available at www.sciencedirect.com

ScienceDirect

www.metabolismjournal.com

Low-density lipoprotein cholesterol to apolipoprotein B ratio is independently associated with metabolic syndrome in Korean men

Chang Hee Kwon, Byung Jin Kim, Bum Soo Kim, Jin Ho Kang*

Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Jongno-gu, Seoul 110-746, South Korea

ARTICLE INFO

Article history:
Received 23 September 2010
Accepted 14 December 2010

ABSTRACT

The low-density lipoprotein cholesterol to apolipoprotein B (LDL-C/apo B) ratio is associated with cardiovascular risk factors and the prevalence of metabolic syndrome. The aim of this study was to assess the relationship between LDL-C/apo B ratio and metabolic syndrome in Korean men. This study included 499 men (mean age, 49.1 years) without metabolic syndrome at baseline who were followed for an average of 2.9 years. Subjects were divided into 4 groups according to baseline LDL-C/apo B ratio quartiles: greater than 1.243 in group I, 1.164 to 1.243 in group II, 1.070 to 1.163 in group III, and less than 1.070 in group IV. The incidence of metabolic syndrome at follow-up was compared according to LDL-C/apo B ratio group. Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria. The overall incidence of metabolic syndrome was 9.6%: 1.6% in the highest quartile (group I), 9.7% in group II, 11.2% in group III, and 16.0% in the lowest quartile (group IV) ($P = .001$). In multivariable regression analysis model adjusting for age, lifestyle status, homeostasis model assessment of insulin resistance, LDL-C, and high-sensitivity C-reactive protein, groups II, III, and IV had significantly increased odds ratio for the incidence of metabolic syndrome compared with the highest LDL-C/apo B quartile (group I). The LDL-C/apo B ratio is independently associated with metabolic syndrome in Korean men, indicating that this ratio may provide additional information when assessing cardiometabolic risks and predicting future development of metabolic syndrome.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a strong predictive marker of coronary artery disease (CAD). Lowering LDL-C levels is considered a primary therapeutic goal for the treatment of hypercholesterolemia [1]. Many studies have demonstrated that lowering of LDL-C with statins reduces the risk of cardiovascular disease (CVD). Nevertheless, many patients on statin therapy remain at relatively high residual CVD risk [2]. Recently, the number of LDL particles has been proposed as a more reliable method reflecting atherogenicity of the LDL fraction [3]. In addition, the size of LDL particles may also contribute to the atherogenicity of LDL-C [4]. Actually, a recent study reported that LDL particle number was more closely associated with CAD than LDL-C, whereas LDL particle size was inversely related to CAD in apparently

Author contributions: Chang Hee Kwon contributed to interpret data and write manuscript. Bum Soo Kim and Jin Ho Kang contributed to design and discuss this study. Byung Jin Kim contributed to design this study, interpret data, and review manuscript.

* *Corresponding author*. Tel.: +82 2 2001 2401; fax: +82 2 2001 2400.
E-mail address: bjjake.kim@samsung.com (B.J. Kim).

0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2010.12.007

healthy men and women [5]. However, the determination of LDL particle size and number is not easy because density gradient ultracentrifugation and electrophoresis on gradient polyacrylamide gels are required for the determination of LDL particle size and because nuclear magnetic resonance for LDL particle number are cumbersome and time-consuming.

Apolipoprotein B (apo B) is present in atherogenic lipoproteins (very low-density lipoprotein, intermediate-density lipoprotein, and both large buoyant LDL and small dense LDL), with one molecule of apo B in each of these atherogenic particles [6]. Therefore, the total apo B level reflects the total number of atherogenic particles. Moreover, plasma apo B is suggested as a surrogate marker for an estimate of LDL particle number because all LDL and very low-density lipoprotein particles contain a single molecule of apo B protein and more than 90% of apo B is found on LDL [7]. For this reason, apo B may be a more sensitive measure of atherogenicity and a better index for assessing cardiovascular risk than LDL-C [8]. In addition, the LDL-C/apo B ratio indirectly determines LDL particle size. Several studies have shown that lower LDL-C/apo B ratio identifies subjects who predominantly have small dense LDL particles [9-11].

Metabolic syndrome (MetS) is a constellation of interrelated cardiometabolic risk that appears to directly promote the development of atherosclerotic CVD [12]. These patients with cardiometabolic risk have relatively normal levels of LDL-C but increased numbers of small dense LDL particles [13]. Some studies have revealed that individuals with an apo B value higher than the predicted LDL-C were significantly more likely to have MetS than those with an apo B value lower than the predicted LDL-C [14,15]. In addition, a recent population-based cohort study performed in Turkey revealed that serum apo B/LDL-C ratio was weakly associated with MetS [16]. However, there are not many supporting evidences for the relationship between LDL-C/apo B ratio and incident MetS. Thus, we aimed to assess the relationship between LDL-C/apo B ratio and the incident MetS at 3-year follow-up in Korean men.

2. Methods

2.1. Study population and design

We selected study subjects among a total of 5407 men who visited Kangbuk Samsung Hospital for health examinations in 2002 and 2005. Among the potential study subjects, 4893 individuals were excluded: 865 individuals had MetS and 15 individuals had type 2 diabetes mellitus in 2002 (baseline visit), and 4028 individuals did not have apolipoprotein A_1 (apo A_1) and apo B level measurements available. In all, 499 men (mean age, 49.1 years; range, 23-81 years) who did not have MetS in 2002 (baseline visit) were enrolled in the study and were followed up for 3 years (the average follow-up period was 2.9 years). The study subjects were divided into 4 groups according to baseline LDL-C/apo B ratio quartiles: greater than 1.243 in group I, 1.164 to 1.243 in group II, 1.070 to 1.163 in group III, and less than 1.070 in group IV. We then compared the incidence of MetS according to different LDL-C/apo B ratio group after a follow-up survey.

2.2. Subject data

Medical and medication history, smoking status (current or nonsmoker), alcohol consumption (≥3 times per week), and physical activity (≥3 times per week) were assessed using the same standard questionnaire in 2002 and 2005.

Blood pressure (BP) was measured with a standard sphygmomanometer following at least 5 minutes of seated rest. Height and weight were estimated using automated instruments, with individuals wearing light clothing and no shoes. Body mass index (BMI) was calculated as body weight (kilograms) divided by height squared (meters). Waist circumference (WC) was measured at the level of the umbilicus in a standing position.

2.3. Biochemical measurements

Morning blood samples were drawn from the antecubital vein after the participants had fasted for at least 12 hours. Serum glucose levels were determined using the hexokinase method (Advia 1650 AutoAnalyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin concentrations were measured using immunoradiometric assays (Biosource, Nivelles, Belgium), with intra- and interassay coefficients of variation of 2.1% to 4.5% and 4.7% to 12.2%, respectively. Insulin resistance was estimated using the *homeostasis model assessment of insulin resistance index* (HOMA-IR), which is defined as fasting insulin (micro–international units per milliliter) × fasting glucose (millimoles per liter)/22.5. Fasting total cholesterol (TC) and triglycerides (TG) were measured enzymatically by an automatic analyzer (Advia 1650 AutoAnalyzer, Bayer Diagnostics). High-density lipoprotein cholesterol (HDL-C) concentrations were measured by a selective inhibition technique (Bayer Diagnostics). Levels of LDL-C were determined by a homogeneous enzymatic calorimetric test (Hitachi 747; Hitachi, New York, USA). Concentrations of apo B and apo A_1 concentrations were measured by rate nephelometry (IMMAGE System; Beckman Coulter, CA, USA). High-sensitivity C-reactive protein (hsCRP) was measured by particle-enhanced immunonephelometry (Behring Nephelometer II; Dade Behring, Marburg, Germany).

2.4. Definition of MetS

Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria [12]. According to these criteria, MetS is diagnosed when at least 3 of the following 5 components are present: (1) abdominal obesity (WC >90 cm for men or BMI ≥25 kg/m^2); (2) TG concentration of at least 150 mg/dL; (3) HDL-C less than 40 mg/dL; (4) systolic/diastolic BP of at least 130/85 mm Hg; and (5) fasting glucose of at least 110 mg/dL.

2.5. Statistical analysis

Data were expressed as mean ± SD for continuous variables and percentages for categorical variables. Among the variables, serum TG and hsCRP concentrations were log-transformed for analysis to correct skewed distributions; but the values in the tables are expressed as untransformed data

for easy interpretation. Comparisons of baseline cardiovascular risk factors according to the presence/absence of incident MetS were analyzed using Student t test for continuous variables or the χ^2 test for categorical variables. Comparisons of baseline variables and follow-up changes among the LDL-C/apo B ratio quartile groups were performed with the 1-way analysis of variance (ANOVA) or the χ^2 test. Comparisons of development of individual MetS components and MetS according to LDL-C/apo B quartiles were obtained from χ^2 tests with Bonferroni multiple comparison post hoc analysis. Spearman rank correlation coefficient was conducted to evaluate a correlation of continuous variables like lipoproteins and other cardiovascular risk factors. Multivariable logistic regression analyses were conducted to assess the relationship between LDL-C/apo B ratio quartiles and the risk of incident MetS: model 1 was adjusted for age and lifestyle status (alcohol, smoking, and exercise); model 2 was adjusted as model 1 and for HOMA-IR; and model 3 was adjusted as model 2 and for LDL-C and hsCRP. All statistical analyses were performed using PASW for Windows, version 17.0 (SPSS, Chicago, IL). All statistical tests were 2-tailed, and P values < .05 were considered statistically significant.

This study protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBC10091).

3. Results

The overall incidence of MetS in all population was 9.6% (48 of 499 men). The incidence of MetS was 1.6% in the highest quartile (group I), 9.7% in the second (group II), 11.2% in the third (group III), and 16.0% in the lowest quartile (group IV) (P = .001). The overall incidence of MetS in the included subjects was similar to that of the excluded subjects (9.6% [48/499] vs 10.7% [434/4043], P = .445).

Baseline characteristics between the non-MetS group and the MetS group at follow-up are presented in Table 1. The MetS group had higher mean BP, BMI, WC, TG, apo B, apo B/apo A_1, fasting glucose, HOMA-IR, and hsCRP levels, and lower HDL-C, apo A_1, and LDL-C/apo B ratio values compared with the non-MetS group.

Table 2 shows the comparison of baseline characteristics according to LDL-C/apo B ratio quartiles. In the lowest LDL-C/apo B quartile (group IV), WC, TG, apo B, apo B/apo A_1, and HOMA-IR were significantly higher than those in the highest LDL-C/apo B quartile (group I). However, HDL-C and LDL-C were significantly lower in the lower LDL-C/apo B quartiles (groups II-IV) than those in the highest quartile (group I). Especially, mean values of LDL-C and apo B of the highest LDL-C/apo B quartile (group I) were located between 25th and 50th estimated percentiles of LDL-C and apo B from the Framingham Heart Study [17]. On the other hand, in the lowest LDL-C/apo B quartile (group IV), baseline mean value of LDL-C was within 25th estimated percentiles; but mean value of apo B was located around 50th percentiles.

The changes of variables between baseline and follow-up are presented in Table 3. The change of serum TG was more decreased in the lowest LDL-C/apo B ratio quartile (group IV) than in the other groups (groups II, III, and IV) (P < .0001); however, mean value of TG at follow-up was still highest in group IV ([mean ± SE, millimoles per liter] 1.16 ± 0.53 in group I, 1.24 ± 0.53 in group II, 1.51 ± 0.67 in group III, and 2.11 ± 1.09 in group IV; P < .0001). The change of serum LDL-C was more increased in the lowest LDL-C/apo B quartile (group IV) than in the highest quartile (group I), but mean value at follow-up was significantly lower in group IV than group I (P = .002).

Table 1 – Baseline characteristics between non-MetS and MetS group at follow-up

	Non-MetS group (n = 451)	MetS group (n = 48)	P value
Age, y	49.0 ± 9.4	49.7 ± 9.7	.635
Systolic BP, mm Hg	114.9 ± 12.4	119.5 ± 15.1	.016
Diastolic BP, mm Hg	75.8 ± 9.4	78.7 ± 9.5	.046
BMI, kg/m^2	23.6 ± 2.5	25.7 ± 2.1	<.0001
WC, cm	82.8 ± 7.0	86.3 ± 5.5	.007
TC, mmol/L	5.27 ± 0.83	5.44 ± 0.74	.176
TG, mmol/L	1.50 ± 0.84	1.94 ± 0.76	<.0001
HDL-C, mmol/L	1.42 ± 0.28	1.28 ± 0.23	.001
LDL-C, mmol/L	3.07 ± 0.70	3.17 ± 0.66	.336
Apo B, g/L	1.025 ± 0.225	1.138 ± 0.226	.001
Apo A_1, g/L	1.228 ± 0.179	1.184 ± 0.163	.100
LDL-C/apo B	1.16 ± 0.16	1.08 ± 0.11	.001
Apo B/apo A_1	0.85 ± 0.22	0.98 ± 0.26	<.0001
Lipoprotein (a), μmol/L	0.607 ± 0.443	0.673 ± 0.620	.346
Glucose, mmol/L	4.97 ± 0.48	5.09 ± 0.51	.112
HOMA-IR	1.625 ± 0.578	1.876 ± 0.639	.005
hsCRP, mg/L	1.0 ± 1.7	1.5 ± 1.8	.003
Smoking (current), n (%)	175 (39.2)	26 (56.5)	.023
Alcohol consumption (≥3 times/wk), n (%)	83 (18.5)	10 (21.7)	.591
Physical activity (≥3 times/wk), n (%)	103 (23.2)	12 (27.3)	.544

Values are mean ± SD for continuous variables and number (percentages) for categorical variables. P values for continuous variables were obtained from the t test. P values for categorical variables were obtained from χ^2 tests. Triglycerides and hsCRP were expressed as raw data, but were applied for statistical analysis after natural logarithmic transformation.

The development of individual MetS component was compared to assess the progression of BP, glucose, obesity, TG, and HDL-C according to LDL-C/apo B quartiles (Table 4). The development of glucose, TG, and HDL-C component among the subjects without individual MetS component at baseline was significantly increased according to LDL-C/apo ratio quartiles (from group I to group IV) (P < .05).

In the Spearman rank correlation coefficient for lipoproteins and other cardiovascular risk factors, LDL-C/apo B showed negative correlation with TG and apo B (ρ = –0.486 and –0.273, P < .01) and positive correlation with HDL-C and LDL-C (ρ = 0.302 and 0.303, P < .01).

In age-adjusted logistic regression analyses, the lower quartiles of LDL-C/apo B ratio had higher odds ratio (OR) for the incident MetS compared with the highest quartile group (7.03 [1.55-31.84] in group II, 8.79 [1.97-39.11] in group III, and 13.00 [2.99-56.60] in group IV; P < .0001). The OR results from models 1, 2, and 3 were also attenuated but were still significant (Table 5). Moreover, model 3 analysis including BMI, HDL-C, TG, glucose, and systolic and diastolic BP revealed that the OR in groups II, III, and IV were significantly high compared with the highest quartile group (5.01 [1.01-24.89] in

Table 2 – Baseline characteristics according to LDL-C/apo B quartiles

	Group I (>1.243) (n = 125)	Group II (1.164-1.243) (n = 124)	Group III (1.070-1.163) (n = 125)	Group IV (<1.070) (n = 125)	P value
Age, y	48.1 ± 9.6	48.8 ± 9.4	50.2 ± 9.0	49.2 ± 9.5	.372
Systolic BP, mm Hg	114.9 ± 11.8	114.1 ± 11.7	116.4 ± 12.9	115.9 ± 14.3	.527
Diastolic BP, mm Hg	75.9 ± 8.3	75.3 ± 9.9	77.4 ± 9.5	75.8 ± 10.0	.344
BMI, kg/m^2	23.5 ± 2.3	23.7 ± 2.8	23.8 ± 2.6	24.1 ± 2.2	.309
WC, cm	80.5 ± 6.9	83.0 ± 7.7	84.2 ± 6.7 *	84.5 ± 5.9 *	.001
TC, mmol/L	5.47 ± 0.80	5.19 ± 0.81 *	5.32 ± 0.83	5.15 ± 0.82 *	.010
TG, mmol/L	1.17 ± 0.49	1.24 ± 0.50	1.48 ± 0.58 *,†	2.28 ± 1.11 *,†,‡	<.0001
HDL-C, mmol/L	1.52 ± 0.27	1.42 ± 0.27 *	1.42 ± 0.30 *	1.29 ± 0.23 *,†,‡	<.0001
LDL-C, mmol/L	3.37 ± 0.68	3.11 ± 0.65 *	3.11 ± 0.68 *	2.71 ± 0.61 *,†,‡	<.0001
Apo B, g/L	0.969 ± 0.202	1.000 ± 0.214	1.078 ± 0.238 *,†	1.097 ± 0.231 *,†	<.0001
Apo A_1, g/L	1.237 ± 0.174	1.216 ± 0.160	1.224 ± 0.208	1.219 ± 0.169	.809
LDL-C/apo B	1.35 ± 0.12	1.20 ± 0.02 *	1.11 ± 0.02 *,†	0.95 ± 0.09 *,†,‡	<.0001
Apo B/apo A_1	0.79 ± 0.18	0.83 ± 0.20	0.91 ± 0.26 *,†	0.91 ± 0.23 *,†	<.0001
Lipoprotein (a), μmol/L	0.691 ± 0.553	0.534 ± 0.288 *	0.641 ± 0.464	0.585 ± 0.494	.046
Glucose, mmol/L	4.94 ± 0.50	4.93 ± 0.45	4.99 ± 0.47	5.07 ± 0.52	.087
HOMA-IR	1.589 ± 0.582	1.561 ± 0.553	1.635 ± 0.593	1.809 ± 0.598 *,†	.004
hsCRP, mg/L	1.2 ± 0.18	1.0 ± 1.7	1.2 ± 2.1	0.9 ± 1.2	.877
Smoking (current), n (%)	44 (35.8)	46 (37.7)	35 (28.7)	50 (41.0)	.230
Alcohol consumption (≥3 times/wk), n (%)	30 (24.4)	31 (25.4)	32 (26.2)	22 (18.2)	.439
Physical activity (≥3 times/wk), n (%)	17 (13.7)	18 (14.6)	26 (21.0)	32 (25.8)	.049

Values are mean ± SD for continuous variables and number (percentages) for categorical variables. *P* values for continuous variables were obtained from the 1-way ANOVA test. *P* values for categorical variables were obtained from χ^2 tests. Triglycerides and hsCRP were expressed as raw data, but were applied for statistical analysis after natural logarithmic transformation.

* $P < .05$ vs group I.

† $P < .05$ vs group II.

‡ $P < .05$ vs group III.

group II, 5.65 [1.16-27.47] in group III; and 6.75 [1.23-37.13] in group IV; $P < .0001$).

4. Discussion

In the present study of 499 Korean men, the subjects in the lower LDL-C/apo B ratio quartiles have higher incidences of newly developed MetS at 3-year follow-up than those in the highest LDL-C/apo B ratio quartile group, independent of other risk factors. The LDL-C/apo B ratio was not only significantly associated with WC, TG, apo B, and HOMA-IR at baseline, but also inversely associated with HDL-C and LDL-C. This finding indicates that even subjects with normal or low LDL-C levels may be at high risk for developing MetS and potentially CVD.

Elevated LDL-C is an independent risk factor of CAD and the primary target of lipid-lowering therapy [1]. A number of trials have demonstrated that lowering LDL-C with statins

Table 3 – The changes of variables between at baseline and at follow-up according to LDL-C/apo B quartiles

	Group I	Group II	Group III	Group IV	P value
Systolic BP, mm Hg	−4.1 ± 12.8	−0.4 ± 12.5	−0.1 ± 15.8	−2.3 ± 14.4	.82
Diastolic BP, mm Hg	−0.2 ± 10.9	1.7 ± 9.7	1.9 ± 12.0	2.48 ± 10.8	.230
BMI, kg/m^2	0.2 ± 1.1	0.1 ± 0.9	0.1 ± 0.9	0.1 ± 0.9	.727
TC, mmol/L	5.47 ± 0.80	5.19 ± 0.81	5.32 ± 0.83	5.15 ± 0.82	.010
TG, mmol/L	−0.007 ± 0.541	−0.003 ± 0.528	0.036 ± 0.551	−0.167 ± 1.093 *,†,‡	<.0001
HDL-C, mmol/L	−0.05 ± 0.23	−0.02 ± 0.23	−0.01 ± 0.26	−0.01 ± 0.18	.389
LDL-C, mmol/L	−0.28 ± 0.51	−0.12 ± 0.52	−0.09 ± 0.48 *	0.06 ± 0.52 *,†	<.0001
Apo B, g/L	0.004 ± 0.180	−0.035 ± 0.175	−0.057 ± 0.152 *	−0.054 ± 0.177	.029
Apo A_1, g/L	0.263 ± 0.186	0.257 ± 0.195	0.266 ± 0.220	0.242 ± 0.195	.819
Glucose, mmol/L	0.29 ± 0.44	0.34 ± 0.43	0.42 ± 0.60	0.41 ± 0.74	.235
HOMA-IR	0.358 ± 0.721	0.358 ± 0.713	0.469 ± 0.865	0.329 ± 0.813	.509
hsCRP, mg/L	−0.28 ± 2.11	−0.11 ± 2.25	−0.02 ± 3.10	0.04 ± 1.86	.427

Values are mean ± SD for continuous variables. *P* values for continuous variables were obtained from the 1-way ANOVA test. Triglycerides and hsCRP were expressed as raw data, but were applied for statistical analysis after natural logarithmic transformation.

* $P < .05$ vs group I.

† $P < .05$ vs group II.

‡ $P < .05$ vs group III.

Table 4 – The development of individual MetS component and MetS according to LDL-C/apo B quartiles

	Group I	Group II	Group III	Group IV	P value
BP (≥130/85 mm Hg)	20/97 (20.6)	15/91 (16.5)	23/78 (29.5)	16/89 (18.0)	.170
Glucose (≥110 mg/dL)	2/125 (1.6)	8/123 (6.5)	12/123 (9.8)*	14/123 (11.4)*	.016
BMI (≥25 kg/m^2)	11/94 (11.7)	9/86 (10.5)	11/89 (12.4)	14/85 (16.5)	.666
TG (≥150 mg/dL)	9/107 (8.4)	11/104 (10.6)	16/82 (19.5)	9/42 (21.4)	.047
HDL-C (<40 mg/dL)	2/123 (1.6)	6/117 (5.1)	5/120 (4.2)	12/115 (10.4)*	.031
Incident MetS	2 (1.6)	12 (9.7)*	14 (11.2)*	20 (16.0)*	.001

Values are number of subjects with developed MetS component at follow-up/number of subjects without individual MetS component at baseline (percentages). *P* values were obtained from χ^2 tests.
* $P < .0083$ vs group I by Bonferroni multiple comparison post hoc analysis.

reduces the risk of CVD [18], and intensive lipid lowering with statins provides significant benefits beyond the standard regimen [19,20]. However, despite adequate LDL-C lowering, many patients on statin therapy have significant residual CVD risk. One possible explanation for this finding is that LDL-C does not reflect the atherogenicity of all apo B–containing lipoproteins nor does it necessarily represent the total number of LDL particles or the size distribution of those particles [17].

Serum apo B has been proposed as a better index for predicting the risk of CVD than TC or LDL-C. The Quebec Cardiovascular Study reported that apo B was strongly associated (relative risk of 1.4) with developing coronary heart disease in 2155 men at 5 years of follow-up [21]. The AMORIS (Apolipoprotein-related MOrality RISk) study demonstrated that apo B is more strongly related to increased risk of fatal myocardial infarction than non–HDL-C [22]. The results of the Insulin Resistance Atherosclerosis Study also suggested that elevated apo B is more strongly associated with insulin resistance, obesity, dyslipidemia, dysglycemia, and hypertension than LDL-C [23]. Furthermore, a review conducted by Sniderman and Faraj [24] concluded that apo B is associated more closely with inflammatory markers and insulin resistance than all other cholesterol markers and is an independent predictor of future myocardial infarction. In our study, apo B was also significantly correlated with obesity, dyslipidemia, and insulin resistance.

Several studies have suggested that the LDL-C/apo B ratio is associated with other cardiovascular risk factors and the prevalence of MetS. We previously reported that individuals who had proportionally higher apo B levels than LDL-C concentrations (discordant values according to the regression line between LDL-C and apo B) had higher prevalence of MetS and more manifestations of MetS (high TG and non–HDL-C, low HDL-C) [14]. The result of a Japanese study was also consistent with that of our previous study [15]. These studies have the limitation of being cross-sectional studies, but are meaningful in suggesting that the LDL-C/apo B ratio could be a predictive marker of newly developed MetS.

Recently, a Turkish cohort study with 7 years of follow-up has reported predictive values of serum apo B/LDL-C in cardiometabolic risk [16]. The incidence of Mets in the study was 26.4% (169/640) in men, which is different from that of our study (9.6%). The difference could be attributed to shorter follow-up duration and younger population in our study. The previous study also showed that apo B/LDL-C ratio was not significantly associated with incident MetS in men, which is not consistent with our results. This difference might be due to the lower median LDL-C/apo B ratio in the previous study and the difference of covariates for the analysis.

Three lines of evidence could support the relationship between LDL-C/apo B ratio and incident MetS. First, previous studies have revealed that the LDL-C/apo B ratio determines LDL particle size. Second, dyslipidemia in MetS is characterized by high plasma TG, low HDL-C, an increased number of small dense LDL particles, and high concentrations of apo B–containing lipoproteins [25,26]. Third, our result also demonstrated that subjects in the MetS group have higher TG levels and lower LDL-C/apo B ratio. In addition, the subjects in the lower LDL-C/apo B ratio quartiles had higher TG and lower HDL-C as a characteristic dyslipidemia of MetS than those in the highest quartile. Thus, low LDL-C/apo B ratio, reflecting small LDL size, may be associated with the development of MetS.

Table 5 – Multivariable logistic regression analysis for the association between LDL-C/apo B and incident MetS

LDL-C/apo B	Age adjusted	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Group I	1	1	1	1
Group II	7.03 (1.55-31.84)*	5.59 (1.20-26.12)*	5.72 (1.20-27.40)*	6.14 (1.31-28.73)*
Group III	8.79 (1.97-39.11)†	7.82 (1.72-35.64)*	7.96 (1.72-36.91)	7.60 (1.67-34.64)†
Group IV	13.00 (2.99-56.60)†	10.32 (2.30-46.28)†	9.38 (2.06-42.79)†	9.33 (2.08-41.73)†
P for trend	<.0001	<.0001	<.0001	<.0001

Model 1 was adjusted for age and lifestyle status. Model 2 was adjusted for age, lifestyle status, and HOMA-IR. Model 3 was adjusted for age, lifestyle status, HOMA-IR, LDL-C, and hsCRP.
* $P < .01$.
† $P < .05$.

This study has several limitations. First, there is the possibility of selection bias because most participants were residents of an urban community. There were no women in the sample. Second, the total number of included subjects was relatively small; and all subjects were of Korean descent. Therefore, our study has a limitation in generalizing its results to the worldwide population. However, the present study is meaningful as a first study to clarify the relationship between LDL-C/apo B ratio and incident MetS among an Asian population.

In conclusion, LDL-C/apo B ratio is independently associated with incident MetS in Korean men, independent of traditional risk factors, HOMA-IR, LDL-C, and hsCRP. This result indicates that LDL-C/apo B ratio could provide additional information in assessing cardiometabolic risk and predicting the future development of MetS.

REFERENCES

[1] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486-97.

[2] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267-78.

[3] Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep 2004;6:381-7.

[4] Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, Couture P, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. J Intern Med 2006;259: 247-58.

[5] El Harchaoui K, van der Steeg WA, Stroes ES, Kuivenhoven JA, Otvos JD, Wareham NJ, et al. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population Study. J Am Coll Cardiol 2007; 49:547-53.

[6] Elovson J, Chatterton JE, Bell GT, Schumaker VN, Reuben MA, Puppione DL, et al. Plasma very low density lipoproteins contain a single molecule of apolipoprotein B. J Lipid Res 1988; 29:1461-73.

[7] Sniderman A, Vu H, Cianflone K. Effect of moderate hypertriglyceridemia on the relation of plasma total and LDL apo B levels. Atherosclerosis 1991;89:109-16.

[8] Davidson MH. Apolipoprotein measurements: is more widespread use clinically indicated? Clin Cardiol 2009;32: 482-6.

[9] Wagner AM, Jorba O, Rigla M, Alonso E, Ordonez-Llanos J, Perez A. LDL-cholesterol/apolipoprotein B ratio is a good predictor of LDL phenotype B in type 2 diabetes. Acta Diabetol 2002;39:215-20.

[10] Sniderman AD, St-Pierre AC, Cantin B, Dagenais GR, Despres JP, Lamarche B. Concordance/discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk. Am J Cardiol 2003;91:1173-7.

[11] Jungner I, Sniderman AD, Furberg C, Aastveit AH, Holme I, Walldius G. Does low-density lipoprotein size add to atherogenic particle number in predicting the risk of fatal myocardial infarction? Am J Cardiol 2006;97:943-6.

[12] Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.

[13] Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008;51:1512-24.

[14] Kim BJ, Hwang ST, Sung KC, Kim BS, Kang JH, Lee MH, et al. Comparison of the relationships between serum apolipoprotein B and serum lipid distributions. Clin Chem 2005;51:2257-63.

[15] Vaverkova H, Karasek D, Novotny D, Jackuliakova D, Lukes J, Halenka M, et al. Apolipoprotein B versus LDL-cholesterol: association with other risk factors for atherosclerosis. Clin Biochem 2009;42:1246-51.

[16] Onat A, Can G, Cicek G, Ayhan E, Dogan Y. Predictive value of serum apolipoprotein B/LDL-cholesterol ratio in cardiometabolic risk: population-based cohort study. Clin Biochem 2010;43:1381-6.

[17] Mudd JO, Borlaug BA, Johnston PV, Kral BG, Rouf R, Blumenthal RS, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. J Am Coll Cardiol 2007;50:1735-41.

[18] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.

[19] Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291: 1071-80.

[20] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350:1495-504.

[21] Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation 1996;94: 273-8.

[22] Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. 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.

[23] Williams K, Sniderman AD, Sattar N, D'Agostino Jr R, Wagenknecht LE, Haffner SM. Comparison of the associations of apolipoprotein B and low-density lipoprotein cholesterol with other cardiovascular risk factors in the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2003;108: 2312-6.

[24] Sniderman AD, Faraj M. Apolipoprotein B, apolipoprotein A-I, insulin resistance and the metabolic syndrome. Curr Opin Lipidol 2007;18:633-7.

[25] Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28: 2289-304.

[26] Chan DC, Barrett PH, Watts GF. Lipoprotein kinetics in the metabolic syndrome: pathophysiological and therapeutic lessons from stable isotope studies. Clin Biochem Rev 2004;25: 31-48.