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Adiponectin is independently associated with apolipoprotein B to A-1 ratio in Koreans

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Abstract

Apolipoprotein B to A-1 (apo B/A-1) ratio is reportedly a better predictor of atherosclerotic vascular disease than low-density lipoprotein cholesterol (LDL-C). The aim of this study was to assess the association of serum apo B/A-1 ratio with insulin resistance and adiponectin in patients with different grades of glucose intolerance. Patients were divided according to glucose tolerance into 3 groups: normal glucose tolerance without metabolic syndrome (n = 229), impaired fasting glucose (subjects with fasting plasma glucose level between 100 and 125 mg/dL, n = 658), and type 2 diabetes mellitus (n = 381). Serum concentrations of apo B, apo A-1, glucose, total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C) and adiponectin were measured. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance index (HOMA-IR). There were significant differences in metabolic parameters among the groups, including waist circumference, insulin, HOMA-IR, and apo B/A-1 ratio, which increased sequentially with glucose intolerance, whereas adiponectin level decreased with increasing severity of glucose intolerance. The apo B/A-1 ratio was significantly correlated with TC, triglycerides, LDL-C, HDL-C, adiponectin, and HOMA-IR in normal glucose tolerance, impaired fasting glucose, and type 2 diabetes mellitus. Multiple regression analysis showed that apo B/A-1 ratio was significantly associated with TC, LDL-C, HDL-C, and adiponectin. In conclusion, apo B/A-1 ratio was significantly associated with insulin resistance according to glucose intolerance; and serum adiponectin was an important independent factor associated with apo B/A-1 ratio in Koreans.

1. Introduction

Serum low-density lipoprotein cholesterol (LDL-C) concentration is a good index to predict the risk of cardiovascular disease [1], but recent studies indicate that apolipoprotein B to A-1 ratio (apo B/A-1) is an even better predictor of atherosclerotic vascular disease [2-5].

Insulin resistance is one of the important risk factors associated with obesity, dyslipidemia, hyperglycemia, and hypertension and independently increases the risk for atherosclerosis [6-9]. In nondiabetic subjects, insulin resistance is also associated with apo B/A-1 ratio [10,11], and Matsumoto et al [12] recently reported that insulin resistance correlates with serum apo B levels in type 2 diabetes mellitus patients.

Adiponectin, an adipocytokine specifically synthesized in the adipose tissue, plays an important role in lipid metabolism and development of atherosclerosis [13,14]. A low adiponectin level was shown to be correlated with hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) level, independent of insulin resistance and body fat mass [15]. Although the mechanisms for the relationship between adiponectin and dyslipidemia are complex and undefined, in recent studies done with normoglycemic subjects, plasma adiponectin level was found to be related to apo B and apo A-1 levels. However, the numbers of subjects are relatively small; and these studies show inconsistent results [16,17]. Therefore, in the present study, we investigated the

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association of serum apo B/A-1 ratio with insulin resistance and adiponectin and attempted to identify factors associated with apo B/A-1 ratio in patients with different grades of glucose intolerance.

2. Methods

2.1. Subjects

This study was part of a population-based, multicenter, cross-sectional study designed to evaluate the prevalence and characteristics of metabolic syndrome (MetS) in habitants of Seoul, Korea. The study included 3134 participants recruited from 17 different tertiary medical centers in Seoul, Korea.

Subjects were excluded if they were suspected of having acute illnesses through history taking, physical examination, or serologic tests. Subjects with clinically significant infectious diseases, fever, leukocytosis, a significant hepatic (alanine aminotransferase or aspartate aminotransferase ≥2.5-fold the normal value) or renal (serum creatinine ≥1.5 mg/dL) disease, or other malignancies, and those taking lipid-lowering medication (fibrate or statin) were excluded. We also excluded subjects who had a history of cardiovascular disease. Patients were divided into 3 groups according to glucose tolerance: normal glucose tolerance (NGT) without MetS, impaired fasting glucose (IFG) (subjects with fasting plasma glucose level between 100 and 125 mg/dL), and type 2 diabetes mellitus. The diagnosis of type 2 diabetes mellitus was based on a previous history of diabetes or on the American Diabetes Association's diagnostic guidelines. The included diabetic patients were not treated with insulin or thiazolidinedione, allowing us to compare the effects of obesity and insulin resistance without the possible confounding effects of glucose-lowering pharmacologic treatment. Ultimately, 1268 subjects between the ages of 40 and 75 years were enrolled. The Institutional Review Board of Yonsei University College of Medicine approved the study protocol, and written informed consent was obtained from all participants.

2.2. Clinical characteristics

Height, weight, and waist circumference (WC) were measured; and body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in square meters). Each patient's personal medical history of chronic and acute illnesses and medication history were evaluated. In type 2 diabetes mellitus patients, the duration of diabetes, concomitant diseases, and current medications were assessed. Systolic and diastolic blood pressures were taken after a 5-minute rest.

2.3. Biochemical parameters

Blood samples were taken from all subjects after 8 hours of fasting. Samples were immediately centrifuged, and plasma and serum samples were stored at −70°C until analysis. Glucose was measured with a standard glucose oxidase reference method (747 automatic analyzer; Hitachi, Tokyo, Japan). Total cholesterol (TC), HDL-C, and triglycerides (TG) were measured with an enzymatic color test (Hitachi 747; Daiichi, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated according to the Friedewald formula. Fasting serum insulin was determined by means of chemiluminescence (radioimmunoassay kit, Daiichi); and insulin resistance was estimated using the homeostasis model assessment of insulin resistance index (HOMA-IR), calculated from the following formula: HOMA-IR = fasting insulin (in microunits per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5. Plasma adiponectin level was measured by enzyme-linked immunosorbent assay (Mesdia, Seoul, Korea) [18]. Apolipoprotein A-1 and apo B were measured by immunoturbidimetry (Hitachi autoanalyzer, model 705, Daiichi). Standardization was performed with commercially available material (Boehringer, Mannheim, Germany). Measurement ranges were 250 to 5000 and 200 to 4000 mg/L for apo B and A-1, respectively. The intraassay coefficients of variation for apo B were between 2.5% and 1.5%. The corresponding values for the interassay coefficients of variation were between 5.7% and 3.2% [19].

2.4. Definition of metabolic syndrome

Metabolic syndrome was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria applying the Asia-Pacific World Health Organization guidelines for WC. Accordingly, subjects with 3 or more of the following characteristics were diagnosed with MetS: fasting plasma glucose of at least 100 mg/dL or diabetes diagnosis, WC of at least 90 cm for men or at least 80 cm for women, blood pressure of at least 130/85 mm Hg or on blood pressure medication, TG of at least 150 mg/dL or on TG-lowering medication, and HDL-C less than 40 mg/dL for men or less than 50 mg/dL for women.

2.5. Statistical analysis

Data are expressed as mean ± SD. Student *t* test or 1-way analysis of variance was used to compare continuous variables, and the χ^2 test was used to compare proportions among groups. A Pearson correlation analysis and multiple regression analysis were also performed to evaluate the relationship between the apo B/A-1 ratio and various clinical factors where indicated. Stepwise multiple linear regression analysis was performed to analyze the influence of different factors on apo B/A-1 ratio. Statistical analyses were carried out using SPSS for Windows 11.0 (SPSS, Chicago, IL). *P* values < .05 were considered statistically significant.

3. Results

Clinical characteristics of the study subjects are presented in Table 1. The subjects were divided into 3 groups

Table 1
Baseline characteristics of subjects according to glucose tolerance status

	NGT /s MetS	IFG	DM
n	229	658	381
Sex (M/F)	121/108	317/341	196/185
Age (y)	55.2 ± 12.7	54.4 ± 10.97	55.49 ± 10.22
BMI (kg/m^2)	23.5 ± 3.4	25.1 ± 3.3†	25.2 ± 2.8†
WC (cm)	2.1 ± 9.9	6.3 ± 8.9†	8.0 ± 8.6†§
FPG (mg/dL)	90.0 ± 6.3	107.8 ± 6.7†	141.6 ± 38.3§
TC (mg/dL)	184.04 ± 33.11	183.65 ± 37.63	194.63 ± 29.42§
TG (mg/dL)	122.08 ± 73.28	137.27 ± 101.95*	145.15 ± 57.09†
LDL-C (mg/dL)	105.30 ± 29.21	116.46 ± 51.23†	123.29 ± 40.90‡
HDL-C (mg/dL)	53.76 ± 14.39	51.89 ± 13.61	41.30 ± 20.64§
HbA_{1c} (%)	NA	5.87 ± 0.50	7.53 ± 1.33§
Insulin (μIU/mL)	4.19 ± 2.64	4.81 ± 2.94†	5.57 ± 4.47†§
SBP (mm Hg)	117.5 ± 10.3	128.0 ± 14.3†	125.1 ± 12.5†
DBP (mm Hg)	74.8 ± 8.3	1.1 ± 10.8†	2.6 ± 8.6†
HOMA-IR	0.93 ± 0.60	1.49 ± 1.19†	1.66 ± 1.10†§
Adiponectin (μg/mL)	7.69 ± 3.58	7.19 ± 3.85*	6.68 ± 3.04†‡
Apo B/A-1	0.67 ± 0.23	0.72 ± 0.30*	0.80 ± 0.20†§
Aortic PWV (m/s)	7.50 ± 1.05	7.68 ± 1.20*	7.99 ± 1.19†§
Peripheral PWV (m/s)	9.15 ± 1.36	9.63 ± 1.46†	9.98 ± 1.51†§

Data are mean ± SD. HbA_{1c} indicates hemoglobin A_{1c}; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; NA, not available.

* $P < .05$ vs NGT.

† $P < .01$ vs NGT.

‡ $P < .05$ vs IFG.

§ $P < .01$ vs IFG.

according to glucose tolerance (NGT, IFG, and type 2 diabetes mellitus). There were significant differences in metabolic parameters among the groups, including WC, insulin, HOMA-IR, and apo B/A-1 ratio, which increased sequentially with glucose intolerance, whereas adiponectin level decreased with increasing severity of glucose intolerance (Table 1).

As expected, BMI, WC, lipid profiles, blood pressure, insulin, HOMA-IR, and apo B/A-1 ratio were significantly higher, and adiponectin levels were lower, in the IFG group and type 2 diabetes mellitus group with MetS when compared with those without MetS (Table 2).

Fig. 1 shows the association of apo B/A-1 ratio quartiles with insulin resistance after adjusting for age and sex. After adjusting for age and sex, apo B/A-1 ratio was significantly correlated with TC (NGT, IFG, type 2 diabetes mellitus, respectively: $r = 0.33$, $r = 0.21$, $r = 0.38$; all Ps < .01), TG ($r = 0.28$, $r = 0.22$, $r = 0.29$; all Ps < .01), LDL-C ($r = 0.47$, $r = 0.29$, $r = 0.39$; all Ps < .01), HDL-C ($r = -0.46$, $r = -0.28$, $r = -0.34$; all Ps < .01), adiponectin ($r = -0.35$, $r = -0.28$ $r = -0.21$; all Ps < .01), and HOMA-IR ($r = 0.20$, $r = 0.09$, $r = 0.08$; all Ps < .05). Adiponectin was significantly inversely related to the apo B/A-1 ratio in subjects with NGT, IFG, and type 2 diabetes mellitus (Fig. 2).

Multiple regression analysis revealed that apo B/A-1 ratio was significantly associated with TC, LDL-C, HDL-C, TG, and adiponectin in subjects with NGT, IFG, and type 2 diabetes mellitus after adjusting for age and sex (Table 3). When we included all 1268 subjects, the results were similar (data not shown).

4. Discussion

In the present study, apo B/A-1 ratio was associated with insulin resistance in patients with different grades of glucose

Table 2
Clinical characteristics of IFG and type 2 diabetes mellitus patients with and without MetS

	IFG without MetS	IFG with MetS	DM without MetS	DM with MetS
n	195	463	138	242
Sex (M/F)	106/89	221/242	72/66	124/118
Age (y)	53.99 ± 11.28	54.64 ± 10.84	54.46 ± 10.65	57.66 ± 8.82*
BMI (kg/m^2)	23.7 ± 3.0	26.7 ± 3.1†	23.9 ± 2.4	25.9 ± 2.7†
WC (cm)	82.9 ± 8.0	92.0 ± 7.9†	83.9 ± 7.9	92.4 ± 8.1†
FPG (mg/dL)	107.7 ± 6.8	107.9 ± 6.7	143.9 ± 39.3	140.2 ± 37.8
TC (mg/dL)	170.58 ± 52.62	189.16 ± 85.47†	186.55 ± 29.24	196.67 ± 29.64*
TG (mg/dL)	79.14 ± 50.12	161.50 ± 85.14†	115.51 ± 48.35	162.17 ± 54.89†
LDL-C (mg/dL)	102.69 ± 33.11	118.08 ± 57.11†	104.01 ± 46.62	117.26 ± 28.11†
HDL-C (mg/dL)	58.73 ± 12.91	49.03 ± 12.87†	53.19 ± 10.72	40.21 ± 37.58†
HbA_{1c} (%)	5.77 ± 0.50	5.91 ± 0.49*	7.45 ± 1.49	7.66 ± 1.23
Insulin (μIU/mL)	3.85 ± 2.59	6.25 ± 4.90†	3.96 ± 2.44	6.36 ± 3.07†
SBP (mm Hg)	124.1 ± 13.3	129.6 ± 14.4	120.9 ± 10.3	127.5 ± 13.0†
DBP (mm Hg)	78.5 ± 9.6	82.2 ± 11.1†	78.2 ± 6.7	80.4 ± 8.5†
HOMA-IR	1.05 ± 0.97	1.67 ± 1.30†	1.35 ± 0.99	1.83 ± 1.12†
Adiponectin (μg/mL)	7.61 ± 3.62	7.00 ± 3.93†	6.91 ± 3.09	6.38 ± 3.01*
Apo B/A-1	0.69 ± 0.41	0.75 ± 0.25†	0.76 ± 0.17	0.82 ± 0.20†
Aortic PWV (m/s)	7.50 ± 1.21	7.71 ± 1.21	7.90 ± 1.12	8.18 ± 1.30
Peripheral PWV (m/s)	9.62 ± 1.49	9.77 ± 1.45	9.78 ± 1.54	9.84 ± 1.41

Data are mean ± SD.

* $P < .05$ vs without MetS.

† $P < .01$ without MetS.

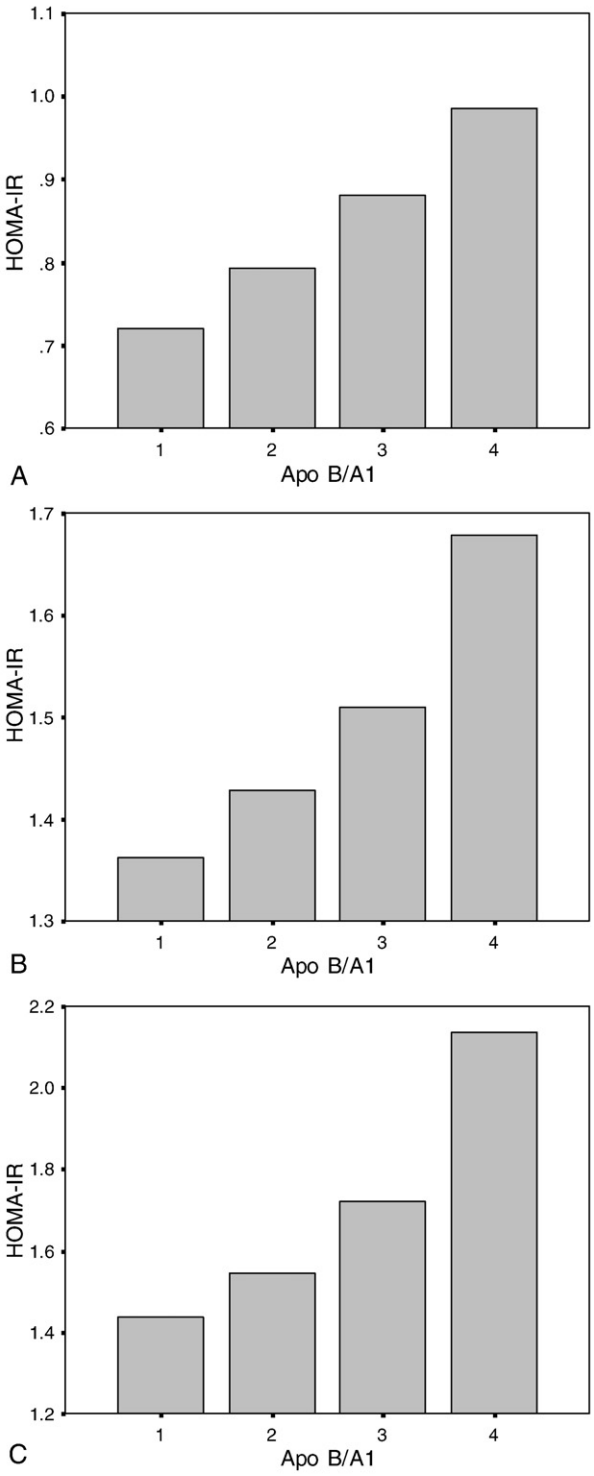

Fig. 1. Relationship between apo B/A-1 quartiles and HOMA-IR according to glucose tolerance. Patients with (A) NGT without MetS, (B) IFG, and (C) type 2 diabetes mellitus (P <01).

intolerance. We found that adiponectin was independently related to apo B/A-1 ratio.

Recent studies report that apo B, which indicates the number of potentially atherogenic lipoprotein particles; apo A-1, which reflects antiatherogenic HDL particles; and apo B/A-1 ratio are more informative risk markers for cardiovascular disease compared with conventional lipids (LDL-C, HDL-C or non–HDL-C, and TG) [2-5]. The results from the AMORIS (Apolipoprotein-Related Mortality Risk) [2] and

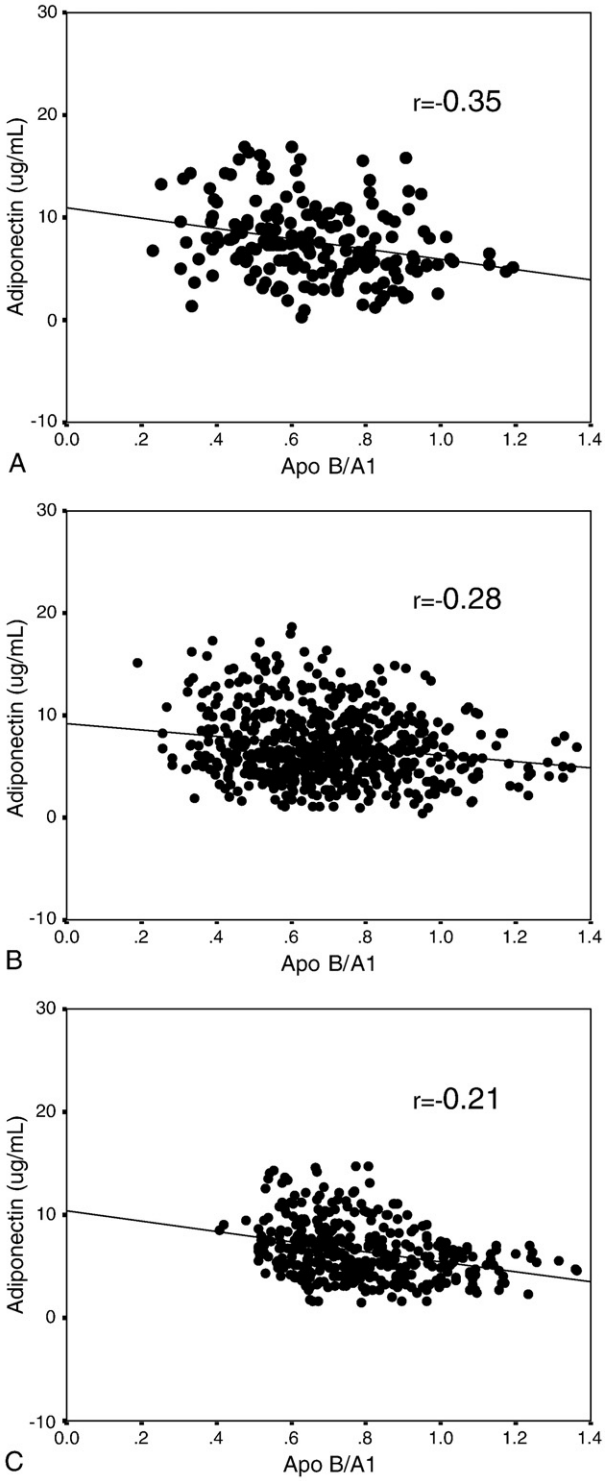

Fig. 2. Relationship between serum adiponectin and apo B/A-1 ratio according to glucose tolerance. Patients with (A) NGT without MetS, (B) IFG, and (C) type 2 diabetes mellitus (P <01).

Table 3
Multiple regression analyses with apo B/A-1 as a dependent variable

	NGT (r^2 = 0.493)	IFG (r^2 = 0.290)	DM (r^2 = 0.322)
TC	0.50†	0.18†	0.27†
TG	0.25†	0.15†	0.18†
HDL-C	−0.59†	−0.32†	−0.29†
LDL-C	0.44†	0.22†	0.18†
Adiponectin	−0.11*	−0.09*	−0.13†

* $P < .05$.
† $P < .01$.

Inter-heart studies [20-22] indicate that apo B/A-1 ratio is strongly related to the risk of myocardial infarction and stroke, and provides a future risk marker of myocardial infarction.

Insulin resistance is considered an important risk factor for atherosclerosis, and insulin resistance correlates significantly with apo B/A-1 ratio. Sung and Hwang [11] found that HOMA-IR correlates significantly with apo B in nondiabetic patients, and Matsumoto et al [12] observed a significant correlation between HOMA-IR and apo B in type 2 diabetes mellitus patients. To minimize the possible confounding effects, patients taking thiazolidinedione, insulin, and lipid-lowering drugs were excluded from this study. When we stratified the subjects into 4 groups based on their apo B/A-1 ratio, insulin resistance (determined by HOMA-IR) increased along with apo B/A-1 ratio in a linear manner. As expected, apo B/A-1 ratio was related to insulin resistance in subjects with NGT, IFG, and type 2 diabetes mellitus.

The MetS is a cluster of cardiovascular disease risk factors for which insulin resistance is believed to be of pathogenic importance. Our data are similar to a report associating mean apo B/A-1 ratio with the presence of MetS in subjects with IFG and type 2 diabetes mellitus [19,23].

In addition, apo B/A-1 ratio was positively correlated with serum LDL-C, HDL-C, TC, TG, and adiponectin; and adiponectin was an independent determinant of apo B/A-1A-1 ratio in different grades of glucose intolerance. Most of the previous studies were conducted on NGT subjects, and they reported correlations between apo B/A-1 ratio and insulin resistance as well as lipid profiles. However, in this study, we analyzed various factors that are related to apo B/A-1 ratio in subjects with different degrees of glucose tolerance who were placed into NGT without MetS, impaired glucose tolerance, and DM groups, and then compared these factors among the groups, thereby assessing possible differences in factors related to apo B/A-1 ratio according to glucose tolerance. In addition, we analyzed the relationship between apo B/A-1 ratio and adiponectin, which is a protective factor for cardiovascular diseases. As a result, we could extend the findings from previous studies and suggest that apo B/A-1 ratio is related to MetS, insulin resistance, and adiponectin in different grades of glucose intolerance. Some studies indicate that plasma adiponectin levels are significantly lower in patients with coronary heart disease [24,25], and high plasma adiponectin predicts a lower risk of future myocardial infarction in both nondiabetic and diabetic patients [26,27]. Although the exact mechanism remains to be elucidated, the link between adiponectin and cardiovascular disease may be partially mediated by its effects on apo B or apo A-1 metabolism. Kazumi et al [16] reported that adiponectin was positively associated with apo A-1 and negatively associated with apo B; but after adjustment for BMI, no significant associations were found between adiponectin and apo B in Japanese young men. Ng et al [17] demonstrated that plasma adiponectin level was inversely correlated with apo B levels and that adiponectin was the most significant independent determinant of apo B concentrations in small numbers of healthy white men. Regarding these inconsistent results, the number of subjects were small; and the possibility exists that the metabolism and characteristics of the adiponectin and apolipoprotein in Koreans are different from those of other race [28]. Results from previous studies have provided possible mechanisms underlying the relationship between adiponectin and apolipoprotein metabolism; Neumeier et al [29] reported that metabolically active high–molecular weight adiponectin reduces hepatic apo B release. Gene expression analysis indicates that hepatic nuclear factor 4-α and hepatic nuclear factor 4-α–regulated genes like apo B are down-regulated by high–molecular weight adiponectin, and this finding is confirmed at the messenger RNA and protein level. Verges et al [30] showed that adiponectin is significantly and negatively associated with apo A-1 catabolic rate and that this association is independent of other risk factors associated with apo A-1. More studies are necessary to elucidate the biochemical interactions.

An important limitation of this study is that an exact test for glucose tolerance, the oral glucose tolerance test, was not performed. Some of the IFG patients might have had concurrent impaired glucose tolerance or undiagnosed type 2 diabetes mellitus. The HOMA-IR calculated in this study did not perfectly correlate with estimates of insulin sensitivity from the euglycemic clamp, which is a good standard method for the measurement of insulin sensitivity.

In conclusion, apo B/A-1 ratio was significantly associated with insulin resistance according to glucose intolerance; and serum adiponectin was an important independent factor associated with apo B/A-1 ratio in Koreans.

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