

# Association of HDL-C and apolipoprotein A-I with the risk of type 2 diabetes in subjects with impaired fasting glucose

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## Abstract

**Objectives:** HDLs have many diverse functions. The goal of this study was to determine the association of HDL cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) with the development of type 2 diabetes (T2D). In particular, this study determined the association between the ratio of HDL-C to apoA-I (HA) and incident T2D.

**Design and methods:** A total of 27 988 subjects with impaired fasting glucose (IFG) (18 266 men and 9722 women) aged 21–91 years (mean age 40.7 years) were followed for a mean duration of 2.81 years.

**Results:** Study subjects were divided into quartiles according to the baseline HA ratio. Age, male sex, current smoking, BMI, waist circumference, and high-sensitivity C-reactive protein decreased across the quartiles, and all metabolic profiles, including blood pressure, fasting glucose, insulin resistance as determined by homeostasis model assessment of insulin resistance, and lipid measurements such as total cholesterol, LDL cholesterol, non-HDL-C, and apoB, improved as the HA ratio increased. In addition, incident cases of T2D decreased as the HA ratio increased, independent of age, sex, BMI, current smoking, systolic blood pressure, HbA1c, fasting serum insulin, family history of diabetes, and serum triglyceride concentrations (HR (95% CI) of fourth quartile vs first quartile; 0.76 (0.67–0.86),  $P < 0.0001$ ).

**Conclusions:** A higher HA ratio was associated with favorable metabolic profiles and a lower risk of T2D development in subjects with IFG.

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## Introduction

Large epidemiological studies have demonstrated an inverse relationship between serum HDL cholesterol (HDL-C) concentrations and the risk of coronary heart disease (CHD) (1, 2), that is, each 1 mg/dl increase in HDL-C is associated with ~2–3% lower risk of CHD (3). The primary mechanism for this inverse relationship is the ability of HDLs and apolipoprotein (apo) A-I to mediate reverse cholesterol transport from non-hepatic cells to the liver and steroidogenic organs (4). ApoA-I is the structural apolipoprotein in HDLs and constitutes about 70% of the apolipoprotein content of HDL particles (4); thus, plasma

apoA-I concentrations closely correlate with plasma HDL-C concentrations (5). However, the degree of this correlation varies and only 43% of the variance in HDL-C can be explained by variation in apoA-I concentrations (5).

It is well known that HDLs protect against atherosclerosis, but additional functions have also been reported, including anti-inflammatory, antioxidative, anti-apoptotic, vasodilatory, antithrombotic, and anti-infectious properties and direct modulation of glucose metabolism (6). Accordingly, recent epidemiological studies have demonstrated the association between low HDL-C concentrations

and the risk of incident type 2 diabetes (T2D) (7, 8). By contrast, while little is known about the role of apoA-I in the development of T2D, the findings of some recent studies have suggested that high serum apoA-I is associated with an increased risk of incident diabetes (9, 10).

Therefore, the goal of this study was to determine the role of HDL-C and apoA-I in the development of T2D in patients with impaired fasting glucose (IFG). Study subjects were divided into quartiles according to the baseline HDL-C to apoA-I (HA) ratio, and independent associations with the development of T2D were analyzed across the quartiles.

## Subjects and methods

### Study population

Study subjects were recruited from a population of patients who visited the Health Screening Center at Kangbuk Samsung Hospital between January 2005 and December 2010 for routine medical examinations. During this period, a total of 130 409 subjects received medical examinations on at least two occasions. Among these patients, 6794 were excluded as they had T2D at baseline. In addition, seven subjects were excluded because anthropometric or lipid data were not available for them. Finally, a total of 123 608 subjects were reviewed and a total of 27 988 subjects with IFG (18 266 men and 9722 women) aged 21–91 years (mean age 40.7 years) were enrolled in this study. Subjects were followed for a mean of 2.81 years, with a range of 1–72 months.

The study protocol and data analysis were approved by the Institutional Review Board of Kangbuk Samsung Hospital. As the data did not include any personal information, the Board determined that the study was exempt from the need to obtain informed consent from study participants.

### Clinical and laboratory examination

A complete physical examination was performed in which information about personal medical history, family history of diabetes, and lifestyle factors including cigarette smoking and alcohol consumption were obtained using a standardized questionnaire. Blood pressure was measured by trained nurses using a mercury sphygmomanometer on the right arm after a 5-min rest interval with the patient in a seated position. Weight and height were measured in the morning with subjects wearing light clothing and no shoes, and BMI was calculated as weight in kilograms

divided by the square of the height in meters. Waist circumference was measured at a level midline between the lower rib margin and iliac crest.

All blood samples were obtained in the morning following an overnight fast of 12–14 h. Serum glucose was measured by the hexokinase method using an autoanalyzer (Advia 1800; Siemens, Berlin, Germany). The inter-assay coefficient of variation (CV) value was 0.6–1.6%. Serum insulin was measured using an IRMA (Biosource, Nivelles, Belgium), with intra- and inter-assay CV values of 2.1–4.5 and 4.7–12.2% respectively. The homeostasis model assessment (HOMA), which is based on fasting glucose and insulin concentrations, was used to estimate insulin sensitivity and  $\beta$ -cell function (11). Serum total cholesterol, triglycerides, HDL-C, and directly measured LDL cholesterol levels were determined using an autoanalyzer (Advia 1800; Siemens). Serum apoB and apoA-I concentrations were determined by immunoturbidometric methods (Advia 2400, autoanalyzer; Siemens), with inter-assay CV values of 2.1–6.1 and 1.8–4.8% respectively. High-sensitivity C-reactive protein (hs-CRP) was analyzed by particle-enhanced immunonephelometry with a BNITM System (Dade Behring, Marburg, Germany). HbA1c levels were determined by immunoassays (Cobas Integra 800; Roche), with an inter-assay CV value of 0.9–3.3%. The clinical laboratory used in this study participates in annual inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories and has been accredited for quality control and performance of these measurements.

In this study, IFG was defined by the presence of one of the following: i) fasting glucose levels of 100–125 mg/dl or ii) HbA1c levels of 5.7–6.4% (39–46 mmol/mol). Incident T2D was defined by the presence of one of the following: i) fasting glucose levels  $\geq$  126 mg/dl; ii) treatment involving oral hypoglycemic agents or insulin therapy; iii) a self-reported history of diabetes; or iv) HbA1c levels  $\geq$  6.5% (48 mmol/mol) (12). Subjects with incident type 1 diabetes that had a history of ketoacidosis at initial presentation, who essentially required insulin therapy for blood glucose control, or who had low to undetectable serum insulin levels were excluded (12).

### Statistical analyses

Data are expressed as mean  $\pm$  s.d. or as proportions. Differences among groups were tested by ANOVA for continuous variables and the  $\chi^2$ -test was used for categorical variables. A Kaplan–Meier survival curve was used to determine differences among groups in terms of

the development of T2D. Multivariate Cox hazard regression analyses were performed to determine whether the HA ratio was associated with T2D independent of age, sex, BMI, current smoking, systolic blood pressure, HbA1c, fasting serum insulin, family history of diabetes, and serum triglyceride concentration. Analyses were performed using R version 2.14.2 (<http://www.r-project.org>). *P* values of <0.05 were considered statistically significant.

## Results

The clinical characteristics of the study population according to the HA ratio quartile are given in Table 1. Age, male sex, current smoking, BMI, waist circumference, and hs-CRP decreased across the quartiles, and all metabolic profiles, including blood pressure, fasting glucose, insulin resistance as determined by HOMA-IR, and lipid measurements such as total cholesterol, LDL-C, non-HDL-C, and apoB, improved as the HA ratio increased.

Serum HDL-C levels were independently associated with a lower incidence of T2D after adjusting for age and sex (HR per 1-s.d., 0.91; 95% CI, 0.88–0.95; *P*<0.0001, Table 2). However, the protective effect of HDL-C

disappeared after further adjusting for BMI, current smoking, systolic blood pressure, HbA1c, fasting serum insulin, family history of diabetes, and triglycerides. However, serum apoA-I levels were independently associated with a higher incidence of T2D even after adjusting for all of the aforementioned confounding factors (HR per 1-s.d., 1.10; 95% CI, 1.07–1.15; *P*<0.0001, Table 2).

During follow-up, 4589 cases (16.4%) of incident T2D developed in patients with IFG. Incident cases of T2D decreased as the HA ratio increased (20.9% (*n*=1265), 18.2% (*n*=1101), 16.0% (*n*=965), and 14.9% (*n*=902) in the first, second, third, and fourth quartiles respectively; *P*<0.001, Fig. 1). This was independent of aforementioned risk factors for T2D (Table 3). In the final model (model V), subjects in the fourth quartile showed a 21% risk reduction compared with subjects in the first quartile for development of T2D (HR (95% CI) of fourth quartile vs first quartile; 0.76 (0.67–0.86), *P*<0.0001).

## Discussion

Apart from the role of HDLs in reverse cholesterol transport, recent studies have uncovered a variety of

**Table 1** Baseline characteristics of study subjects according to quartiles based on the ratio of HDL cholesterol to apolipoprotein A-I. Data are expressed as mean  $\pm$  s.d. or frequency (%). Smoking data were available for 16 573 subjects.

Variables	First quartile ( <i>n</i> =6997)	Second quartile ( <i>n</i> =6997)	Third quartile ( <i>n</i> =6997)	Fourth quartile ( <i>n</i> =6997)
HDL cholesterol/apolipoprotein A-I (range)	0.31 $\pm$ 0.02 (0.16–0.33)	0.34 $\pm$ 0.01 (0.33–0.36)	0.37 $\pm$ 0.01 (0.36–0.39)	0.43 $\pm$ 0.05 (0.39–2.41)
Age (years)	41.2 $\pm$ 8.1	41.0 $\pm$ 8.1	40.7 $\pm$ 8.0	39.8 $\pm$ 7.9
Female (%)	1193 (17.1)	1755 (25.1)	2603 (37.2)	4171 (59.6)
BMI (kg/m <sup>2</sup> )	25.6 $\pm$ 2.9	24.9 $\pm$ 3.0	24.0 $\pm$ 3.0	22.6 $\pm$ 2.9
Waist circumference (cm)	86.6 $\pm$ 8.1	84.6 $\pm$ 8.9	82.3 $\pm$ 9.0	77.2 $\pm$ 9.3
Current smoking (%)	1561 (37.7)	1305 (31.1)	1067 (25.4)	613 (15.2)
Family history of diabetes (%)	797 (11.4)	736 (10.5)	662 (9.5)	553 (7.9)
Systolic blood pressure (mmHg)	119.5 $\pm$ 14.1	117.3 $\pm$ 14.3	115.2 $\pm$ 14.2	112.1 $\pm$ 14.2
Diastolic blood pressure (mmHg)	78.3 $\pm$ 9.8	76.5 $\pm$ 9.9	74.9 $\pm$ 9.8	72.4 $\pm$ 9.7
Fasting serum glucose (mmol/l)	5.7 $\pm$ 0.4	5.7 $\pm$ 0.4	5.6 $\pm$ 0.4	5.5 $\pm$ 0.5
Fasting serum insulin (pmol/l)	76.4 $\pm$ 27.1	70.8 $\pm$ 25.7	66.7 $\pm$ 23.6	61.1 $\pm$ 20.1
HbA1c (%)	5.6 $\pm$ 0.3	5.6 $\pm$ 0.3	5.6 $\pm$ 0.3	5.6 $\pm$ 0.3
HbA1c (mmol/mol)	38 $\pm$ 4	38 $\pm$ 4	38 $\pm$ 3	38 $\pm$ 3
HOMA-IR	2.80 $\pm$ 1.05	2.57 $\pm$ 0.97	2.40 $\pm$ 0.90	2.15 $\pm$ 0.77
HOMA-B%	102.2 $\pm$ 41.1	98.1 $\pm$ 42.5	96.2 $\pm$ 38.9	96.2 $\pm$ 43.5
High-sensitivity C-reactive protein (mg/l)	0.14 $\pm$ 0.28	0.13 $\pm$ 0.29	0.12 $\pm$ 0.32	0.12 $\pm$ 0.44
Total cholesterol (mmol/l)	5.00 $\pm$ 0.85	5.14 $\pm$ 0.86	5.11 $\pm$ 0.90	5.07 $\pm$ 0.88
Triglyceride (mmol/l)	2.33 $\pm$ 1.39	1.69 $\pm$ 0.84	1.37 $\pm$ 0.67	1.00 $\pm$ 0.58
Calculated LDL cholesterol (mmol/l)	2.81 $\pm$ 0.79	3.10 $\pm$ 0.75	3.10 $\pm$ 0.76	2.95 $\pm$ 0.78
LDL cholesterol (mmol/l)	2.85 $\pm$ 0.70	3.08 $\pm$ 0.72	3.05 $\pm$ 0.76	2.84 $\pm$ 0.78
HDL cholesterol (mmol/l)	1.12 $\pm$ 0.18	1.26 $\pm$ 0.19	1.39 $\pm$ 0.22	1.66 $\pm$ 0.31
Non-HDL cholesterol (mmol/l)	3.88 $\pm$ 0.82	3.87 $\pm$ 0.84	3.72 $\pm$ 0.78	3.41 $\pm$ 0.88
Apolipoprotein B (g/l)	1.05 $\pm$ 0.22	1.05 $\pm$ 0.23	0.99 $\pm$ 0.24	0.89 $\pm$ 0.23
Apolipoprotein A-I (g/l)	1.41 $\pm$ 0.21	1.42 $\pm$ 0.22	1.44 $\pm$ 0.22	1.50 $\pm$ 0.24
Apolipoprotein B/A-I	0.76 $\pm$ 0.18	0.75 $\pm$ 0.20	0.71 $\pm$ 0.21	0.61 $\pm$ 0.21

All *P*<0.0001 across all quartiles. HOMA, homeostasis model assessment.

**Table 2** Multivariate Cox proportional hazards regression analysis of HDL cholesterol and apolipoprotein A-I for the development of type 2 diabetes. Data are expressed as HR per 1-s.d. increase in variables with 95% CI.

	HDL cholesterol		Apolipoprotein A-I	
	HR (95% CI)	P	HR (95% CI)	P
Model I	0.87 (0.84–0.90)	<0.001	1.01 (0.99–1.04)	0.36
Model II	0.91 (0.88–0.95)	<0.001	1.03 (1.00–1.06)	0.06
Model III	0.97 (0.94–1.01)	0.12	1.06 (1.03–1.09)	<0.001
Model IV	1.00 (0.96–1.05)	0.91	1.10 (1.06–1.14)	<0.001
Model V	1.04 (1.00–1.09)	0.07	1.10 (1.07–1.15)	<0.001

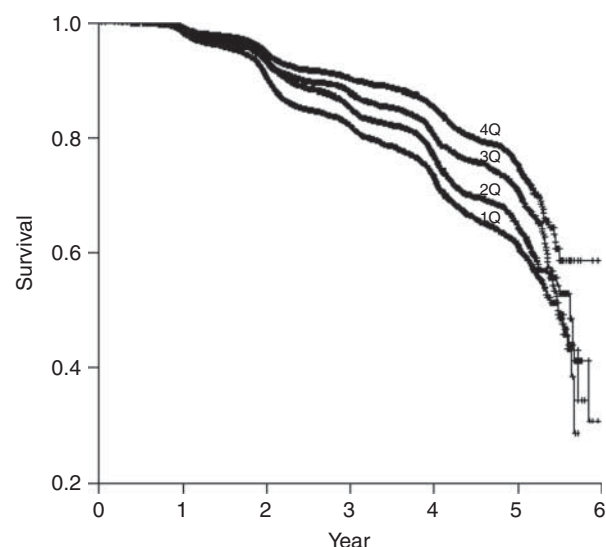
Model I: no adjustment. Model II: adjusted for age and sex. Model III: model II + adjusted for BMI. Model IV: model III + adjusted for current smoking, systolic blood pressure, HbA1c, fasting serum insulin, and family history of diabetes. Model V: model IV + adjusted for triglyceride.

other HDL functions. Anti-inflammatory and antioxidative functions of HDLs have been described in addition to the innate immune function of HDLs as a defense against viral, bacterial, and parasitic infections (6). In addition, HDLs are directly involved in glucose metabolism through insulin secretion in pancreatic  $\beta$ -cells (13) and improvement of insulin sensitivity (14, 15). Although little is known about the role of apoA-I in the development of T2D, the findings of some recent studies are in agreement with the observations described in this study. Among 2111 middle-aged and elderly Turkish adults, subjects in the high serum apoA-I tertile had a nearly twofold increased risk for incident diabetes compared with subjects in the low serum apoA-I tertile during a 7.4 year follow-up. The authors of that study speculated that dysfunctional adiponectin associated with systemic inflammation and insulin resistance might transform apoA-I into pro-inflammatory particles and thus enhance the development of diabetes (9). Another study involving a Finnish cohort showed that apoA-I was an independent risk factor for the development of diabetes during a median 10.8-year follow-up (10).

Recent studies have suggested that the cardioprotective effects of HDLs can be altered in cases of systemic inflammation and T2D. In these situations, the lipid and protein composition of HDLs can be changed via oxidative processes. As a result, the protective effect of HDLs against CHD was lost and HDLs became proatherogenic, which are known as dysfunctional HDLs (16, 17, 18). Ansell *et al.* (19) showed that HDLs from subjects with CHD were pro-inflammatory despite very high HDL-C levels, indicating that HDLs from CHD subjects are dysfunctional. In addition, treatment with torcetrapib, an inhibitor of cholesteryl ester transfer protein, was associated with an

increase in cardiovascular events, despite a 72% increase in HDL-C levels (20). One possible mechanism for dysfunctional HDLs is the alteration in the protein composition of HDLs in the setting of systemic inflammation and T2D. In this situation, inflammatory cytokines such as plasma interleukin-6 levels are elevated and the liver consequently produces serum amyloid A, which replaces apoA-I and paraoxonase 1 in HDL particles (16). In addition, myeloperoxidase specifically binds to apoA-I and produces reactive oxidative species. As a result, modified HDLs show an impaired cholesterol efflux in macrophages (17).

Human HDLs are a heterogeneous group of particles showing a range of densities, sizes, and electrophoretic mobilities as a result of the differences in the apolipoprotein compositions and lipid contents of HDL particles. It has been reported that the biological activities of HDLs differ according to HDL subpopulations (21). For example, the Framingham Offspring Study showed that large  $\alpha$ 1 HDL particles are inversely associated with CHD prevalence after adjusting for established CHD risk factors (22). Similarly, small discoid HDL particles are often elevated in patients with CHD, whereas large  $\alpha$ 2 HDL particles are decreased in patients with CHD (23). Previous studies suggested that the HA ratio reflects the core to surface ratio, or the particle size of HDL particles (24, 25, 26). The HA ratio is lower in patients with metabolic syndrome



**Figure 1**

Kaplan-Meier survival curve for incident type 2 diabetes according to HDL cholesterol to apolipoprotein A-I ratio quartiles ( $P < 0.0001$  across the quartiles).

**Table 3** Multivariate Cox proportional hazards regression analysis for the development of type 2 diabetes according to quartiles based on the ratio of HDL cholesterol to apolipoprotein A-I. Data are expressed as HR with 95% CI.

	First quartile	Second quartile	Third quartile	Fourth quartile
Model I	1	0.85 (0.78–0.91)	0.69 (0.64–0.75)	0.55 (0.50–0.60)
Model II	1	0.86 (0.80–0.93)	0.73 (0.68–0.80)	0.62 (0.57–0.68)
Model III	1	0.90 (0.83–0.97)	0.79 (0.73–0.86)	0.72 (0.66–0.79)
Model IV	1	0.88 (0.80–0.97)	0.76 (0.69–0.84)	0.69 (0.61–0.78)
Model V	1	0.93 (0.85–1.03)	0.83 (0.74–0.92)	0.76 (0.67–0.86)

Reference quartile was defined as the first HDL cholesterol to apolipoprotein A-I ratio quartile. All  $P < 0.0001$  across all quartiles. Model I: no adjustment. Model II: adjusted for age and sex. Model III: model II+adjusted for BMI. Model IV: model III+adjusted for current smoking, systolic blood pressure, HbA1c, fasting serum insulin, and family history of diabetes. Model V: model IV+adjusted for triglyceride.

compared with patients without metabolic syndrome, which is indicative of the presence of smaller denser HDL particles in patients with metabolic syndrome (26).

This study divided subjects by quartile according to the HA ratio. At baseline, as the HA ratio increased, BMI, waist circumference, blood pressure, fasting glucose, HOMA-IR, and hs-CRP levels decreased, which suggests that large HDL particle size is associated with healthy metabolic profiles. In addition, a higher HA ratio was associated with a lower incidence of T2D independent of other risk factors for T2D and serum triglyceride levels. Therefore, not only do large HDL particles have an effect on the development of CHD, but they also appear to be associated with a lower risk of developing T2D in subjects with IFG.

The results of this study may have clinical implications. The measurement of HDL-C alone is not sufficient to assess the association between cardiovascular risk and future development of T2D. At a given serum HDL-C concentration, additional measurement of serum apoA-I concentration may be needed to determine the relationship between cardiovascular risk and future development of T2D, that is, lower apoA-I at a given HDL-C concentration is associated with a lower cardiovascular risk and lower incidence of T2D, and thus, HA ratio may be used as a simple measurement for assessing cardiovascular risk and future development of T2D.

There are other limitations that should be considered in addition to the retrospective nature of this study. First,

study subjects were in a state of IFG and thus might have some degree of insulin resistance compared with subjects with normal glucose tolerance. Therefore, it is possible that they already had some dysfunctional HDL particles and thus the results are less generalized. Secondly, the study had a relatively short follow-up period (2.81 years), which limited the interpretation of results in the setting of long-term effects of serum HDL-C and/or apoA-I on the development of T2D. In addition, subjects were selected from a population who visited the Health Screening Center for routine medical examinations, and thus, they were not representative of the general population and might be healthier than the general population.

In summary, the data suggest that the measurement of serum HDL-C alone is not sufficient to assess cardiometabolic risk, especially T2D. Simultaneous measurement of apoA-I provides a more accurate risk assessment for future development of T2D. Collectively, high HDL-C combined with low apoA-I was associated with a low incidence of T2D; however, the protective effect of HDL-C lessened as apoA-I increased, that is, a high HA ratio was associated with a lower risk of developing future T2D and could be used to assess the risk of T2D.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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