standard deviation or geometric mean (95% confidence intervals). Values in parentheses are percentages. A1C = glycated hemoglobin, apoA-I = apolipoprotein A-I, apoB = apolipoprotein B, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, UACR = urinary albumin excretion rate.

(Table 3, Fig. 1). After adjustment for sex, age, body mass index, hypertension, diabetes duration, A1C, and use of insulin, oral antihyperglycemic drugs, and lipid-lowering drugs (Model 2), the association between apoA-1 and diabetic retinopathy was statistically significant (odds ratio [OR] per standard deviation [SD] increase in the log-transformed value, 0.55; 95% CI, 0.32–0.97, $P = .038$). The χ^2 value for the Hosmer–Lemeshow test was 10.895 with 8 degrees of freedom ($P = .208$), and the AUROC was 0.660 (SE 0.016, 95% CI 0.629–0.669, Supplementary Fig. 1, http://links.lww.com/MD/C985). Additional adjustment for UACR treated as continuous or categorical variable negated its statistically significant relationship (Model 3a). Similarly, additional adjustment for eGFR treated as continuous or categorical variable abolished its statistically significant relationship (Model 3b). For these final models (model 3a and 3b), the Hosmer-Lemeshow test showed significant goodness of fit (all $P > .05$).

After adjusting for sex, age, body mass index, hypertension, diabetes duration, A1C, and use of insulin, oral antihyperglycemic drugs, and lipid-lowering drugs (Model 2), the association between the apoB/apoA-I ratio and diabetic retinopathy came out statistically significant (OR per SD increase in the log-transformed value, 2.83; 95% CI, 1.18–6.76, $P = .019$). The χ^2 value for the Hosmer-Lemeshow test was 12.864 with 8 degrees of freedom ($P = .117$), and the AUROC was 0.691 (SE 0.016, 95% CI 0.660–0.722, Supplementary Fig. 1, http://links.lww.com/MD/C985). Additional adjustment for UACR treated as continuous or categorical variable canceled its statistically significant relationship (Model 3a). Likewise, additional adjustment for eGFR treated as continuous or categorical variable also invalidated its statistically significant relationship (Model 3b). For these final models (model 3a and 3b), the Hosmer-Lemeshow test showed significant goodness of fit (all $P > .05$).

A test of interaction between apolipoprotein-related parameters and other covariates with diabetic retinopathy as the dependent variable was carried out in the multivariable model, but no significant interactions were found between apolipoprotein-related parameters and any of the covariates ($P > .05$ for interactions).

Table 2

Comparison of mean values of serum apoB- and apoA-I- associated factors according to the grade of diabetic retinopathy in individuals with type 2 diabetes.

	No diabetic retinopathy (n = 743)	NPDR (n = 294)	PDR (n = 178)	*P* for trend
Model 1				
ApoA-I, g/L	1.26 (1.24–1.29)	1.21 (1.18–1.25)	1.18 (1.14–1.23)	.002
ApoB, g/L	0.87 (0.85–0.89)	0.86 (0.83–0.90)	0.89 (0.84–0.93)	.705
ApoB/apoA-I ratio	0.72 (0.70–0.74)	0.74 (0.71–0.77)	0.78 (0.74–0.82)	.023
Triglyceride, mmol/L	1.52 (1.47–1.58)	1.47 (1.38–1.56)	1.53 (1.42–1.66)	.537
HDL-C, mmol/L	1.17 (1.14–1.19)	1.12 (1.08–1.16)	1.10 (1.04–1.15)	.023
LDL-C, mmol/L	2.83 (2.76–2.90)	2.79 (2.67–2.91)	2.81 (2.66–2.96)	.844
Model 2				
ApoA-I, g/L	1.26 (1.24–1.29)	1.22 (1.18–1.26)	1.19 (1.15–1.24)	.030
ApoB, g/L	0.86 (0.84–0.88)	0.87 (0.84–0.91)	0.91 (0.86–0.96)	.210
ApoB/apoA-I ratio	0.71 (0.69–0.73)	0.75 (0.71–0.78)	0.78 (0.74–0.83)	.021
Triglyceride, mmol/L	1.51 (1.45–1.57)	1.49 (1.40–1.59)	1.58 (1.46–1.71)	.511
HDL-C, mmol/L	1.16 (1.13–1.19)	1.13 (1.09–1.17)	1.11 (1.05–1.16)	.208
LDL-C, mmol/L	2.78 (2.71–2.86)	2.85 (2.73–2.97)	2.92 (2.76–3.07)	.349

apoA-I = apolipoprotein A-I, apoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Results are given as mean or geometric mean (95% confidence interval). Each risk factor is in separate model.

Model 1: Adjusted for sex and age.

Model 2: Adjusted for Model 1 plus body mass index, hypertension, diabetes duration, glycated hemoglobin, and use of lipid-lowering drugs, oral antihyperglycemic drugs, and insulin.

Table 3

Odds ratios (95% confidence interval) for diabetic retinopathy according to serum apoB- and apoA-I- associated parameters in individuals with type 2 diabetes.

	Model 1	Model 2	Model 3a	Model 3b
Variables	OR (95% CI) & *P*-value	OR (95% CI) & *P*-value	OR (95% CI) & *P*-value	OR (95% CI) & *P*-value
Apo A-I†	0.45 (0.28–0.72) 0.001	0.55 (0.32–0.97) 0.038	0.62 (0.35–1.10) 0.105 (0.64 (0.36–1.14) 0.130)	0.65 (0.37–1.15) 0.135 (0.64 (0.36–1.14) 0.129)
ApoB†	1.02 (0.72–1.44) 0.924	1.28 (0.85–1.93) 0.231	–	–
ApoB/apoA-I ratio†	2.44 (1.16–5.13) 0.019	2.83 (1.18–6.76) 0.019	1.97 (0.80–4.84) 0.141 (2.04 (0.84–4.99) 0.118)	2.25 (0.93–5.45) 0.074 (2.32 (0.96–5.63) 0.063)
Triglyceride†	0.83 (0.49–1.40) 0.870	1.10 (0.59–2.02) 0.769	–	–
HDL-C	0.99 (0.98–1.00) 0.009	0.99 (0.98–1.00) 0.096	–	–
LDL-C	1.00 (1.00–1.00) 0.592	1.00 (1.00–1.01) 0.252	–	–

apoA-I = apolipoprotein A-I, apoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Data† were logarithmically transformed before analysis. Each risk factor is in separate model.

Model 1: adjusted for sex and age

Model 2: adjusted for Model 1 plus body mass index, hypertension, diabetes duration, glycated hemoglobin, and use of lipid-lowering drugs, oral antihyperglycemic agents, and insulin

Model 3a: adjusted for Model 1 plus UACR† [alternatively, UACR treated as categorical variable (≥30 mg/gCr vs <30 mg/gCr)]

Model 3b: adjusted for Model 1 plus eGFR† [alternatively, eGFR treated as categorical variable (<60 mL/min/1.73 m^2 vs ≥60 mL/min/1.73 m^2)]

4. Discussion

From the present study of Korean individuals with type 2 DM, we found that serum apoA-I levels and the apoB/apoA-I ratio were associated with the presence of diabetic retinopathy after adjustment for traditional risk factors including A1C, the duration of diabetes and hypertension. Furthermore, our results suggest that the relations of apoA-I and the apoB/apoA-I ratio with diabetic retinopathy might be partly mediated by the correlated changes in UACR and eGFR in individuals with type 2 DM.

Even though many studies have explored the relationships between serum lipids and diabetic retinopathy, the results are mixed,[14–17] suggesting there is no single parameter of serum lipids consistently linked to the risk of diabetic retinopathy. Rema et al[14] reported a positive association between serum triglycerides and diabetic retinopathy in type 2 diabetes. Tan et al[18] showed that LDL cholesterol was associated with diabetic retinopathy.[18] In contrast, Wong et al[15] reported no associations between serum lipid levels such as triglycerides, HDL-C, and LDL-C, and diabetic retinopathy. Similar to the findings by Wong et al,[15] our results also revealed nonsignificant relations of serum lipid levels with diabetic retinopathy after adjustment for traditional risk factors including A1C, diabetes duration, and hypertension.

It has been increasingly interesting to know whether apolipoproteins such as apoA-I and apoB and the apoB/apoA-I ratio are implicated in development of angiopathy.[19–21] ApoA-I, which is a chief component of antiatherogenic HDL, is known to be a protecting factor against cardiovascular disease.[4] On the other hand, total apoB concentrations indicate the total number of atherogenic particles, and increased values of total apoB are suggested as a risk factor for cardiovascular disease.[3] In addition, the apoB/apoA-I ratio reflects the 2 sides of atherogenic and antiatherogenic risk.[5] A growing body of evidence indicates that apoA-I, apoB and the apoB/apoA-I ratio may impart better risk prediction for cardiovascular disease than traditional lipid parameters.[3,5,19] Recently, the relationship of these apolipoproteins with diabetic retinopathy has been investigated in several studies. After studying 224 patients with type 1 diabetes or type 2 diabetes, Sasongko et al[6] reported the inverse relationship between apoA-I levels and the prevalence of diabetic retinopathy, and the positive relationship of the apoB/apoA-I ratio and apoB with the prevalence of diabetic retinopathy, and also suggested that these apolipoproteins might be more accurate biomarkers for diabetic retinopathy than traditional lipid parameters. In a follow-up study, Sasongko et al[9] showed that apoA-I revealed more prominent association with the risk of diabetic retinopathy than apoB. Hu et al reported that in 50 Chinese type 2 diabetes patients with very mild NPDR or PDR, the low apoA-I/apoB ratio and decreased levels of apoA-I were associated with PDR.[7] Deguchi et al[8] reported that in 116 Japanese type 2 diabetes patients with NPDR or PDR, the apoB/apoA-I ratio might be related to PDR progression in patients with diabetic retinopathy. Furthermore, our data showed that apoA-I and the apoB/apoA-I ratio, but not apoB, were associated with the presence of diabetic retinopathy after adjustment for sex, age, body mass index, hypertension, A1C, diabetes duration, and use of insulin, oral antihyperglycemic drugs, and lipid-lowering drugs in the multiple regression models (Model 2 in Table 3). Therefore, our results support the previous evidence that apoA-I levels and a balance between serum levels of apoA-I and apoB might be implicated in the pathogenesis of diabetic retinopathy.

Previous investigations encompass few data regarding the underlying factors linking apoA-I and apoB/apoA-I ratio with diabetic retinopathy in individuals with type 2 DM. ApoA-I mRNA is detected in the retina and retinal pigment epithelium, and apoA-I is found in the vitreous fluid.[22–25] ApoA-I might be involved in intraretinal reverse lipid transport.[26] ApoA-I overexpression in the retina and increased apoA-I levels in the vitreous fluid and retinal pigment epithelium are thought to play a role in protective mechanism against lipid deposition in diabetic patients.[24,26,27] ApoA-I also has anti-inflammatory and antioxidant effects.[3,28,29] In addition, genetic deficiency of ApoA-I has been shown to be associated with retinopathy.[30,31] Furthermore, plasma apolipoprotein levels might have an impact on urinary albumin excretion and renal function in diabetic patients.[32,33] Sasongko et al[34] reported that serum apoA-I and

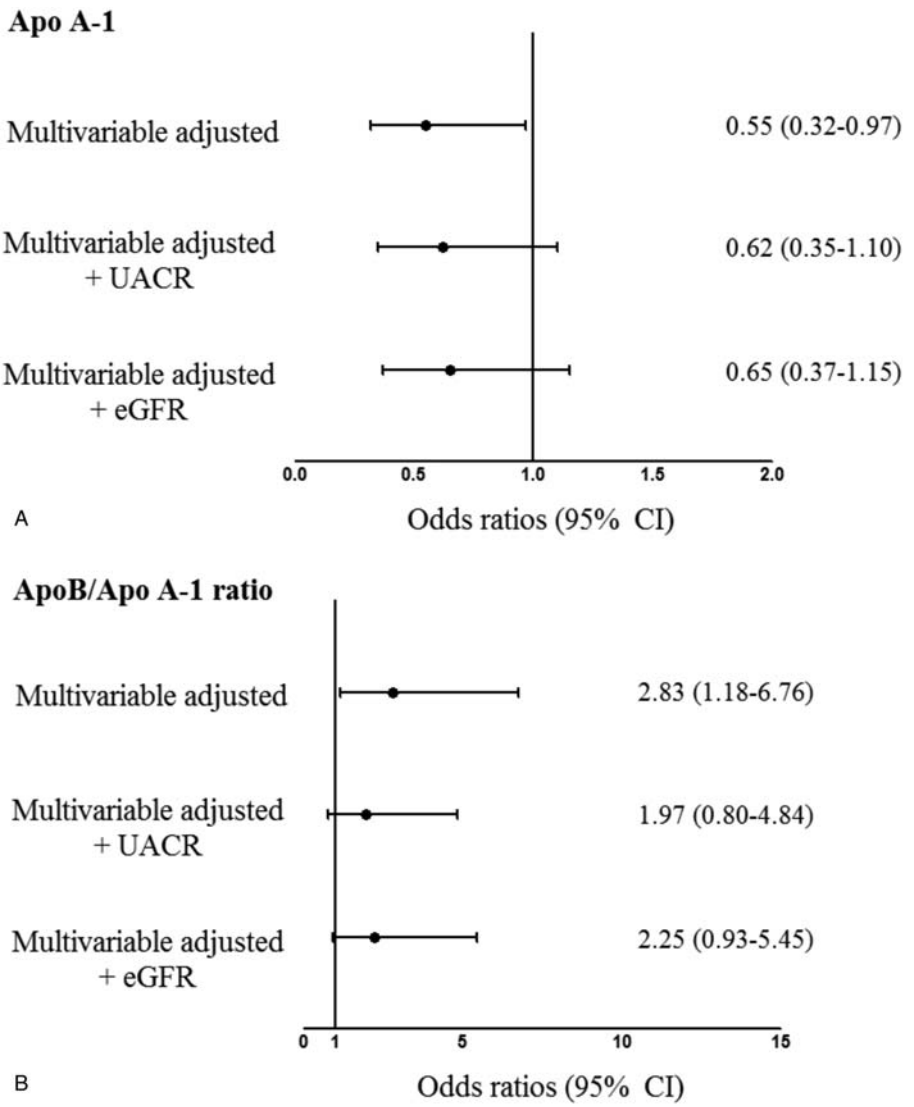

Figure 1. Odds ratios for diabetic retinopathy according to serum apoA-I and apoB/apoA-I ratio in individuals with type 2 diabetes after adjustment for confounders. A: apoA-I as an independent variable, B: apoB/apoA-I ratio as an independent variable. Adjusted for sex, age, body mass index, hypertension, diabetes duration, glycated hemoglobin, and use of lipid-lowering drugs, oral antihyperglycemic agents, and insulin. UACR and eGFR were treated as continuous variables. eGFR = estimated glomerular filtration rate, UACR = urinary albumin excretion rate.

apoB/apoA-I ratio might affect endothelial function in the microvasculature in individuals with diabetes. Tolonen et al[35] have shown that the apoB/apoA-I ratio might be a predictive marker for progression to macroalbuminuria and end-stage renal disease in individuals with type 1 DM, after adjustment for the risk factors such as A1C, diabetes duration, smoking, sex, systolic BP, and body mass index. Goek et al[36] reported strong relationship of apoA-I and apoB/apoA-I ratio with eGFR in multiethnic population study. Therefore, we presume that the relations between apolipoproteins and diabetic retinopathy might be linked to renal status including UACR and eGFR. Statistically significant relations of apoA-I and the apoB/apoA-I ratio with diabetic retinopathy diminished when UACR or eGFR was further added into the Model 2 after adjustment for other covariates in the multiple regression models (Model 3 in Table 3). Therefore, our findings suggest that the putative risk of increased apoB/apoA-I ratio and decreased apoA-I levels for diabetic retinopathy in individuals with type 2 DM might be in part mediated by the correlated changes in UACR and eGFR, to the extent that apolipoproteins might be causally related to the pathogenesis of diabetic retinopathy.

There are some limitations in this study. Because of cross-sectional nature, we could not establish the causality of the associations observed in this study. In addition, diabetic retinopathy grading in our study was not based on fluorescein angiography which can visualize retinal vasculature, although dilated fundus examination is widely used to evaluate diabetic retinopathy in clinical practice.[1,37] Therefore, the degree of diabetic retinopathy might be underestimated. However, despite these limitations, our study might provide important information on relationships between apolipoproteins, urinary albumin excretion, renal function, and diabetic retinopathy.

In conclusion, our study shows that in individuals with type 2 DM the associations of apoA-I and the apoB/apoA-I ratio with

diabetic retinopathy might be attributable to the correlated changes in UACR and eGFR. Further larger prospective investigations are necessary to identify temporal relationships among apolipoproteins, urinary albumin excretion, renal function, and diabetic retinopathy in individuals with type 2 DM.

Author contributions

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References

[1] Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–36.
[2] Cheung N, Wong TY. Diabetic retinopathy and systemic vascular complications. Prog Retin Eye Res 2008;27:161–76.
[3] Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern Med 2006;259:437–46.
[4] Walldius G, Jungner I. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. J Intern Med 2004;255:188–205.
[5] Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy—a review of the evidence. J Intern Med 2006;259:493–519.
[6] Sasongko MB, Wong TY, Nguyen TT, et al. Serum apolipoprotein AI and B are stronger biomarkers of diabetic retinopathy than traditional lipids. Diabetes Care 2011;34:474–9.
[7] Hu A, Luo Y, Li T, et al. Low serum apolipoprotein A1/B ratio is associated with proliferative diabetic retinopathy in type 2 diabetes. Graefes Arch Clin Exp Ophthalmol 2012;250:957–62.
[8] Deguchi Y, Maeno T, Saishin Y, et al. Relevance of the serum apolipoprotein ratio to diabetic retinopathy. Jpn J Ophthalmol 2011;55:128–31.
[9] Sasongko MB, Wong TY, Nguyen TT, et al. Novel versus traditional risk markers for diabetic retinopathy. Diabetologia 2012;55:666–70.
[10] Maioli M, Tonolo G, Pacifico A, et al. Raised serum apolipoprotein (a) in active diabetic retinopathy. Diabetologia 1993;36:88–90.
[11] Expert Committee on the Diagnosis and Classification of Diabetes MellitusReport of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(suppl 1):S5–20.
[12] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[13] Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
[14] Rema M, Srivastava BK, Anitha B, et al. Association of serum lipids with diabetic retinopathy in urban South Indians—the Chennai Urban Rural Epidemiology Study (CURES) Eye Study–2. Diabet Med 2006;23:1029–36.
[15] Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multiethnic cohort in the United States. Am J Ophthalmol 2006;141:446–55.
[16] Wong TY, Cheung N, Tay WT, et al. Prevalence and risk factors for diabetic retinopathy: the Singapore Malay Eye Study. Ophthalmology 2008;115:1869–75.
[17] Zhou Y, Wang C, Shi K, et al. Relationship between dyslipidemia and diabetic retinopathy: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e12283.
[18] Tan GS, Gan A, Sabanayagam C, et al. Ethnic differences in the prevalence and risk factors of diabetic retinopathy: the Singapore epidemiology of eye diseases study. Ophthalmology 2018;125:529–36.
[19] McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008;372:224–33.
[20] Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026–33.
[21] Emerging Risk Factors C, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009;302:1993–2000.
[22] Li CM, Chung BH, Presley JB, et al. Lipoprotein-like particles and cholesteryl esters in human Bruch's membrane: initial characterization. Invest Ophthalmol Vis Sci 2005;46:2576–86.
[23] Li CM, Clark ME, Chimento MF, et al. Apolipoprotein localization in isolated drusen and retinal apolipoprotein gene expression. Invest Ophthalmol Vis Sci 2006;47:3119–28.
[24] Simo R, Garcia-Ramirez M, Higuera M, et al. Apolipoprotein A1 is overexpressed in the retina of diabetic patients. Am J Ophthalmol 2009;147:319–25.
[25] Yamane K, Minamoto A, Yamashita H, et al. Proteome analysis of human vitreous proteins. Mol Cell Proteomics 2003;2:1177–87.
[26] Tserentsoodol N, Gordiyenko NV, Pascual I, et al. Intraretinal lipid transport is dependent on high density lipoprotein-like particles and class B scavenger receptors. Mol Vis 2006;12:1319–33.
[27] Simo R, Higuera M, Garcia-Ramirez M, et al. Elevation of apolipoprotein A-I and apolipoprotein H levels in the vitreous fluid and overexpression in the retina of diabetic patients. Arch Ophthalmol 2008;126:1076–81.
[28] Hill SA, McQueen MJ. Reverse cholesterol transport—a review of the process and its clinical implications. Clin Biochem 1997;30:517–25.
[29] Yui Y, Aoyama T, Morishita H, et al. Serum prostacyclin stabilizing factor is identical to apolipoprotein A-I (Apo A-I). A novel function of Apo A-I. J Clin Invest 1988;82:803–7.
[30] Ng DS, O'Connor PW, Mortimer CB, et al. Case report: retinopathy and neuropathy associated with complete apolipoprotein A-I deficiency. Am J Med Sci 1996;312:30–3.
[31] Ng DS, Leiter LA, Vezina C, et al. Apolipoprotein A-I Q[-2]X causing isolated apolipoprotein A-I deficiency in a family with analphalipoproteinemia. J Clin Invest 1994;93:223–9.
[32] Jensen T, Stender S, Deckert T. Abnormalities in plasmas concentrations of lipoproteins and fibrinogen in type 1 (insulin-dependent) diabetic patients with increased urinary albumin excretion. Diabetologia 1988;31:142–5.
[33] Tolonen N, Forsblom C, Thorn L, et al. Relationship between lipid profiles and kidney function in patients with type 1 diabetes. Diabetologia 2008;51:12–20.
[34] Sasongko MB, Wong TY, Nguyen TT, et al. Serum apolipoproteins are associated with systemic and retinal microvascular function in people with diabetes. Diabetes 2012;61:1785–92.
[35] Tolonen N, Forsblom C, Thorn L, et al. Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia 2009;52:2522–30.
[36] Goek ON, Kottgen A, Hoogeveen RC, et al. Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multiethnic population samples. Nephrol Dial Transplant 2012;27:2839–47.
[37] Cole ED, Novais EA, Louzada RN, et al. Contemporary retinal imaging techniques in diabetic retinopathy: a review. Clin Exp Ophthalmol 2016;44:289–99.