Discordance Between Apolipoprotein B and Low-Density Lipoprotein Cholesterol and Progression of Coronary Artery Calcification in Middle Age

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Background: A high level of apolipoprotein B (apoB) is associated with incident coronary artery disease (CAD) when low-density lipoprotein cholesterol (LDL-C) level is discordantly low or concordantly high. However, data on the relationship of apoB with subclinical measure of CAD are limited.

Methods and Results: A total of 14,205 men (mean age 41.0 years) who were free of cardiovascular disease at baseline and who underwent a health checkup exam, including measurement of coronary artery calcium (CAC), were studied. Of the study group, 2,773 participants (19.5%) had CAC at baseline, and CAC progression was observed in 2,550 (18.0%). The multivariate-adjusted CAC score ratios (95% confidence interval) comparing discordantly high apoB/low LDL-C and concordantly high apoB/high LDL-C with concordantly low apoB/low LDL-C were 1.51 (0.98–2.32) and 2.70 (2.19–3.33), respectively. The corresponding relative risks for CAC progression were 1.26 (1.02–1.56) and 1.49 (1.34–1.66), respectively. These associations did not change appreciably after adjustment for insulin resistance and subclinical inflammation.

Conclusions: Discordant analysis showed that a high apoB level was strongly associated with prevalence and progression of CAC independent of LDL-C in a large cohort of healthy adults. The present study results highlighted the importance of an apoB measure as a potential target for primary prevention of coronary atherosclerosis in healthy adults.

Key Words: Apolipoproteins; Atherosclerosis; Cholesterol; Coronary artery disease

Arterial retention of apolipoprotein B (apoB)-containing particles plays a critical role in the pathogenesis of atherosclerosis.¹ To evaluate the atherogenic risk attributable to apoB particles, measures of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apoB have been proposed.² The first two measures account for the mass of cholesterol within LDL, intermediate density lipoprotein (IDL), lipoprotein (a) (Lp(a)), or very low-density lipoprotein (VLDL) particles. A measure of apoB is the sum of the number of LDL, IDL, Lp(a), and VLDL particles, because each of these lipoprotein particles contains one molecule of apoB.² Although the levels of apoB in most people are highly correlated with those of LDL-C (concordant), cholesterol mass associated with apoB is either greater or lesser than the

average cholesterol mass (discordant) in 10–30% of individuals.^{3,4} These features can explain why conventional analyses, which treated these 2 measures as independent variables, have produced largely negative results in evaluating the predictive superiority of one measure over another.⁵ Accordingly, it is of paramount importance to evaluate differential effects of apoB and LDL-C on the study outcome using discordant analysis, which analyzes these highly correlated factors by categorizing their distribution into concordant or discordant groups. A high correlation between measures in concordant groups is less likely to affect the predictive ability than in the discordant groups.⁴

Multiple epidemiological studies using discordant analysis showed that apoB predicts residual risk in patients with optimal control of LDL-C.^{6,7} Moreover, a recent Mendelian

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randomization study showed that risk of cardiovascular events was determined by a concentration of apoB-containing lipoprotein particles rather than by total cholesterol (TC) mass.⁸ Hence, a measure of apoB is of considerable significance for predicting coronary artery disease (CAD) events beyond a measure of LDL-C.⁹ Nevertheless, few studies have quantified apoB as an early marker of coronary atherosclerosis in a population-based study. Coronary artery calcium (CAC) score is a subclinical measure of calcified atherosclerotic plaque burden used to predict the development of coronary events.¹⁰ Progression of CAC can be helpful as an intermediate outcome in the prediction of cardiovascular disease events in healthy middle-aged adults not likely to experience a clinical CAD event.¹¹

Therefore, we examined the association between LDL-C and apoB with the presence and progression of CAC in a large sample of young and middle-aged asymptomatic men and women participating in a health screening program.

Methods

Subjects

The Kangbuk Samsung Health Study is an ongoing cohort study of adults who underwent comprehensive annual or biennial examinations at the clinics of the Kangbuk Samsung Hospital Screening Center in Seoul and Suwon, South Korea, from 2002 to the present.¹² More than 80% of the examinees were employees of various companies or local governmental organizations. In South Korea, annual or biennial health screening exams are widely performed, as they are mandatory for all workers under the Industrial Safety and Health Law. The remaining examinees voluntarily paid for screening exams. The study population consists of 14,574 Korean men who underwent a comprehensive health check-up examination including CAC measurement on 2 occasions between March 2011 and December 2016. For our data analyses, we excluded participants with CAD ($n=53$), those with cerebrovascular disease ($n=33$), and those with missing data on baseline lipid measures ($n=289$). The total number of eligible participants for this study was 14,205. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (reference number: 2018-06-016), and informed consent was waived because researchers only retrospectively accessed a deidentified database for analysis purposes.

Exposure Assessment

Data on medical history, medication use, family history, smoking history, physical activity, alcohol consumption, and education level were collected through a self-administered questionnaire. Smoking status was categorized into 3 levels: never, former, and current smoker. Excessive alcohol consumption was defined as an average daily alcohol intake ≥ 20 g. Physical activity level was assessed using the Korean-validated short version of the International Physical Activity Questionnaire (IPAQ) and was defined as weekly energy expenditure in metabolic equivalent (MET) hours per week. Body weight was measured to the nearest 0.1 kg using a digital scale with the patient wearing light clothing and no shoes, and height was measured by trained nurses. Body mass index (BMI) was calculated as weight/height squared (kg/m^2), and obesity was defined as a BMI of 25 or higher according to Asian-specific criteria. Depression was assessed by using the Korean version of the Center for Epidemiologic Studies Depression (CES-D) Scale.

Blood pressure (BP) was measured using an automated oscillometric device (Model 53000; Welch Allyn, New York, USA) while participants were in a seated position with the arm supported at heart level. Three BP readings were recorded for each participant, and the average of the second and third readings was used in the analyses to reduce measurement error. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current use of antihypertensive medication. Blood samples were collected after an at least 10-h fast. The methods for measuring serum levels of high sensitive C-reactive protein (hsCRP), TC, LDL-C, triglycerides (TG), and HDL-C have been reported elsewhere.¹³ ApoB was measured using Roche diagnostics reagent kits on an automated chemistry analyzer (Modular DPP; Roche Diagnostics, Tokyo, Japan). Serum insulin was measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics, Tokyo, Japan). Insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-IR): fasting serum glucose (FSG; mg/dL) $\times$ fasting insulin ($\mu\text{IU}/\text{mL}$)/405. We used the low serum LDL-C/apoB ratio as an indirect measure of LDL particle size, and fasting remnant cholesterol was calculated as TC minus LDL-C minus HDL-C.

Outcomes

The CAC was measured using a Lightspeed VCT XTe-64 slice multidetector computed tomography (CT) scanner (GE Healthcare, Tokyo, Japan) following the same protocol in both study centers. CT scans were obtained using a standard procedure with slice thickness, 2.5 mm; rotation time, 400 ms; tube voltage, 120 kV; and tube current, 124 mAs (310 mA $\times$ 0.4 s) under electrocardiogram-gated dose modulation. CAC scores were calculated by using the method described in Agatston et al.¹⁴ The presence of CAC was defined as a CAC score >0 , and CAC progression was defined as follows: CAC score >0 at follow-up examination among those who had no CAC at baseline; change in CAC score/year ≥ 10 at follow up for those with $0 < \text{baseline CAC} < 100$; or a percentage change in CAC score (annualized change in CAC score divided by that at baseline) $\geq 10\%$ at follow up for those who had baseline a CAC score ≥ 100 .¹⁵ Intra- and inter-observer reliability of the CAC scores was excellent (intra-class correlation coefficient, 0.99).

Statistical Analyses

The characteristics of participants are displayed as mean and standard deviation for continuous variables with normal distribution, interquartile ranges for continuous variables with skewed distribution, and percentages for categorical variables. Participants were classified into low, middle, and high tertile groups based on apoB and LDL-C measures. After computing the median values of apoB and LDL-C, we categorized the participants into the following 4 groups: (1) both apoB and LDL-C measures less than the corresponding median values; (2) apoB measure less than its median value and LDL-C measure greater than or equal to its median value; (3) apoB measure greater than or equal to its median value and LDL-C measure less than its median value; and (4) both apoB and LDL-C measures greater than the corresponding median values (**Figure**). The association between discordance/concordance of apoB and LDL-C and CAC progression was evaluated using Poisson regression with robust error variance estimation to compute risk ratio (RR) and the 95% confidence interval

Figure. Quadrant plot of low-density lipoprotein-cholesterol (LDL-C) vs. apolipoprotein B (ApoB). Median values were LDL-C 131 mg/dL and ApoB 102 mg/dL.

Characteristics	ApoB tertile (range)			P value*
	Low (22–92)	Middle (93–113)	High (114–251)	
No.	4,756	4,846	4,603	
Age, years	40.5 (6.2)	41.2 (6.1)	41.4 (5.8)	<0.001
Seoul center, %	43.2	47.0	50.4	<0.001
Education, % ^A	88.5	87.8	86.9	0.089
Depression, % ^B	6.9	6.7	7.3	0.636
Current smoking, %	31.1	32.5	37.1	<0.001
Alcohol intake, % ^C	16.4	15.1	12.8	<0.001
HEPA, %	16.4	15.1	12.8	<0.001
BMI, kg/m ²	24.1 (2.9)	25.0 (2.9)	25.7 (2.9)	0.096
WC, cm	85.0 (8.0)	87.5 (7.6)	89.2 (7.3)	<0.001
Systolic BP, mmHg	114.0 (11.6)	115.4 (12.0)	116.6 (12.3)	<0.001
Diastolic BP, mmHg	74.1 (9.3)	75.7 (9.6)	77.1 (9.9)	<0.001
Hypertension, %	17.5	19.6	21.2	<0.001
FSG, mg/dL	98.2 (14.6)	99.1 (15.4)	101.7 (21.6)	<0.001
HOMA-IR	1.2 (0.8–1.8)	1.4 (1.0–2.1)	1.7 (1.2–2.6)	<0.001
Diabetes, %	7.2	5.5	7.9	<0.001
TC, mg/dL	173.8 (22.4)	203.7 (19.2)	239.6 (27.9)	<0.001
Triglycerides, mg/dL	97.0 (73.0–137.0)	129.0 (96.0–176.0)	164.0 (121.0–223.0)	<0.001
LDL-C, mg/dL	100.5 (18.0)	130.3 (14.9)	163.6 (23.9)	<0.001
HDL-C, mg/dL	55.0 (13.8)	50.6 (11.8)	48.3 (10.3)	<0.001
hsCRP, mg/dL	0.05 (0.03–0.09)	0.06 (0.03–0.11)	0.07 (0.04–0.13)	<0.001
CAC				
0	86.0	81.6	73.5	<0.001
>0, Agatston unit	21.0 (7.0–65.0)	17.0 (4.0–48.0)	18.0 (5.0–53.0)	<0.001

Data are presented as mean (standard deviation), median (interquartile range), or percentage. ^AAt least a college graduate. ^BThe Center for Epidemiologic Studies Depression (CES-D) score of 16 or higher. ^CAlcohol intake of ≥ 20 g/day. ApoB, Apolipoprotein B; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; FSG, fasting serum glucose; HDL-C, high density lipoprotein cholesterol; HEPA, health enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; WC, waist circumference. *P values derived from χ^2 test for categorical variables and 1-way analysis of variance test for continuous variables.

Table 2. Baseline Characteristics by Concordance/Discordance Group

	Concordance/discordance groups (apoB and LDL-C)				P value*
	Low apoB/ Low LDL-C	Low apoB/ High LDL-C	High apoB/ Low LDL-C	High apoB/ High LDL-C	
No.	6,257	1,113	751	6,084	
Age, years	40.8 (6.2)	40.4 (6.2)	41.7 (6.0)	41.3 (5.9)	<0.001
Seoul center, %	44.4	41.8	54.3	49.3	<0.001
Education, % ^A	88.1	89.9	84.8	87.4	0.010
Depression, % ^B	6.8	5.7	9.9	7.0	0.009
Current smoking, %	32.0	27.1	40.6	35.3	<0.001
Alcohol intake, % ^C	32.2	28.7	45.2	34.9	<0.001
HEPA, %	15.9	17.4	14.3	13.2	<0.001
BMI, kg/m ²	24.3 (3.0)	24.5 (2.9)	25.8 (2.8)	25.5 (2.9)	0.016
Obesity, %	34.0	38.7	57.8	52.0	<0.001
WC, cm	85.7 (8.0)	86.0 (7.6)	89.7 (7.1)	88.7 (7.4)	<0.001
Systolic BP, mmHg	114.1 (11.7)	115.9 (11.7)	117.6 (12.9)	116.2 (12.2)	<0.001
Diastolic BP, mmHg	74.5 (9.4)	74.6 (9.2)	78.5 (10.5)	76.5 (9.8)	<0.001
Hypertension, %	18.6	14.1	31.4	19.7	<0.001
FSG, mg/dL	98.6 (15.2)	97.3 (12.8)	105.2 (26.0)	100.4 (18.9)	<0.001
HOMA-IR	1.3 (0.9–1.9)	1.1 (0.8–1.7)	2.0 (1.4–2.8)	1.6 (1.1–2.4)	<0.001
Diabetes, %	6.8	3.3	12.1	6.4	<0.001
TC, mg/dL	177.1 (21.1)	211.7 (16.8)	201.7 (28.9)	233.6 (26.6)	<0.001
Triglycerides, mg/dL	106.0 (77.0–153.0)	106.0 (83.0–140.0)	210.0 (141.0–304.0)	150.0 (112.0–203.0)	<0.001
LDL-C, mg/dL	105.3 (17.1)	139.5 (8.5)	121.5 (9.2)	160.6 (22.3)	<0.001
HDL-C, mg/dL	52.0 (43.0–61.0)	54.0 (47.0–62.0)	42.0 (36.0–49.0)	48.0 (42.0–55.0)	<0.001
Non HDL-C, mg/dL	123.8 (21.1)	156.3 (15.0)	158.3 (29.1)	184. (26.0)	<0.001
ApoB, mg/dL	83.3 (12.6)	97.3 (5.2)	110.0 (6.6)	124.9 (6.6)	<0.001
LDL-C/apoB ratio	1.27 (0.14)	1.44 (0.12)	1.11 (0.10)	1.29 (0.10)	<0.001
Remnant-C, mg/dL	16.0 (10.0–23.0)	16.0 (11.0–22.0)	29.0 (20.0–43.0)	22.0 (15.0–30.0)	<0.001
Medication for dyslipidemia, %	5.2	0.9	8.4	3.4	<0.001
CAC					
0	84.3	86.3	75.4	76.1	<0.001
>0, Agatston unit	21.0 (6.0–62.0)	12.5 (3.0–42.0)	15.0 (6.0–48.0)	17.0 (5.0–52.0)	<0.001

Data are presented as mean (standard deviation), median (interquartile range), or percentage. ^AAt least a college graduate. ^BThe Center for Epidemiologic Studies Depression (CES-D) score of 16 or higher. ^CAlcohol intake of ≥ 20 g/day. Remnant-C, Remnant cholesterol. Other abbreviations as in Table 1. *P values derived from χ^2 test for categorical variables and 1-way analysis of variance test for continuous variables.

(CI). We used 3 multivariate models with progressive adjustments: Model 1 was adjusted for age, sex, year of examination, and study center (Seoul or Suwon); Model 2 was further adjusted for family history of CAD, education, marital status, employment status (yes/no), depressive symptom scores, antidepressant use, smoking status, alcohol consumption, and physical activity level (inactive, minimally active, health-enhancing physical activity [HEPA], or unknown); and Model 3 was further adjusted for systolic BP, diastolic BP, antihypertensive medication, history of type 2 diabetes mellitus, HDL-C, and lipid-lowering medication use. To evaluate the dose-response relationship, we also modeled the association between lipid measure and risk of CAC progression using a restricted cubic spline model. All P values were 2-tailed, and P values <0.05 were considered statistically significant. We used STATA version 14.0 (Stata Corp., College Station, TX, USA) for all data analyses.

Results

The demographic, lifestyle behaviors, and cardio-metabolic features of participants at baseline are summarized in

Table 1. The average age of the study participants was 41.0 years. Participants in the low tertile of apoB were more likely to have a HEPA level and less likely to be current smokers and to have hypertension compared with those in the middle or high apoB tertiles. The high tertile of apoB had participants with the highest baseline BMI, BP, FSG, TC, LDL-C, TG, hsCRP, and HOMA-IR levels. Education and depressive symptoms were not significantly related to the apoB tertile.

The baseline characteristics of the 4 concordance/discordance groups, into which the participants were categorized according to apoB and LDL-C levels (concordantly low apoB/low LDL-C, discordantly low apoB/high LDL-C, discordantly high apoB/low LDL-C, and concordantly high apoB/high LDL-C), are presented in **Table 2**. The proportion of participants with discordantly low and discordantly high apoB was 7.8% and 5.3%, respectively. Participants in the higher apoB groups tended to have unhealthy lifestyle behaviors, such as a current smoking status, excessive alcohol consumption, and lower physical activity. Likewise, BMI, waist circumference, BP, and glucose parameters were higher in the high apoB groups than in the low apoB groups. As expected, unfavorable risk

Table 3. CAC Score Ratios by Tertile for ApoB, Cholesterol Levels, and Concordance/Discordance Between ApoB and LDL-C Levels†

	Multivariate CAC score ratios (95% confidence interval)			
	Crude	Model 1	Model 2	Model 3
ApoB				
First tertile	1.00	1.00	1.00	1.00
Second tertile	2.13 (1.61–2.81)	1.66 (1.29–2.14)	1.88 (1.47–2.40)	1.63 (1.27–2.09)
Third tertile	7.01 (5.38–9.12)	4.50 (3.53–5.74)	4.98 (3.91–6.33)	3.93 (3.06–5.04)
LDL-C				
First tertile	1.00	1.00	1.00	1.00
Second tertile	1.46 (1.11–1.92)	1.45 (1.13–1.85)	1.81 (1.42–2.30)	1.63 (1.28–2.07)
Third tertile	3.14 (2.42–4.09)	2.89 (2.28–3.66)	3.76 (2.97–4.76)	3.24 (2.56–4.10)
Non-HDL-C				
First tertile	1.00	1.00	1.00	1.00
Second tertile	1.60 (1.22–2.11)	1.63 (1.28–2.08)	1.86 (1.46–2.37)	1.62 (1.27–2.07)
Third tertile	3.31 (2.54–4.31)	3.46 (2.73–4.39)	3.92 (3.10–4.96)	3.07 (2.40–3.92)
ApoB/LDL-C				
Low apoB/Low LDL-C	1.00	1.00	1.00	1.00
Low apoB/High LDL-C	0.59 (0.37–0.93)	0.98 (0.64–1.51)	1.33 (0.88–2.03)	1.36 (0.90–2.07)
High apoB/Low LDL-C	3.94 (2.48–6.26)	2.49 (1.63–3.82)	2.05 (1.34–3.13)	1.51 (0.98–2.32)
High apoB/High LDL-C	3.61 (2.87–4.55)	2.84 (2.30–3.49)	3.22 (2.62–3.96)	2.70 (2.19–3.33)
ApoB/Non-HDL-C				
Low apoB/Low non-HDL-C	1.00	1.00	1.00	1.00
Low apoB/High non-HDL-C	0.66 (0.43–1.00)	1.03 (0.69–1.53)	1.22 (0.83–1.79)	1.06 (0.72–1.56)
High apoB/Low non-HDL-C	6.21 (3.58–10.75)	2.61 (1.58–4.32)	2.46 (1.49–4.06)	2.15 (1.31–3.55)
High apoB/High non-HDL-C	3.50 (2.78–4.41)	2.83 (2.30–3.49)	3.10 (2.52–3.81)	2.50 (2.02–3.10)

†CAC ratios derived from Tobit regression models using $\ln(\text{CAC}+1)$ as the outcome. Multivariable model 1 was adjusted for age, year of screening examination, and study center; model 2 was further adjusted for family history of coronary artery disease, education, diabetes, hypertension, smoking status, alcohol consumption, physical activity, and medication for dyslipidemia; model 3 was further adjusted for systolic BP, diastolic BP, BMI, and HDL-C. Abbreviations as in Table 1.

factor profiles were higher in participants with concordantly high apoB/high LDL-C than in those with concordantly low apoB/low LDL-C. However, interestingly and unexpectedly, we found that the discordantly low apoB/high LDL-C group had the lowest prevalence of hypertension and diabetes, and the discordantly high apoB/low LDL-C group had the highest prevalence of both hypertension and diabetes and the lowest levels of HDL-C. The discordantly high apoB/low LDL-C group had the lowest LDL-C/apoB ratio and the highest fasting remnant cholesterol.

In **Table 3**, individuals in the middle and the high tertiles of apoB had a higher prevalence of coronary calcification than those in the lowest tertile (adjusted CAC score ratios for coronary calcification: 1.63, 95% CI 1.27–2.09 in the middle tertile; 3.93, 95% CI 3.06–5.04 in the high tertile). We observed similar results across tertiles of LDL-C. The results of a cross-sectional analysis showed that the prevalence of a positive CAC score was significantly higher than that of the reference (low apoB/low LDL-C) when LDL-C was either high or low and apoB was high.

Median follow-up duration was 2.6 years, and CAC progression was found in 2,550 participants (18.0%). Within the study group, 2,773 participants (19.5%) had CAC at baseline, whereas 835 of these (7.3%) developed incident CAC during the study period. The associations of apoB and LDL-C tertiles and CAC progression are shown in **Table 4**. Compared with the lowest tertile (reference), the relative risk of CAC progression for the middle and high apoB tertiles was 1.14 (95% CI, 1.00–1.29) and 1.64 (95% CI, 1.44–1.85),

respectively, and adjustment for relevant behaviors, comorbidities, and biological factors did not appreciably change these associations. By using these covariates at baseline, the adjusted relative risk for CAC progression comparing high apoB/low LDL-C and high apoB/high LDL-C with the reference (low apoB/low LDL-C) was 1.26 (95% CI, 1.02–1.56) and 1.49 (95% CI, 1.34–1.66), respectively. These associations were similar across concordance and discordance between apoB and non HDL-C.

Discussion

In this large study of young and middle-aged adults, apoB and LDL-C demonstrated a dose-response relationship with both incidence and progression of CAC, independent of demographic variables, relevant behaviors, and cardiovascular risk factors. In the fully adjusted model, the discordant high-risk group (high apoB/high LDL-C) and the concordant highest-risk group were associated with higher risk for CAC incidence and progression than the reference group (low apoB/low LDL-C), whereas there was no significant difference in the risk between the discordant low-risk group (low apoB/high LDL-C) and the reference group. These findings suggest that apoB is more predictive of CAC progression than LDL-C. In addition, we found that the discordant high-risk group (high apoB/low LDL-C) had the highest prevalence of hypertension and diabetes, whereas the occurrence of these comorbidities was lowest in the discordant low-risk group (low apoB/high LDL-C).

Table 4. ApoB and LDL-C Levels and Their Concordance/Discordance in Relation to Risk of CAC Progression

	Multivariate relative risk (95% confidence interval)			
	Crude	Model 1	Model 2	Model 3
ApoB				
First tertile	1.00	1.00	1.00	1.00
Second tertile	1.22 (1.09–1.37)	1.17 (1.04–1.31)	1.24 (1.10–1.40)	1.14 (1.00–1.29)
Third tertile	1.84 (1.65–2.05)	1.76 (1.57–1.97)	1.88 (1.67–2.12)	1.64 (1.44–1.85)
LDL-C				
First tertile	1.00	1.00	1.00	1.00
Second tertile	1.16 (1.03–1.30)	1.16 (1.03–1.30)	1.28 (1.14–1.44)	1.21 (1.07–1.36)
Third tertile	1.52 (1.36–1.70)	1.52 (1.36–1.70)	1.73 (1.54–1.95)	1.60 (1.42–1.80)
Non-HDL-C				
First tertile	1.00	1.00	1.00	1.00
Second tertile	1.14 (1.02–1.27)	1.17 (1.04–1.31)	1.25 (1.11–1.41)	1.15 (1.02–1.30)
Third tertile	1.58 (1.42–1.76)	1.72 (1.54–1.92)	1.85 (1.65–2.08)	1.62 (1.43–1.83)
ApoB/LDL-C				
Low apoB/Low LDL-C	1.00	1.00	1.00	1.00
Low apoB/High LDL-C	0.82 (0.68–0.99)	0.92 (0.75–1.13)	1.03 (0.83–1.26)	1.02 (0.84–1.26)
High apoB/Low LDL-C	1.66 (1.38–2.00)	1.58 (1.29–1.93)	1.49 (1.21–1.83)	1.26 (1.02–1.56)
High apoB/High LDL-C	1.55 (1.41–1.70)	1.53 (1.38–1.69)	1.64 (1.48–1.82)	1.49 (1.34–1.66)
ApoB/Non-HDL-C				
Low apoB/Low non-HDL-C	1.00	1.00	1.00	1.00
Low apoB/High non-HDL-C	0.88 (0.74–1.04)	0.99 (0.83–1.20)	1.06 (0.88–1.28)	0.97 (0.80–1.18)
High apoB/Low non-HDL-C	1.83 (1.48–2.28)	1.51 (1.19–1.91)	1.51 (1.18–1.93)	1.40 (1.10–1.79)
High apoB/High non-HDL-C	1.55 (1.41–1.70)	1.55 (1.40–1.71)	1.64 (1.48–1.82)	1.46 (1.31–1.62)

Multivariable model 1 was adjusted for age, year of screening examination, and study center; model 2 was further adjusted for family history of coronary artery disease, education, diabetes, hypertension, smoking status, alcohol consumption, physical activity, and medication for dyslipidemia; model 3 was further adjusted for systolic BP, diastolic BP, BMI, and HDL-C. Abbreviations as in Table 1.

Because a considerable proportion of individuals who experience cardiovascular events have a normal or moderate level of LDL-C, the addition of predictive information about biological markers such as apoB and non-HDL-C is of great interest;¹⁶ however, there has been controversy about whether apoB would be a more accurate index of coronary event risk than non-HDL-C and LDL-C. In the Emerging Risk Factors Collaboration meta-analysis, the risk estimate of apoB and non-HDL-C and of non-HDL-C and LDL-C were statistically indistinguishable.¹⁷ One recent meta-analysis showed that apoB is a better predictor of vascular events than non-HDL-C and LDL-C, and one study estimated that targeting apoB rather than LDL-C as a preventive treatment strategy could reduce the number of incident cases among adult residents in the USA by an additional 800,000 over 10 years.¹⁸ In the Health Professional Follow-up Study using a nested case-control design, patients with CAD had a higher apoB level than the healthy controls, and apoB displayed the strongest association with CAD.¹⁹ In one prospective cohort study conducted in the USA, women whose level of LDL-C was discordant with apoB (<median LDL-C and ≥median apoB), compared with being concordant (<median LDL-C and <median apoB), were at higher risk of CAD incidence.²⁰ Our findings are in line with the results of those studies and extended previous findings, showing that the risk of CAC progression was significantly higher in both the discordant high-risk group (high apoB/low LDL-C) and the concordant high-risk group (high apoB/high LDL-C) than in the concordant low-risk group (low apoB/low

LDL-C; reference group). However, there was no significant difference between the discordant low-risk group and the reference group.

Just a few studies evaluated the association of discordance between apoB and LDL-C with subclinical coronary atherosclerosis measured by CAC using a longitudinal study design. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the plasma level of apoB in young adulthood has been associated with CAC in middle age.⁴ In this study, discordantly high apoB (greater than or equal to the median of apoB and lower than the median of LDL-C) was significantly associated with higher risk for presence of CAC in midlife, but apoB below the median was not associated with the risk. However, the CARDIA study was limited by the absence of baseline coronary calcium measurements. In the Multi-Ethnic Study of Atherosclerosis (MESA) of 4,623 adults (aged 45–84 years), discordantly high apoB relative to LDL or non-HDL-C was modestly associated with CAC progression, which is in line with the present study findings.²¹ Compared to the MESA group, our study population was younger and the association was stronger, suggesting that a risk of CAC progression related to discordantly high apoB/low LDL-C may be greater in younger compared to older individuals. Recent epidemiological studies supported this notion by showing that the risk of cardiovascular events associated with apoB was greater in younger individuals.²²

Although participants with concordant values of apoB and LDL-C (or non-HDL-C) have a likelihood of CAC progression proportional to their concentrations, the risk

of CAC progression was significantly higher in those with high apoB/low LDL-C, but not in those with low apoB/high LDL-C. The difference in the risk of CAC progression among discordant participants was consistent with the previous literature and explained by the notion that LDL particles were smaller and denser in the high apoB group than in the low apoB group, leading to higher risk of initiation and maturation of atherosclerotic plaque.²³ These observations can also be accounted for by elevated remnant cholesterol, which is the cholesterol content of TG-rich lipoproteins (IDL and VLDL in the fasting state) and a causal risk factor for a coronary event.²⁴ Our study provides a pathological basis for linking discordantly high apoB/low LDL-C with an increased risk of CAC progression. In addition, it is increasingly recognized that obesity and insulin resistance contributing to this process can also lead to production of cholesterol-depleted LDL particles through modulation of cholesterol ester transfer protein driven by an increase in VLDL relative to LDL.^{25,26} Our study indeed showed that participants with discordantly high apoB (cholesterol-depleted LDL particles) had the highest levels of obesity and insulin resistance, suggesting that these phenotypes are related to modulation of cholesterol ester transfer protein.

Several limitations should be considered when interpreting our findings. First, we used CAC scores instead of CAD events as the outcome; however, the association between CAC and CAD events has been shown in previous studies.²⁷ Second, study participants were notified of the initial CAC results, which may have contributed to modifying behavior in a healthy direction. As a result, the effect of discordance of apoB and LDL-C on CAD may be underestimated. Third, the follow-up period is relatively short compared with the previous study (25 years).⁴ Significant progression of coronary artery calcification has been shown to occur within approximately 3–6 years.^{27,28} Fourth, our study findings might be underestimated due to a potential healthy worker effect. This effect is a phenomenon in which employees have lower morbidity and mortality compared to the general population because healthy workers tend to remain employed.²⁹ Although our study sample comprised mostly employees, this effect is likely to emerge in older populations with more common and symptomatic conditions compared with younger populations.³⁰ Our study participants were young and middle aged and free of diagnosed cardiovascular disease. Therefore, the healthy worker effect was less likely to affect our results. Finally, our results were based on a sample of relatively healthy young Korean adults comprised of men and may not be generalizable to other populations.

The major strengths of our study were the large sample size, the use of high-quality data collection methods to obtain a detailed panel of potential confounders and mediators, and the use of a relatively healthy population without a history of CVD. Furthermore, the advantage of this study compared to previous studies is the presence of a baseline CAC score, which allows for calculation of estimated change in coronary calcium score. Thanks to those factors, the association of lipid profiles (including apoB and LDL-C) with the presence and progression of CAC was less likely to be confounded by comorbidities or medication use.

Conclusions

In conclusion, we found that discordantly or concordantly high apoB was associated with increased risk of CAC presence and its progression, independent of LDL-C. These findings suggest that screening of apoB in healthy middle-aged persons may help predict progression of coronary atherosclerosis.

Authors' Contributions

C.-W.K., Y.C., S.R., and H.S. planned and designed the study and directed its implementation. C.-W.K. made substantial contribution to the study conception and design. C.-W.K., Y.C., and S.R. were responsible for data acquisition and analysis. C.-W.K. and S.H. wrote the draft of the article, and all authors approved the final article for publication.

Disclosures

Potential conflict of interest: Nothing to report. The name of the ethics committee: The Institutional Review Board of Kangbuk Samsung Hospital.

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Supplementary Files

Please find supplementary file(s);
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