Association of Lipid and Lipoprotein Profiles with Future Development of Type 2 Diabetes in Nondiabetic Korean Subjects: A 4-Year Retrospective, Longitudinal Study

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Context: Traditional lipid measures are known to be associated with incident type 2 diabetes.

Objective: Our objective was to assess the independent association between lipid profiles and the development of type 2 diabetes in nondiabetic Korean subjects over a 4-yr period.

Design and Methods: A total of 5577 Koreans without diabetes who underwent consecutive comprehensive health check-ups annually for 5 yr were enrolled. We measured concentrations of total cholesterol (TC), triglyceride (TG), apolipoprotein B (apoB), apolipoprotein A-I, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) and calculated lipid ratios. The association between incident type 2 diabetes and the initial values for lipid ratios and other lipoprotein components was examined.

Results: Over the course of 4 yr, 330 subjects (5.9%) developed type 2 diabetes. TC, LDL-C, TG, non-HDL, apoB, apoB to apolipoprotein A-I ratio, TC to HDL ratio, TG to HDL ratio, LDL to HDL ratio and apoB to HDL ratio were associated with incident type 2 diabetes in multivariate analysis after adjustment for age and gender. Of these, the ratio of TC to HDL and apoB to HDL showed a significant association with increased risk of type 2 diabetes, compared with other lipoprotein parameters: odds ratio (1.340, 95% confidence interval 1.166–1.538; and 1.338, 95% confidence interval 1.162–1.540), respectively. The odds ratio for the development of type 2 diabetes increased significantly as the tertiles of the baseline ratio of TC to HDL and apoB to HDL increased from the first to the third tertile.

Conclusions: This study suggests that lipid and lipoprotein profiles can be independently associated with later development of type 2 diabetes in nondiabetic Korean adults in a longitudinal analysis. **(*J Clin Endocrinol Metab* 96: E2050–E2054, 2011)**

In patients with type 2 diabetes, dyslipidemia is common (1), and traditional lipid measures are known to predict type 2 diabetes (2). However, there are limited epidemiologic data suggesting that dyslipidemia, particularly lipid and lipoprotein profiles, could predict future development of type 2 diabetes. To our knowledge, only two recent studies have reported an association of increased apolipoprotein B (apoB) level alone with incident type 2 diabetes (3, 4). In addition, no study has been conducted that compares with lipoprotein parameters. The aim of this

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Abbreviations: apoA-I, Apolipoprotein A-I; apoB, apolipoprotein B; BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; TC, total cholesterol; TG, triglyceride.

study was to assess the independent association between lipid and lipoprotein profiles and type 2 diabetes in nondiabetic Korean subjects over a 4-yr period. We also compared ratios of lipids and/or apolipoproteins with traditional lipid profiles for assessment of the risk for development of type 2 diabetes.

Subjects and Methods

Subjects

The study population consisted of subjects who had undergone comprehensive health examinations annually for 4 yr (between January 2005 and December 2009) at the Kangbuk Samsung Hospital, Seoul, Korea. Initially, 10,950 Koreans were identified. Among these subjects, 437 were excluded due to type 2 diabetes at baseline. Based on 2005 medical records, subjects were also excluded for the following reasons: absence of data (n = 3000), including hemoglobin A1c (HbA1c), apoB and apolipoprotein A-I (apoA-I); alcohol intake greater than 20 g/d (n = 1755); positive serologic markers for hepatitis B (n = 558) or hepatitis C virus (n = 17); and liver cirrhosis (n = 8). After these exclusions, 5577 subjects (3918 men and 1659 women ≥20 yr of age; mean age 44.5 yr) were eligible for the study. The study was approved by the Institutional Review Board at Kangbuk Samsung Hospital. Informed consent requirement was waived because personal identifying information was not accessed.

Measurements

Anthropometric and biochemical variables were measured as described in Supplementary Methods, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. Lifestyle information was self-reported by obtaining questionnaire. All blood samples were collected from the antecubital vein after an overnight fast for 8–12 h. An enzymatic calorimetric test was used for measurement of total cholesterol (TC) and triglyceride (TG) concentrations. The selective inhibition method was used for the measurement of the level of high-density lipoprotein (HDL) cholesterol, and a homogeneous enzymatic calorimetric test was used for measurement of the level of low-density lipoprotein (LDL) cholesterol (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). ApoB and apoA-I levels were measured with the nephelometric method using a BN II system (Dade Behring Co., Marburg, Germany). Coefficients of variation of both within-run and total precisions were less than 2.5% for apoA-I and apoB (see Supplemental Methods for details).

Diagnosis of type 2 diabetes

Development of type 2 diabetes was assessed from the annual records of all 5577 subjects and determined: fasting plasma glucose 126 mg/dl or greater; or a HbA1c 6.5% or greater (6). In addition, subjects who had a history of diabetes or currently used insulin or oral antidiabetic drugs based on a self-report questionnaire at each visit were considered to have developed type 2 diabetes [diagnosis of impaired fasting glucose (6) and hypertension (7) described in Supplemental Methods].

Statistical analysis

Continuous variables were reported as the mean ± SD and compared using an independent *t* test. Categorical variables were expressed as percentages and compared using a χ^2 test. Multiple logistic regression analysis was conducted to evaluate associations of lipid measures with incident type 2 diabetes. The odds ratio (OR) per 1 SD increased in the corresponding lipid variable and 95% confidence intervals (CI) were calculated. To compare the ability of different logistic models in discrimination between participants with and without incident type 2 diabetes, we calculated C statistics, which are analogous to the area under the receiver-operating characteristic curve, and used the DeLong algorithm for determination of statistical significance (8). We then used multiple logistic regression analysis to determine the OR of developing type 2 diabetes in subjects stratified by tertiles of the ratio of TC to HDL and apoB to HDL. Adjustments were made for the following variables: age, gender, body mass index (BMI), smoking status (never or past or current), hypertension, fasting glucose, and fasting insulin. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the 5577 subjects, including those who developed type 2 diabetes during follow-up, are shown in Table 1. During a 4-yr follow-up period, 330 of the 5577 (5.9%) patients had new type 2 diabetes. The prevalence of impaired fasting glucose and hypertension was significantly higher in patients who developed type 2 diabetes ($P < 0.001$) (Table 1). Individuals who developed type 2 diabetes had significantly higher baseline values for TC, LDL cholesterol, HDL cholesterol, non-HDL, apoB, apoB to apoA-I ratio, TC to HDL ratio, TG to HDL ratio, LDL to HDL ratio, and apoB to HDL ratio and lower baseline values for HDL and apoA-I than patients who did not develop type 2 diabetes.

Comparing C statistics of multivariate regression models, although no significant differences were observed between lipoprotein parameters, the point estimates for C statistics of TC, LDL-C, TG, non-HDL, apoB, apoB to A-I ratio, TC to HDL ratio, TG to HDL ratio, LDL to HDL ratio, and apoB to HDL ratio were all above 0.84 (Table 2).

Logistic regression analysis was used for evaluating lipoprotein components for risk of development of type 2 diabetes during the follow-up period. In multivariate analyses adjusted for age and gender, TC, LDL-C, TG, non-HDL, apoB, apoB to A-I ratio, TC to HDL ratio, TG to HDL ratio, LDL to HDL ratio, and apoB to HDL ratio were associated with incident type 2 diabetes, whereas HDL cholesterol, and apoA-I were not associated with incident type 2 diabetes. Among several lipid parameters, the ratio of TC to HDL and apoB to HDL showed higher OR for incident type 2 diabetes, compared with the others after adjustment for multivariate adjustment, including

TABLE 1. Baseline characteristics of participants according to development of type 2 diabetes during a 4-yr period

	Incident type 2 diabetes			
n (%)	No 5247 (94.1)	Yes 330 (5.9)	*P* value	Overall
Mean follow-up (months)	48 ± 2.8	35 ± 13.1		47.4 ± 5.2
Age (yr)	44.4 ± 4.9	46.3 ± 6.0	<0.001	44.5 ± 5.0
Male (%)	3650 (69.6)	268 (81.2)	<0.001	3918 (70.3)
Current smoking (%)	1179 (22.6)	91 (27.7)	0.035	1270 (22.9)
BMI (kg/m^2)	23.7 ± 2.8	25.4 ± 3.0	<0.001	23.8 ± 2.8
Blood pressure				
Systolic (mm Hg)	112.9 ± 14.1	118.3 ± 14.7	<0.001	113.2 ± 14.2
Diastolic (mm Hg)	75.1 ± 9.8	79.1 ± 10.4	<0.001	75.3 ± 9.9
Hypertension (%)[a]	810 (15.4)	80 (24.3)	<0.001	890 (16)
Glucose homeostasis				
IFG	1200 (22.9)	242 (73.3)	<0.001	1442 (25.9)
HbA1c (%)	5.4 ± 0.3	5.8 ± 0.4	<0.001	5.4 ± 0.3
Fasting glucose (mg/dl)	94.3 ± 7.8	107.8 ± 10.1	<0.001	95.0 ± 8.4
Fasting insulin (IU/ml)	8.4 ± 3.1	9.7 ± 4.3	<0.001	8.5 ± 3.2
HOMA-IR	1.98 ± 0.78	2.57 ± 1.19	<0.001	2.01 ± 0.82
Lipid profile				
TC (mg/dl)	193.0 ± 31.5	204.1 ± 36.4	<0.001	193.7 ± 31.9
LDL cholesterol (mg/dl)	112.4 ± 26.5	120.7 ± 31.0	<0.001	112.8 ± 26.8
HDL cholesterol (mg/dl)	51.4 ± 11.6	48.6 ± 11.3	<0.001	51.2 ± 11.6
TG (mg/dl)	132.4 ± 80.8	171.7 ± 112.0	<0.001	134.7 ± 83.5
Non-HDL (mg/dl)	141.7 ± 31.5	155.6 ± 35.3	<0.001	142.5 ± 31.9
ApoB (mg/dl)	96.3 ± 22.2	107.7 ± 24.9	<0.001	97.0 ± 22.5
ApoA-I (mg/dl)	140.8 ± 22.7	138.6 ± 24.5	0.090	140.7 ± 22.8
ApoB/A-I ratio	0.70 ± 0.21	0.80 ± 0.24	<0.001	0.71 ± 0.21
TC to HDL ratio	3.91 ± 0.95	4.35 ± 1.01	<0.001	3.93 ± 0.96
TG to HDL ratio	2.85 ± 2.17	3.87 ± 3.07	<0.001	2.91 ± 2.25
LDL to HDL ratio	2.29 ± 0.0.71	2.57 ± 0.76	<0.001	2.30 ± 0.72
ApoB to HDL ratio	1.98 ± 0.67	2.32 ± 0.70	<0.001	2.00 ± 0.68

Data are n (%) or mean ± SD (by *t* test). IFG, Impaired fasting glucose; HOMA-IR, homeostasis model assessment of insulin resistance.

[a] Defined as systolic blood pressure 140 mm Hg or greater or diastolic pressure 90 mm Hg or greater or antihypertensive medication.

age and gender: OR (1.505, 95% CI 1.346–1.684; and 1.553, 95% CI 1.386–1.739), respectively. The OR from models 1, 2, and 3 were attenuated but were still significant (model 3; TC to HDL ratio, OR 1.340, 95% CI 1.166–1.538; apoB to HDL ratio, OR 1.338, 95% CI 1.162–1.540) (Table 2).

The OR for development of type 2 diabetes increased as the tertile of the baseline ratios of TC to HDL and apoB to

TABLE 2. Logistic regression analysis of OR (1 SD change) for development of type 2 diabetes according to lipid parameters during 4 yr of follow-up

		OR (95% CI)[a]		
Variables	C statistics[b]	Model 1[c]	Model 2[d]	Model 3[b]
TC	0.846	1.336 (1.202–1.485)	1.227 (1.099–1.369)	1.184 (1.047–1.338)
LDL cholesterol	0.845	1.288 (1.157–1.433)	1.182 (1.058–1.320)	1.180 (1.045–1.333)
HDL cholesterol	0.844	0.791 (0.693–0.903)	0.927 (0.807–1.064)	0.877 (0.753–1.021)
TG	0.847	1.349 (1.243–1.465)	1.224 (1.120–1.338)	1.165 (1.051–1.291)
Non-HDL	0.847	1.435 (1.289–1.597)	1.273 (1.136–1.426)	1.246 (1.097–1.415)
ApoB	0.846	1.516 (1.359–1.690)	1.335 (1.189–1.499)	1.262 (1.107–1.438)
ApoA-I	0.844	0.928 (0.825–1.045)	1.014 (0.898–1.145)	0.927 (0.809–1.062)
ApoB to apoA-I ratio	0.847	1.453 (1.306–1.617)	1.272 (1.135–1.427)	1.292 (1.137–1.468)
TC to HDL ratio	0.847	1.505 (1.346–1.684)	1.285 (1.137–1.452)	1.340 (1.166–1.538)
TG to HDL ratio	0.847	1.336 (1.231–1.450)	1.212 (1.110–1.324)	1.184 (1.071–1.310)
LDL to HDL ratio	0.846	1.405 (1.257–1.570)	1.218 (1.081–1.372)	1.281 (1.121–1.465)
ApoB to HDL ratio	0.847	1.553 (1.386–1.739)	1.323 (1.169–1.497)	1.338 (1.162–1.540)

[a] OR (95% CI) per 1-SD change.

[b] Adjusted for model 3: model 1 + BMI, smoking status (never, past, or current), hypertension, fasting glucose, fasting insulin.

[c] Adjusted for model 1: age and gender.

[d] Adjusted for model 2: model 1 + BMI.

HDL increased from the first to the third tertile after adjustment for age and gender (TC to HDL ratio, OR 1 *vs.* 2.805 $P < 0.005$; apoB to HDL ratio, OR 1 *vs.* 2.860 $P < 0.005$) (Supplemental Tables 1 and 2). This difference remained significant, even after adjustment for age, gender, BMI, smoking status, hypertension, fasting glucose, and fasting insulin.

Discussion

In this study, we found that, among apparently healthy Koreans, the baseline lipid and lipoprotein profiles were significantly associated with subsequent development of type 2 diabetes over a 4-yr period. This was particularly evident in subjects in the highest tertile of the ratios of TC to HDL and apoB to HDL when compared with subjects in the lowest tertile of the ratios of TC to HDL and apoB to HDL than the traditional lipid profiles. Our results go further by adding important information on the sequential link between baseline atherogenic dyslipidemia with later development of new type 2 diabetes. In addition, these data might inform clinicians on how to risk stratify individuals who are screened for type 2 diabetes.

This study has important clinical implications. Dyslipidemia has shown strong correlation with insulin resistance, hyperinsulinemia (9), and type 2diabetes (10). This dyslipidemia is often found in prediabetes (11). Although development of dyslipidemia may be a harbinger of future type 2 diabetes, the pathophysiology of dyslipidemia is not completely understood (1). According to a pathophysiological model, lipids are ectopically deposited in nonadipose tissues, such as liver, skeletal muscle, and the pancreatic β-cell (12). These ectopic lipid deposits are associated with lipotoxicity, which in turn leads to insulin resistance and eventual decline of β-cell dysfunction (13). In addition, recent data suggest that changes in HDL and LDL could also influence β-cell function and mass, implying a role for lipoprotein particles in the pathogenesis of type 2 diabetes (14). Our study appears to be the first study using a large database of cohorts for evaluating an independent association between the future development of type 2 diabetes and various lipoprotein components. Although little difference of C-statistics was observed between lipid parameters, C statistics of multivariate regression model, including fasting insulin and glucose, revealed that TC, LDL cholesterol, TG, non-HDL, apoB, apoB to A-I ratio, TC to HDL ratio, TG to HDL ratio, LDL to HDL ratio, and apoB to HDL ratio were good discriminators in predicting type 2 diabetes. These results suggested that abnormalities in the lipid profiles might account for the increased risk for development of type 2 diabetes.

Lipid parameters can be expressed as ratios that reflect the proportion of atherogenic to antiatherogenic (15). Proposed lipid ratios for coronary heart disease risk assessment include TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, triglyceride to HDL cholesterol, and apoB to apoA-I. In addition, one of the major mechanisms underlying atherogenic dyslipidemia of insulin resistance is mediated by the increased flux of free fatty acids to the liver (15, 16). The liver then promotes secretion of apoB-containing particles (9). Recent studies demonstrating the ability of HDL to induce increased uptake of glucose by skeletal muscle and to stimulate secretion of insulin from pancreatic β-cells raise the possibility that the low HDL concentration in type 2 diabetes may also contribute to a worsening of diabetic control or to progression of prediabetes to the diabetic state (5, 17). Hence, the atherogenic dyslipidemia reflected by lipid and lipoprotein profiles may contribute to development of type 2 diabetes. In addition, we demonstrated that the ratio of TC to HDL and apoB to HDL, which is cheap and easy to be calculated, displayed the most significant association with incident type 2 diabetes among the various lipid parameters. Our study is also the only one in which lipid and lipoprotein profiles was measured for evaluation of the risk of developing type 2 diabetes over a 4-yr period among an Asian population.

We acknowledge certain limitations to the present study. First, the lack of a 2-h postload glucose test was a limitation because it might have resulted in inclusion of subjects with undiagnosed diabetes at baseline. Second, we did not have information on the medication histories for dyslipidemia. However, it is likely that both the small number as well as the characteristics of these individuals make it unlikely that this substantially affected the reported incidence of type 2 diabetes. Third, because most participants were residents of an urban community and all subjects were Korean, there is the possibility of selection bias. 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 lipid and lipoprotein profiles and incident type 2 diabetes among an Asian population.

In conclusion, we have demonstrated a significant association of an elevated lipid and lipoprotein profiles with future development of type 2 diabetes among this large number of nondiabetic Korean subjects during a 4-yr follow-up period. This result indicates that lipid and lipoprotein profiles could provide additional information in prediction future development of type 2 diabetes.

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References

1. **Goldberg IJ** 2001 Clinical review 124: diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab 86:965–971
2. **von Eckardstein A, Schulte H, Assmann G** 2000 Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American Diabetes Association. Prospective Cardiovascular Munster. J Clin Endocrinol Metab 85:3101–3108
3. **Ley SH, Harris SB, Connelly PW, Mamakeesick M, Gittelsohn J, Wolever TM, Hegele RA, Zinman B, Hanley AJ** 2010 Association of apolipoprotein B with incident type 2 diabetes in an aboriginal Canadian population. Clin Chem 56:666–670
4. **Onat A, Can G, Hergenc G, Yazici M, Karabulut A, Albayrak S** 2007 Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation. Int J Obes (Lond) 31:1119–1125
5. **Fryirs MA, Barter PJ, Appavoo M, Tuch BE, Tabet F, Heather AK, Rye KA** 2010 Effects of high-density lipoproteins on pancreatic β-cell insulin secretion. Arterioscler Thromb Vasc Biol 30:1642–1648
6. 2010 Standards of medical care in diabetes—2010. Diabetes Care 33(Suppl 1):S11–S61
7. **Himmelmann A, Kjeldsen SE, Hedner T** 2003 Recent hypertension guidelines: JNC-7 and 2003 ESH/ESC. Blood Press 12:196–197
8. **DeLong ER, DeLong DM, Clarke-Pearson DL** 1988 Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845
9. **Adiels M, Olofsson SO, Taskinen MR, Borén J** 2008 Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arterioscler Thromb Vasc Biol 28:1225–1236
10. **Albers JJ, Marcovina SM, Imperatore G, Snively BM, Stafford J, Fujimoto WY, Mayer-Davis EJ, Petitti DB, Pihoker C, Dolan L, Dabelea DM** 2008 Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with type 1 and type 2 diabetes. J Clin Endocrinol Metab 93:735–742
11. **Haffner SM, Mykkänen L, Festa A, Burke JP, Stern MP** 2000 Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation 101:975–980
12. **Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW** 2007 Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic β-cell dysfunction. Diabetes 56:2328–2338
13. **Brunham LR, Kruit JK, Verchere CB, Hayden MR** 2008 Cholesterol in islet dysfunction and type 2 diabetes. J Clin Invest 118:403–408
14. **Kruit JK, Brunham LR, Verchere CB, Hayden MR** 2010 HDL and LDL cholesterol significantly influence β-cell function in type 2 diabetes mellitus. Curr Opin Lipidol 21:178–185
15. **Arsenault BJ, Boekholdt SM, Kastelein JJ** 2011 Lipid parameters for measuring risk of cardiovascular disease. Nat Rev Cardiol 8:197–206
16. **Irving BA, Nair KS, Srinivasan M** 2011 Effects of insulin sensitivity, body composition, and fitness on lipoprotein particle sizes and concentrations determined by nuclear magnetic resonance. J Clin Endocrinol Metab 96:E713–E718
17. **Barter PJ** 2011 The causes and consequences of low levels of high density lipoproteins in patients with diabetes. Diabetes Metab J 35:101–106