Prospective Study of Serum Adiponectin and Incident Metabolic Syndrome

The ARIRANG study

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OBJECTIVE—Increased adiponectin levels may play a protective role in the development of metabolic abnormalities, but prospective studies of the predictive value of serum adiponectin to identify individuals at high risk of new-onset metabolic syndrome are lacking. We investigated whether serum adiponectin predicts incident cases of the metabolic syndrome in a population-based longitudinal study.

RESEARCH DESIGN AND METHODS—A prospective cohort study was conducted of 2,044 adults (831 men and 1,213 women) aged 40–70 years without metabolic syndrome examined in 2005–2008 (baseline) and 2008–2011 (follow-up). Baseline serum adiponectin concentrations were measured by radioimmunoassay.

RESULTS—During an average of 2.6 years of follow-up, 153 men (18.4%) and 199 women (16.4%) developed metabolic syndrome. In multivariable-adjusted models, the odds ratio for incident metabolic syndrome comparing the highest with the lowest quartiles of adiponectin levels was 0.25 (95% CI 0.14–0.47) in men and 0.45 (0.28–0.74) in women. While serum adiponectin did not improve the area under the ROC curve for predicting new-onset metabolic syndrome based on information from metabolic syndrome components, the net reclassification improvement and the integrated discrimination improvement of prediction models including adiponectin were significantly higher compared with those of models not including adiponectin among men, with a significant difference between men and women ($P = 0.001$).

CONCLUSIONS—Increased adiponectin is an independent protective factor for incident metabolic syndrome in men and women, and it may have a clinical role in predicting new-onset metabolic syndrome among men.

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The metabolic syndrome is characterized by a clustering of risk factors including central obesity, elevated blood pressure, hypertriglyceridemia, low HDL cholesterol, elevated fasting glucose, and insulin resistance. Subjects with metabolic syndrome are at increased risk for type 2 diabetes and cardiovascular disease (1,2). Given the high prevalence of the metabolic syndrome and its potential consequences, there is substantial interest in understanding its causes and mechanisms in population-based longitudinal studies.

Since the metabolic syndrome is closely linked to obesity and adipose tissue dysfunction and since adipokines affect insulin resistance and inflammatory status (3), adipokines are strong candidates to predict future development of the metabolic syndrome. Adiponectin is the most abundant serum adipokine and a key regulator of insulin sensitivity, tissue inflammation, endothelial function, and lipid metabolism (4,5). Recent studies suggest that increased serum adiponectin levels are inversely associated with the risk of metabolic syndrome (6–8), but little is known about the ability of circulating adiponectin as a predictor of metabolic syndrome components in stratified analyses by sex or about its ability to predict incident metabolic syndrome beyond the information provided by each of its components.

We thus studied the prospective association of serum adiponectin concentrations with the risk of incident metabolic syndrome and its components, as well as the predictive value of serum adiponectin in identifying individuals who will develop incident metabolic syndrome in analyses stratified by sex. We hypothesized that adiponectin would be a negative predictor of progression to metabolic syndrome.

RESEARCH DESIGN AND METHODS

We used data from the Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG), a population-based prospective cohort study to assess the prevalence, incidence, and risk factors for chronic degenerative disorders such as hypertension, diabetes, osteoporosis, and cardiovascular disease (9–11). KoGES-ARIRANG invited all adults aged 40–70 years who resided in rural areas of Wonju and Pyeongchang in South Korea to participate in the study. Demographic shifts are infrequent in this area, and the population can be followed long term.

The baseline survey, carried out from November 2005 to January 2008, included 5,178 adults (2,127 men and 3,051 women) aged 40–70 years. All study participants were invited to the first follow-up survey (April 2008–January 2011), of whom 3,862 (74.6%) attended. We then excluded 1,345 subjects with metabolic syndrome at baseline, 436 subjects without baseline adiponectin measurements, 24

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subjects with any history or presence of cardiovascular disease at baseline, and 13 subjects with incomplete data. The final sample size for the present analysis was 2,044 participants (831 men and 1,213 women) without metabolic syndrome at baseline (Supplementary Fig. 1). The study protocol was approved by the institutional review board of Wonju Christian Hospital. All participants provided written informed consent.

Data collection

At baseline and at the follow-up examination, study participants completed a standardized medical history and lifestyle questionnaire and underwent a comprehensive health examination according to standard procedures. Body weight and height were measured while participants were wearing light indoor clothing without shoes. Waist circumference was measured in a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest using a tape measure (SECA-200; SECA, Hamburg, Germany). Systolic and diastolic blood pressure were measured twice in the right arm using a standard mercury sphygmomanometer (Baumanometer, Copiague, NY). The mean of the two blood pressure readings was used for data analyses. Smoking status was determined based on self-report. Never smokers were defined as participants who had smoked <100 cigarettes (<5 packs of cigarettes) in their lifetime. Current smokers were defined as participants who had smoked ≥100 cigarettes in their lifetime and who reported "currently smoking" in the questionnaire. Former smokers were defined as participants who had smoked ≥100 cigarettes in their lifetime but who reported "abstain from smoking" in the questionnaire. Subjects who answered yes to the question, "Do you perform physical exercise regularly enough to make you sweat?" were assigned to the regular exercise group.

A venous blood sample was drawn from study participants after fasting for >12 h or overnight. Serum aliquots were stored at −80°C until thawed for adiponectin analysis within 1 week after blood extraction. Serum adiponectin concentrations were measured by radioimmunoassay (Linco Research, St. Charles, MO) with intra-assay and interassay coefficients of variation ranging between 2.9 and 6.6%. Fasting glucose was determined by a glucose oxidase–based assay. Fasting insulin was determined by a double-antibody radioimmunoassay (Biosource Europe SA, Nivelles, Belgium). Serum concentrations of LDL cholesterol, HDL cholesterol, and triglycerides were determined by enzymatic methods (Advia 1650; Siemens, Tarrytown, NY). High-sensitivity C-reactive protein (hs-CRP) was measured by the Denka Seiken (Tokyo, Japan) assay, which has been validated against the Dade Behring method. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) model using the following formula: fasting insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405.

End point definition

The study end point was the development of metabolic syndrome at the follow-up visit, defined following the harmonized definition for metabolic syndrome (12) as the presence of at least three of the following criteria: *1*) abdominal obesity, defined as a waist circumference ≥90 cm for men or ≥85 cm for women (following Korean-specific cutoffs for abdominal obesity defined by the Korean Society of Obesity) (13); *2*) hypertriglyceridemia, defined as a serum triglyceride concentration ≥150 mg/dL (1.69 mmol/L); *3*) low HDL cholesterol, defined as a serum HDL cholesterol concentration <40 mg/dL (1.04 mmol/L) for men or <50 mg/dL (1.29 mmol/L) for women; *4*) high blood pressure, defined as a systolic blood pressure ≥130 mmHg, a diastolic blood pressure ≥85mmHg, or treatment with antihypertensive agents; and *5*) high fasting glucose, defined as a fasting serum glucose ≥100 mg/dL or previously diagnosed type 2 diabetes.

Statistical analysis

Since women have higher levels of adiponectin compared with men, we performed all analyses separately for men and women. We divided the study population into sex-specific quartiles of serum adiponectin levels with cut points 5.94, 8.26, and 11.22 μg/mL for men and 8.91, 11.90, and 15.24 μg/mL for women. We evaluated the association of baseline adiponectin levels with the incidence of new cases of metabolic syndrome and with the incidence of new cases of each component of the metabolic syndrome at the follow-up visit. To evaluate the incidence of new cases of each component, we excluded subjects with the presence of that specific component at baseline. Multivariable logistic regression was used to assess the independent association of baseline adiponectin levels with incident metabolic syndrome. We used three models with progressive degrees of adjustment. First, we performed an age-adjusted analysis. Second, we adjusted for age (continuous variable), BMI (continuous variable), smoking (current, former, or never), LDL cholesterol (continuous variable), and regular exercise (yes or no). Finally, we further adjusted for baseline levels of hs-CRP (log-transformed continuous variable), HOMA-IR (log-transformed continuous variable), and follow-up BMI (continuous variable). Results are expressed as odds ratios (ORs) (95% CI).

To evaluate the added discrimination provided by adiponectin levels to predict incident cases of metabolic syndrome beyond the information provided by the components of the metabolic syndrome, we compared the areas under the receiver operating characteristic (ROC) curve in models that included waist circumference, HDL cholesterol, systolic blood pressure, triglycerides, and glucose levels with and without adiponectin levels. In addition, we calculated reclassification tables for models with and without serum adiponectin four categories of predicted risk (cutoffs at 5, 10, and 20%), as well as the continuous (or category-less) net reclassification improvement (NRI) (14) and the integrated discrimination improvement (IDI) (15). The NRI compared classifications from the model with and without serum adiponectin for changes by incident metabolic syndrome for a net calculation of changes in the right direction. It represents the sum of the percentage of participants with an improvement in sensitivity after considering the new marker among those who develop the event plus the percentage of participants with an improvement in specificity after considering the new marker among those who do not develop the event. The IDI represents the sum of the average increase in sensitivity after considering the new marker among those who develop the event plus the increase in specificity after considering the new marker among those who do not develop the event. All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). *P* values <0.05 were considered statistically significant.

RESULTS—During an average of 2.6 years of follow-up, 153 men (18.4%) and 199 women (16.4%) developed metabolic syndrome. Baseline BMI, waist circumference, systolic and diastolic blood pressures, fasting glucose, triglyceride, HOMA-IR,

and high-sensitivity C-reactive protein (hs-CRP) were significantly higher and HDL cholesterol was significantly lower in men and women who developed metabolic syndrome compared with those who did not (Table 1).

Median adiponectin levels at baseline were significantly lower in subjects who developed metabolic syndrome compared with those who did not in both men (7.09 vs. 8.63 μg/mL, $P < 0.001$) and women (10.96 vs. 12.16 μg/mL, $P < 0.001$) (Table 2). A similar association was observed between adiponectin and each component of the metabolic syndrome except for high blood pressure. Furthermore, serum adiponectin levels progressively decreased with the number of metabolic syndrome components developed by study participants over follow-up (P for trend <0.001 in both men and women) (Table 2).

After an average of 2.6 years of follow-up, the proportions of men who developed new-onset metabolic syndrome, high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 18.4, 14.3, 21.9, 20.7, 18.9, and 15.5%, respectively. In multivariable-adjusted models [model 3 (Table 3)], the OR for developing metabolic syndrome comparing men in the highest with those in the lowest quartile of adiponectin was 0.25 (95% CI 0.14–0.47; P for trend <0.001). The corresponding ORs for high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 0.54 (0.25–1.20), 0.54 (0.30–0.94), 0.27 (0.14–0.50), 0.46 (0.19–1.11), and 0.77 (0.41–1.43), respectively. Among women, the proportions of participants who developed new-onset metabolic syndrome, high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 16.4, 21.1, 32.2, 14.1, 14.4, and 8.4%, respectively.

In multivariable-adjusted models [model 3 (Table 4)], the OR for developing metabolic syndrome comparing women in the highest with those in the lowest quartile of adiponectin was 0.45 (95% CI 0.28–0.74; P for trend = 0.001). The corresponding ORs for new-onset high waist circumference, low HDL cholesterol, high triglycerides, high blood pressure, and high blood glucose were 0.50 (0.28–0.88), 0.93 (0.55–1.56), 0.28 (0.16–0.49), 1.08 (0.57–2.06), and 0.70 (0.38–1.29), respectively. Participants in the highest quartile of baseline adiponectin had the smallest increase in waist circumference, triglycerides, and systolic blood pressure in men and the smallest increase of triglycerides in women (Supplementary Table 1).

We then evaluated how well baseline adiponectin levels predict incident metabolic syndrome beyond the information provided by baseline levels of metabolic syndrome components. The area under the ROC curve to predict incident metabolic syndrome using waist circumference, HDL cholesterol, blood pressure, triglycerides, and blood glucose levels was 0.766 (95% CI 0.726–0.805) in men and 0.783 (0.752–0.814) in women. After adiponectin levels were added to the model, the corresponding areas under the ROC curve were 0.772 (0.734–0.811) and 0.783 (0.752–0.815), respectively. The P values for the comparison in areas under the ROC curve for the models with and without adiponectin levels were 0.29 and 0.88 in men and women, respectively. The reclassification tables for improved prediction after adding serum adiponectin to a model including the components of the metabolic syndrome, separated for participants with and without new-onset metabolic syndrome, are shown in Supplementary Tables 2 and 3. For men, the category-free NRI was 0.21 (95% CI 0.04–0.38; $P = 0.02$), and the IDI was

Table 1—*Baseline characteristics of study population by incident metabolic syndrome*

	Men			Women		
	No metabolic syndrome	Metabolic syndrome	*P*	No metabolic syndrome	Metabolic syndrome	*P*
N (%)	678 (81.6)	153 (18.4)		1,014 (83.6)	199 (16.4)	
Age (years)	56.6 (8.2)	56.0 (8.1)	0.404	52.5 (7.9)	55.4 (7.8)	<0.001
Current smoking, *n* (%)	265 (39.1)	67 (43.8)	0.326	11 (1.1)	6 (3.0)	0.074
Regular exercise, *n* (%)	173 (25.5)	52 (34.0)	0.042	321 (31.7)	57 (28.6)	0.450
BMI (kg/m^2)	23.1 (2.6)	24.7 (2.2)	<0.001	23.4 (2.7)	25.2 (2.8)	<0.001
Waist circumference (cm)	82.8 (6.9)	86.8 (6.1)	<0.001	77.0 (7.3)	81.9 (7.2)	<0.001
Systolic BP (mmHg)	126.1 (16.3)	132.0 (18.2)	<0.001	121.8 (16.3)	130.1 (18.1)	<0.001
Diastolic BP (mmHg)	81.7 (10.9)	84.2 (11.2)	0.013	78.1 (11.4)	81.5 (11.0)	<0.001
Fasting glucose (mg/dL)	93.2 (16.5)	97.9 (16.6)	0.002	88.1 (9.0)	92.7 (20.6)	0.002
HDL cholesterol (mg/dL)	49.4 (11.8)	44.5 (8.9)	<0.001	50.8 (10.7)	47.1 (10.3)	<0.001
LDL cholesterol (mg/dL)	112.7 (30.1)	117.2 (31.5)	0.096	116.4 (30.9)	124.2 (29.2)	0.001
Triglycerides (mg/dL)	120.3 (66.0)	148.9 (89.9)	<0.001	98.5 (46.3)	123.1 (60.7)	<0.001
HOMA-IR (units)	1.38 (1.08–1.77)	1.65 (1.40–2.12)	<0.001[a]	1.55 (1.23–2.05)	1.64 (1.35–2.24)	0.009[a]
hs-CRP (mg/L)	0.74 (0.40–1.73)	0.90 (0.55–2.16)	0.003[a]	0.53 (0.29–1.12)	0.71 (0.37–1.71)	<0.001[a]
Metabolic syndrome components, *n* (%)						
High waist circumference	99 (14.6)	96 (62.8)	<0.001	213 (21.0)	154 (77.4)	<0.001
Low HDL cholesterol	137 (20.2)	108 (70.6)	<0.001	512 (50.5)	171 (85.9)	<0.001
High TG	127 (18.7)	106 (69.3)	<0.001	100 (9.9)	113 (56.8)	<0.001
High systolic BP	183 (27.0)	107 (69.9)	<0.001	228 (22.5)	141 (70.9)	<0.001
High diastolic BP	127 (18.7)	84 (54.9)	<0.001	65 (6.4)	71 (35.7)	<0.001

Data are means (SD) or median (25th–75th percentile) unless otherwise indicated. BP, blood pressure; TG, triglyceride. [a]*P* value from Mann-Whitney *U* test.

Table 2—*Baseline serum adiponectin levels according to presence or absence of components of new-onset metabolic syndrome*

Serum adiponectin (μg/mL)	Men (*n* = 831)			Women (*n* = 1,213)		
	Present	Absent	*P*	Present	Absent	*P*
Metabolic syndrome	7.09 (4.90–9.45)	8.63 (6.27–11.71)	<0.001	10.96 (7.80–14.75)	12.16 (9.10–15.50)	<0.001
High WC	7.38 (5.29–9.84)	8.56 (6.14–11.72)	<0.001	11.25 (8.12–14.39)	12.26 (9.10–15.72)	<0.001
Low HDL cholesterol	7.54 (5.28–10.21)	8.64 (6.27–11.69)	<0.001	11.43 (8.38–14.90)	12.55 (9.52–15.77)	<0.001
High TG	7.00 (4.93–9.07)	8.86 (6.51–11.88)	<0.001	10.51 (7.73–13.47)	12.25 (9.22–15.61)	<0.001
High blood pressure	8.39 (5.70–10.74)	8.18 (6.03–11.60)	0.319	12.15 (8.95–15.39)	11.74 (8.85–15.13)	0.538
High blood glucose	7.38 (5.51–10.56)	8.67 (6.16–11.54)	0.001	11.33 (7.89–14.66)	12.05 (9.02–15.35)	0.059
No. of components						
0	9.97 (7.09–12.90)			12.76 (9.73–16.61)		
1	8.70 (6.43–11.40)			12.19 (9.21–15.62)		
2	7.44 (5.51–9.94)			11.37 (8.26–14.78)		
3	7.31 (4.90–9.46)			10.96 (7.86–14.95)		
≥4	5.72 (4.56–9.22)			11.13 (7.27–13.40)		
P for trend	<0.001			<0.001		

Data are median (lower quartile–upper quartile) unless otherwise indicated. *P* value from Mann-Whitney *U* test. TG, triglyceride; WC, waist circumference.

0.010 (0.001–0.018; *P* = 0.025). The increases in NRI and IDI in men were derived primarily from an increase in sensitivity (20% more cases were reclassified in the correct direction using adiponectin, and the point estimate for the increase in integrated sensitivity was 0.008). For women, the NRI was 0.04 (−0.11 to 0.20; *P* = 0.18) and the IDI was 0.002 (−0.001 to 0.004; *P* = 0.13). The *P* value for the difference in NRI and IDI between men and women was 0.001.

Table 3—*ORs for new-onset metabolic syndrome and its components according to baseline serum adiponectin in men*

	Serum adiponectin in men (*n* = 831)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per 5 μg/dL increase
Serum adiponectin (μg/mL)	<5.94	5.94–8.26	8.26–11.22	≥11.22	
New-onset metabolic syndrome	65 (31.4)	33 (15.9)	38 (18.3)	17 (8.2)	
Metabolic syndrome					
Model 1	1.00	0.41 (0.26–0.66)	0.49 (0.31–0.77)	0.19 (0.11–0.35)	0.76 (0.68–0.85)
Model 2	1.00	0.43 (0.26–0.70)	0.58 (0.36–0.95)	0.25 (0.14–0.46)	0.81 (0.72–0.90)
Model 3	1.00	0.41 (0.25–0.68)	0.61 (0.37–1.01)	0.25 (0.14–0.47)	0.82 (0.73–0.92)
High waist circumference[a]					
Model 1	1.00	0.54 (0.30–0.96)	0.63 (0.36–1.10)	0.31 (0.16–0.59)	0.82 (0.72–0.92)
Model 2	1.00	0.65 (0.34–1.23)	1.05 (0.56–1.98)	0.54 (0.26–1.12)	0.92 (0.81–1.04)
Model 3	1.00	0.65 (0.33–1.28)	1.13 (0.57–2.24)	0.54 (0.25–1.20)	0.93 (0.81–1.07)
Low HDL cholesterol[a]					
Model 1	1.00	0.75 (0.46–1.24)	0.68 (0.41–1.12)	0.46 (0.27–0.79)	0.90 (0.83–1.00)
Model 2	1.00	0.78 (0.47–1.29)	0.75 (0.45–1.25)	0.53 (0.30–0.93)	0.94 (0.85–1.01)
Model 3	1.00	0.76 (0.46–1.28)	0.77 (0.46–1.29)	0.54 (0.30–0.94)	0.94 (0.85–1.04)
High TG[a]					
Model 1	1.00	0.63 (0.38–1.04)	0.37 (0.22–0.63)	0.24 (0.13–0.43)	0.74 (0.66–0.84)
Model 2	1.00	0.68 (0.41–1.14)	0.39 (0.23–0.67)	0.27 (0.15–0.49)	0.76 (0.67–0.85)
Model 3	1.00	0.63 (0.37–1.07)	0.39 (0.22–0.68)	0.27 (0.14–0.50)	0.76 (0.68–0.86)
High blood pressure[a]					
Model 1	1.00	0.60 (0.29–1.23)	0.88 (0.44–1.75)	0.33 (0.15–0.76)	0.86 (0.75–1.00)
Model 2	1.00	0.55 (0.26–1.15)	0.98 (0.47–2.04)	0.45 (0.19–1.06)	0.91 (0.78–1.06)
Model 3	1.00	0.56 (0.27–1.20)	0.96 (0.46–2.03)	0.46 (0.19–1.11)	0.92 (0.79–1.07)
High blood glucose[a]					
Model 1	1.00	0.96 (0.55–1.70)	0.63 (0.35–1.16)	0.73 (0.41–1.33)	0.98 (0.89–1.09)
Model 2	1.00	0.95 (0.53–1.69)	0.63 (0.34–1.17)	0.76 (0.41–1.41)	0.99 (0.89–1.10)
Model 3	1.00	0.95 (0.53–1.70)	0.60 (0.32–1.12)	0.77 (0.41–1.43)	0.99 (0.89–1.11)

Data are OR (95% CI) or *n* (%). Model 1: adjusted for age. Model 2: Model 1 plus additionally adjusted for baseline BMI, LDL cholesterol, smoking, and regular exercise. Model 3: Model 2 plus additionally adjusted for baseline hs-CRP, HOMA-IR, and follow-up BMI. TG, triglyceride. [a]Men with each component of metabolic syndrome at baseline have been excluded.

Table 4—*ORs for new-onset metabolic syndrome and its components according to baseline serum adiponectin in women*

	Serum adiponectin in women (n = 1,213)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per 5 μg/dL increase
Serum adiponectin (μg/mL)	<8.91	8.91–11.90	11.90–15.24	≥15.24	
New-onset metabolic syndrome	68 (22.4)	46 (15.2)	48 (15.8)	37 (12.1)	
Metabolic syndrome					
Model 1	1.00	0.58 (0.38–0.88)	0.53 (0.35–0.81)	0.36 (0.23–0.57)	0.86 (0.80–0.92)
Model 2	1.00	0.59 (0.38–0.92)	0.56 (0.36–0.88)	0.45 (0.28–0.72)	0.89 (0.83–0.96)
Model 3	1.00	0.62 (0.39–0.97)	0.57 (0.36–0.90)	0.45 (0.28–0.74)	0.90 (0.83–0.96)
High waist circumference[a]					
Model 1	1.00	0.79 (0.52–1.20)	0.80 (0.53–1.21)	0.40 (0.25–0.64)	0.87 (0.81–0.93)
Model 2	1.00	0.83 (0.52–1.32)	0.93 (0.58–1.48)	0.51 (0.30–0.86)	0.91 (0.84–0.98)
Model 3	1.00	0.86 (0.52–1.44)	0.98 (0.59–1.62)	0.50 (0.28–0.88)	0.91 (0.84–0.99)
Low HDL cholesterol[a]					
Model 1	1.00	0.97 (0.58–1.62)	0.83 (0.50–1.35)	0.84 (0.51–1.38)	0.97 (0.90–1.03)
Model 2	1.00	0.93 (0.55–1.57)	0.83 (0.50–1.37)	0.91 (0.55–1.52)	0.98 (0.91–1.05)
Model 3	1.00	0.95 (0.56–1.60)	0.85 (0.51–1.41)	0.93 (0.55–1.56)	0.98 (0.92–1.05)
High TG[a]					
Model 1	1.00	0.57 (0.36–0.90)	0.53 (0.34–0.85)	0.29 (0.17–0.50)	0.83 (0.77–0.90)
Model 2	1.00	0.57 (0.36–0.91)	0.52 (0.32–0.84)	0.31 (0.18–0.52)	0.84 (0.77–0.91)
Model 3	1.00	0.58 (0.36–0.94)	0.51 (0.32–0.83)	0.28 (0.16–0.49)	0.83 (0.77–0.91)
High blood pressure[a]					
Model 1	1.00	0.83 (0.45–1.56)	0.85 (0.46–1.59)	0.93 (0.51–1.71)	0.98 (0.91–1.07)
Model 2	1.00	0.76 (0.40–1.44)	0.89 (0.47–1.69)	1.05 (0.56–1.98)	1.01 (0.92–1.10)
Model 3	1.00	0.77 (0.40–1.47)	0.91 (0.48–1.73)	1.08 (0.57–2.06)	1.01 (0.93–1.10)
High blood glucose[a]					
Model 1	1.00	0.68 (0.38–1.20)	0.68 (0.38–1.21)	0.62 (0.34–1.12)	0.94 (0.86–1.03)
Model 2	1.00	0.68 (0.38–1.21)	0.70 (0.39–1.26)	0.68 (0.37–1.26)	0.96 (0.87–1.05)
Model 3	1.00	0.71 (0.40–1.28)	0.71 (0.40–1.29)	0.70 (0.38–1.29)	0.99 (0.89–1.11)

Data are OR (95% CI) or n (%). Model 1: adjusted for age. Model 2: Model 1 plus additionally adjusted for baseline BMI, LDL cholesterol, smoking, and regular exercise. Model 3: Model 2 plus additionally adjusted for baseline hs-CRP, HOMA-IR, and follow-up BMI. TG, triglyceride. [a]Women with each component of metabolic syndrome at baseline have been excluded.

Finally, we also evaluated the prospective association between baseline adiponectin levels and incidence of diabetes among participants with metabolic syndrome and with impaired fasting glucose at baseline. Among 595 men and 748 women with metabolic syndrome but no diabetes at baseline, 37 men and 29 women developed new cases of diabetes during follow-up. Baseline adiponectin levels were inversely associated with the risk of developing diabetes in both men and women, although the association was stronger in women (Supplementary Table 4). Among 318 men and 235 women with impaired fasting glucose but no diabetes at baseline, 39 men and 25 women developed diabetes during follow-up. In this subgroup, baseline adiponectin levels were also inversely associated with the risk of developing diabetes (Supplementary Table 5).

CONCLUSIONS—In this prospective cohort study in a general Asian population, serum adiponectin was a strong negative predictor of incident metabolic syndrome in both men and women. Serum adiponectin levels were also a strong negative predictor of the total number of components of the metabolic syndrome developed and of each individual component of the metabolic syndrome, except for elevated blood pressure. The prospective design, the strength of the associations, and the graded dose-response relationships suggest that adiponectin levels may play a key role in the development of metabolic syndrome and its components. Furthermore, our analyses indicate that in men, serum adiponectin may increase the predictive ability for identification of subjects at risk for developing new-onset metabolic syndrome beyond that of the information provided by the components of the metabolic syndrome and open the possibility of using serum adiponectin in clinical settings as a prognostic tool in men.

Adiponectin, a 30-kDa protein, is the most abundant protein secreted mainly by visceral and subcutaneous adipose tissue. Two subtypes of adiponectin receptors (adipoR1 and adipoR2) have been identified. The binding of adiponectin to these receptors mediates increased AMP-activated protein kinase and peroxisome proliferator–activated receptor-α activity resulting in increased insulin sensitivity, glucose utilization, and fatty acid oxidation in the liver and skeletal muscle (16–18). Adiponectin also increases nitric oxide (NO) synthesis in endothelial cells via AMP-activated protein kinase–mediated phosphorylation of endothelial NO synthase (19) and inhibits inflammatory responses (20) and the production of reactive oxygen species (21,22). Additionally, the collagen-like domain of adiponectin allows oligomerization of the protein and the formation of high–molecular weight (HMW) adiponectin (23). While HMW adiponectin may be a more active form of adiponectin in vitro, both total and HMW adiponectin were inversely associated with progression to metabolic syndrome in two longitudinal cohort studies in Japan (6,8).

Additional studies in larger samples are needed to assess the role of HMW adiponectin in the prediction of metabolic syndrome.

Excess adiposity in obesity is associated with downregulation of adiponectin secretion (hypoadiponectinemia) and with decreased expression of AdipoR1 and -R2 (adiponectin resistance), with both likely contributing to insulin resistance and metabolic dysregulation. Hypoadiponectinemia is associated with obesity-related metabolic disorders, such as type 2 diabetes, hypertension, and dyslipidemia (16–18,24,25). Adiponectin production is also reduced by inflammation, oxidative stress, insulin, growth hormone, smoking, testosterone, and glucocorticoids and increased by peroxisome proliferator–activated receptor agonists, weight loss, and inhibition of the renin-angiotensin-aldosterone system (26,27).

Despite strong evidence of the association between adiponectin and obesity-related metabolic abnormalities, there are limited data on the predictive value of circulating adiponectin for incident metabolic syndrome. In prior studies (6–8), adiponectin levels were also inversely associated with incident metabolic syndrome, but those studies did not evaluate the additional predictive ability of adiponectin beyond the information provided by the components of the metabolic syndrome at baseline. In our study, decreasing levels of adiponectin were progressively associated with an increased incidence of metabolic syndrome as well as an increase in the number of metabolic components affected during follow-up. While we found no improvement in the area under the ROC curve in models that added adiponectin to metabolic syndrome components, the NRI and the IDI were significantly improved in men, and the difference between men and women was statistically significant. The NRI and the IDI may be more sensitive than the area under the ROC curve for identifying improvements in predictive value (28). The IDI measures the estimated improvement in the average sensitivity with the addition of adiponectin minus the estimated decrease in the mean specificity across all possible threshold values (15). Given the large number of people who may be potentially screened for prediction of metabolic risk, this improvement in sensitivity and specificity may result in better predictions in a large number of subjects. Our data indicate that serum adiponectin may have a clinical value in screening for metabolic risk in men, but future studies with a larger sample size and validation samples need to delineate specific risk scoring tools and clinical thresholds for predicting the development of metabolic syndrome including measures of serum adiponectin.

Our results were analyses stratified by sex, a key determinant of serum adiponectin levels. Median adiponectin levels in men were lower than those in women (8.26 vs. 11.90 μg/mL, respectively; $P < 0.001$), despite higher prevalence of metabolic syndrome in women (10). Such sex differences in adiponectin levels have previously been reported, and it has been hypothesized that androgen inhibits adiponectin secretion triggering lower levels of adiponectin in males (29–31). In our study, serum adiponectin improved clinical prediction of new-onset metabolic syndrome in men but not in women. These differences were not due to a lower power of the study in women, as the number of cases of new-onset metabolic syndrome was higher in women. We could not establish the reason for this sex difference, although we note that the area under the ROC curve for metabolic syndrome components was higher in women compared with men, possibly indicating that there is greater room for nontraditional markers to improve prediction among men.

Some limitations of our study should also be considered. First, the study was restricted to middle-aged and elderly Koreans living in a rural area with a relatively high baseline prevalence and high incidence of metabolic syndrome. The prevalence of metabolic syndrome in our cohort was similar to that in the Korean National Health and Nutrition Examination Survey, a representative study of the Korean population (9,32). Furthermore, Korea seems to have experienced a rapid increase in the prevalence of metabolic syndrome during the 2000s, partly due to increasing adoption of Western lifestyle patterns (32). Our cohort may therefore be reflecting a period of rapid increase in the frequency of metabolic syndrome, and our findings may not be generalizable to other populations, particularly to those with different secular trends, with higher levels of adiposity, or with younger age. Serum adiponectin levels, however, have been associated with cardiometabolic factors in other races/ethnicities, suggesting that the associations that we observed also apply to other settings. Second, the follow-up period of our cohort was only 2.6 years, and we could not evaluate whether the association between adiponectin and incident metabolic syndrome would persist in longer follow-up. Third, we could not assess the presence of cardiometabolic abnormalities in 25% of the sample that did not complete the follow-up visit. However, we found no statistical differences in baseline demographics and laboratory findings, including serum adiponectin, between participants who attended the follow-up visit and those who did not (data not shown). Finally, our analyses were based on a single determination of serum adiponectin, which is subject to random measurement error and may have underestimated the strength of the associations.

In conclusion, serum adiponectin was an independent protective factor for incident metabolic syndrome and its components in our longitudinal study. The association was strong and progressive and applied to both men and women. Our findings thus support a central role of adiponectin in the development of cardiometabolic abnormalities in obesity. Furthermore, our findings indicate that serum adiponectin may have a clinical role in predicting new-onset metabolic syndrome among men. Additional studies should corroborate these findings and develop appropriate risk-scoring tools that incorporate serum adiponectin in cardiometabolic risk stratification tools.

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J.-Y.K., S.V.A., and E.G. acquired, analyzed, and interpreted data; wrote the manuscript; and read and approved the final version of the manuscript. J.-H.Y., J.-K.P., and K.-H.C. acquired data, contributed to revising the manuscript critically for important intellectual content, and read and approved the final version of the manuscript. S.-B.K., J.Y., B.-S.Y., and S.-H.L. contributed to the conception and design of the manuscript and the interpretation of data, revised the manuscript critically, and read and approved the final version of the manuscript. J.-Y.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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