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Relationships between Serum Adiponectin with Metabolic Syndrome and Components of Metabolic Syndrome in Non-Diabetic Koreans: ARIRANG Study

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Purpose: Growing evidence suggests that hypoadiponectinemia may play a significant role in the development of metabolic syndrome (MetS). Therefore, the relationships between serum adiponectin with MetS and components of MetS were investigated in non-diabetic samples of drawn from the Koreans general population. **Materials and Methods:** We performed a cross-sectional study in samples of older Koreans (age > 40 years) including 2,471 men and 3,463 women. MetS was defined according to the Asian modified criteria of the National Cholesterol Education Program Adult Treatment Panel III report. Serum adiponectin concentrations were measured by radioimmunoassay. **Results:** The median adiponectin level in MetS was significantly lower than that in non-MetS subjects in men (6.00 vs. 8.00 μg/mL, $p < 0.001$) and women (10.12 vs. 11.74 μg/mL, $p < 0.001$). Adiponectin concentration was negatively correlated with waist circumference and levels of triglyceride, C-reactive protein (CRP), fasting glucose, and insulin, and positively correlated with high-density lipoprotein and age in both genders ($p < 0.001$). In a multivariate regression model after adjustment for age, body mass index, smoking, CRP, and lipid profiles, the odds ratio of MetS comparing extreme quartiles of adiponectin distribution was 0.32 [95% confidence interval (CI), 0.20 to 0.50] in men and 0.57 (95% CI, 0.43 to 0.76) in women. **Conclusion:** Adiponectin levels are independently associated with the phenotype of MetS, as well as components of MetS in the non-diabetic Korean general population.

Key Words: Adiponectin, metabolic syndrome, Korea

INTRODUCTION

Metabolic syndrome (MetS) is characterized by interrelated risk factors [hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and elevated fasting glucose) and insulin resistance that identify individuals at increased risk for type 2 diabetes and progression of cardiovascular disease.[1]

Adiponectin is the most abundant serum adipokine that has been recognized as a

key regulator of insulin sensitivity, tissue inflammation, endothelial function, and lipid metabolism.[1-3] Moreover, a growing body of evidence suggests that hypoadiponectinemia may play a significant role in the development of MetS.[4,5] However, little is known about the significance of circulating adiponectin as a surrogate marker for MetS itself and components of MetS in a non-diabetic general population. Therefore, we sought to address this question and to identify potential relationships between circulating adiponectin concentration and MetS as well as components of MetS.

MATERIALS AND METHODS

Study subjects

The study subjects were selected from four rural areas as enrolled in the Korean Genomic Rural Cohort (KGRC), an ongoing epidemiologic study conducted on a representative sample of older (age > 40) Koreans. A total of 5,934 Korean non-diabetic adult subjects (2,471 men and 3,463 women) were enrolled in the KGRC between November 2005 and December 2006. None of the subjects had a self-reported medical history of cardiovascular disease, diabetes, or cancer, and all responded to a questionnaire on their medical-social history and life style characteristics. Subjects were excluded if they had been treated with any agents for hypertension (n = 676), hyperlipidemia (n = 563), or obesity (n = 102).

The study subjects are expected to be followed with biannual health check-ups with a physical examination, serologic tests, and genomic studies for ten years. All subjects provided informed consent, and the study protocol was approved by the Institutional Review Board of Wonju Christian Hospital.

Definition of MetS

We used the definition for MetS suggested by the National Cholesterol Education Program Adult Treatment Panel III report (ATP III).[6] However, the criterion for abdominal obesity was adopted from the World Health Organization (WHO) Asian Pacific Guideline.[7] We defined MetS as the presence of at least three of the following abnormalities: 1) abdominal obesity: waist circumference ≥ 90 cm in men or ≥ 80 cm in women, modified using Asia Pacific WHO guidelines; 2) hypertriglyceridemia: a serum triglyceride concentration ≥ 150 mg/dL (1.69 mmol/L); 3) low HDL cholesterolemia: a serum HDL cholesterol concentration < 40 mg/dL (1.04 mmol/L) for men or < 50 mg/dL (1.29 mmol/L) in women, 4) hypertension: systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg; and 5) high fasting glucose: serum glucose concentration ≥ 110 mg/dL. To evaluate the consistency of our findings, we also used the criteria of the International Diabetes Federation (IDF),[8] central obesity (waist circumference ≥ 90 cm in men or ≥ 80 cm in women, modified using WHO Asia Pacific guidelines) plus any two of the following four factors: 1) elevated triglyceride level: > 150 mg/dL (1.69 mmol/L); 2) reduced HDL cholesterol: < 40 mg/dL (1.04 mmol/L) in males or < 50 mg/dL (1.29 mmol/L) in females; 3) elevated blood pressure: systolic blood pressure (BP) ≥ 130 or diastolic BP ≥ 85 mmHg; and 4) elevated fasting plasma glucose ≥ 100 mg/dL.

Laboratory measurements

A venous blood sample was drawn from each subject after fasting for 12 hours or overnight. The samples were stored at - 80°C until assay. The samples for adiponectin concentration were analysed within one week after centrifugation. The serum concentrations of adiponectin were measured by radioimmunoassay (RIA)(LINCO Research, Inc., St. Louis, MO, USA). The intra-assay and interassay coefficients of variation for serum adiponectin assays ranged between 2.9% and 6.6%. Fasting glucose and insulin were determined by a glucose oxidase-based assay and double-antibody RIA, respectively. Serum total cholesterol and triglyceride concentrations were determined by enzymatic methods. HDL-cholesterol was measured enzymatically after heparin and calcium precipitation. Insulin resistance was calculated using the homeostasis assessment (HOMA-IR) model using the following formula: fasting insulin (μIU/mL) x fasting plasma glucose (mmol/L)/22.5.

Statistical analysis

Continuous variables are presented as means and standard deviations for clinical characteristics or medians and interquartile ranges for adiponectin levels. These were compared using the unpaired t-test or the Mann-Whitney U-test. The distribution of adiponectin concentrations was markedly skewed and log-transformed in analyses where normality was required. Pearson's correlation coefficients were used to establish the relationships between adiponectin concentrations (log-transformed) and clinical or laboratory parameters of MetS.

Multivariate stepwise logistic regression analysis was used to assess the independent association for the presence or absence of MetS as the dichotomous dependant variable in

quartiles of adiponectin values. Quartile cut-points were 5.18, 7.48, and 10.74 μg/mL for men (n = 2,471) and 8.21, 11.19, and 14.62 μg/mL for women (n = 3,463). Results are expressed as odds ratios (ORs) together with 95% confidence intervals (CI).

Age-adjusted ORs were first calculated (model 1), and the results were further adjusted for BMI as the continuous variable and smoking status as the dichotomous variable (model 2). Additional adjustments were carried out with CRP as the continuous variable (model 3) and cholesterol profile as the continuous variable (total cholesterol and HDL-cholesterol, model 4).

All analyses were performed using the SPSS statistical package for Windows (version 12.0, SPSS, Chicago, IL, USA), and p values < 0.05 were considered significant.

RESULTS

Table 1 shows the clinical and biochemical features of the study cohort. The median adiponectin level in women (11.19 μg/mL) was significantly higher than in men (7.48 μg/mL)(p < 0.001). The proportion of three or more characteristics for MetS was 23.6% in men, compared with 34.1% in women by ATP III.

For every component of MetS examined, adiponectin levels were significantly lower in subjects who had components of MetS than those who did not in both genders (p < 0.001), with the exception of high blood pressure (p = 0.075 in men and 0.720 in women)(Table 2). The median adiponectin level in MetS was also significantly lower than that in non-MetS subjects for men (6.00 vs. 8.00 μg/mL, p < 0.001) and women (10.12 vs. 11.74 μg/mL, p < 0.001).

Table 3 shows interrelationships between serum adiponectin levels and the total numbers of MetS components and HOMA-IR in both genders. A significantly linear decrease in adiponectin levels was observed according to total numbers of MetS components in both men and women. The median serum adiponectin levels in men with 0, 1, 2, 3, or ≥ 4 components of MetS were 8.90, 8.11, 7.31, 6.05, and

Table 1. Baseline Characteristics of the Cohort Population

	Men (n = 2,471)	Women (n = 3,463)	p value
Clinical characteristics			
Age (yrs)	56.6 ± 8.0	54.8 ± 8.3	< 0.001
Current smoker, n (%)	929 (37.8)	131 (3.8)	< 0.001
BMI, kg/m^2	24.3 ± 4.3	24.4 ± 3.5	0.438
Waist Circumference, cm	84.7 ± 8.0	81.0 ± 8.5	< 0.001
Systolic BP, mmHg	130.3 ± 17.4	128.4 ± 17.7	< 0.001
Diastolic BP, mmHg	83.4 ± 11.5	81.1 ± 11.4	< 0.001
Laboratory characteristics			
Total cholesterol, mg/dL	199.7 ± 37.6	205.5 ± 39.1	< 0.001
Triglycerides, mg/dL	161.4 ± 108.8	141.0 ± 91.9	< 0.001
HDL-cholesterol, mg/dL	46.2 ± 11.7	47.2 ± 11.0	0.001
LDL-cholesterol, mg/dL	115.3 ± 32.6	122.7 ± 33.1	< 0.001
Fasting glucose, mg/dL	96.5 ± 23.5	92.7 ± 18.5	< 0.001
Fasting insulin, μIU/mL	7.75 ± 4.61	8.40 ± 4.95	< 0.001
HOMA-IR*	1.54 (1.17 - 2.09)	1.59 (1.26 - 2.14)	0.162
CRP, mg/L*	0.90 (0.47 - 1.95)	0.71 (0.38 - 1.51)	< 0.001
Adiponectin, μg/mL*	7.48 (5.18 - 10.74)	11.19 (8.21 - 14.62)	< 0.001
No. of component for MetS, n (%)			
0	367 (14.9)	313 (9.0)	
1	825 (33.4)	860 (24.8)	
2	696 (28.2)	1,111 (32.1)	
3	422 (17.1)	793 (22.9)	
4	147 (5.9)	352 (10.2)	
5	14 (0.6)	34 (1.0)	

Values are expressed as mean ± SD or number (%) if not stated otherwise.
BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR, homeostasis assessment-insulin resistance; CRP, C-reactive protein; MetS, metabolic syndrome.
*Values are expressed as median (lower quartile-upper quartile), p value from Mann-Whitney U test.

Table 2. Median Serum Adiponectin Levels (Interquartile Ranges) among the Cohort According to the Presence or Absence of Each Component of the MetS Defined as ATP III

Men			
n = 2,471	Present	Absent	*p* value
Obesity (n = 571)	6.14 (4.31 - 9.03)	7.86 (5.54 - 11.33)	< 0.001
Hypertriglyceridemia (n = 1,036)	6.75 (4.74 - 9.75)	8.16 (5.66 - 11.59)	< 0.001
Low HDL-cholesterol (n = 755)	6.63 (4.74 - 9.26)	7.89 (5.49 - 11.40)	< 0.001
High blood pressure (n = 1,493)	7.30 (5.08 - 10.34)	7.80 (5.31 - 11.22)	0.075
Abnormal glucose (n = 249)	6.42 (4.52 - 9.80)	7.61 (5.29 - 10.95)	< 0.001
≥ 3 characteristics (n = 456)	6.00 (4.32 - 8.53)	8.00 (5.62 - 11.33)	< 0.001
Women			
n = 3,463	Present	Absent	*p* value
Obesity (n = 1,221)	10.32 (7.66 - 13.50)	12.08 (8.97 - 15.64)	< 0.001
Hypertriglyceridemia (n = 1,155)	10.21 (7.62 - 13.51)	11.72 (8.66 - 15.16)	< 0.001
Low HDL- cholesterol (n = 2,184)	10.83 (7.95 - 14.08)	12.03 (8.97 - 15.35)	< 0.001
High blood pressure (n = 1,729)	11.24 (8.19 - 14.70)	11.14 (8.28 - 15.54)	0.720
Abnormal glucose (n = 264)	10.18 (7.36 - 13.55)	11.28 (8.31 - 14.48)	< 0.001
≥ 3 characteristics (n = 1,172)	10.12 (7.62 - 13.41)	11.74 (8.80 - 15.22)	< 0.001

Values are expressed as median (lower quartile-upper quartile), *p* value from Mann-Whitney U-test.
ATP III, National Cholesterol Education Program Adult Treatment Panel III report; MetS, metabolic syndrome; HDL, high density lipoprotein.

Table 3. Distribution of Serum Adiponectin Levels among the Cohort According to Presence of 0, 1, 2, 3, or ≥ 4 Components of MetS and Quartile of HOMA-IR in Men (n = 2,471) and Women (n = 3,463)

	Adiponectin, μg/dL Men; n = 2,471	*p* trend	Adiponectin, μg/dL Women; n = 3,463	*p* trend
No. of MetS components		< 0.001		< 0.001
0	8.90 (6.24 - 12.74)		12.82 (9.58 - 16.70)	
1	8.11 (5.80 - 11.88)		11.99 (9.03 - 15.91)	
2	7.31 (5.06 - 10.05)		11.38 (8.29 - 14.36)	
3	6.05 (4.39 - 8.59)		10.65 (7.80 - 13.80)	
≥ 4	5.74 (4.05 - 8.53)		9.38 (7.15- 12.33)	
HOMA-IR		< 0.001		< 0.001
1st quartile (< 1.232)	8.70 (6.03 - 12.38)		12.14 (8.91 - 15.50)	
2nd quartile (1.232 - 1.573)	7.60 (5.27 - 10.16)		11.59 (8.79 - 15.32)	
3rd quartile (1.573 - 2.119)	7.13 (5.16 - 10.27)		11.20 (8.59 - 14.62)	
4th quartile (≥ 2.119)	6.27 (4.35 - 9.31)		9.97 (7.32 - 13.32)	

Values are expressed as median (lower quartile-upper quartile).
HOMA-IR, homeostasis assessment-insulin resistance; MetS, metabolic syndrome; No., number

5.74 μg/L, respectively (*p* trend < 0.001), while those in women were 12.82, 11.99, 11.38, 10.65, and 9.38 μg/L, respectively (*p* trend < 0.001). Using the HOMA-IR, we also estimated the indices of insulin resistance among all subjects. The serum adiponectin levels showed a significantly linear decrease with increasing quartiles of HOMA-IR in both men and women (*p* trend < 0.001).

We estimated the correlation coefficients between serum adiponectin levels and various parameters of MetS. In men, adiponectin levels were negatively correlated with triglyceride (r = - 0.153), low density lipoprotein (LDL) cholesterol (r = - 0.050), waist circumference (r = - 0.281), body mass index (BMI)(r = - 0.056), C-reactive protein (hsCRP)(r = - 0.053), fasting insulin (r = - 0.119), glucose (r = - 0.116), and HOMA-IR (r = - 0.193), and positively correlated with HDL cholesterol (r = 0.219) and age (r = 0.222). However, no significant relationship was found between systolic or diastolic blood pressure in men.

In women, adiponectin levels were negatively correlated with triglyceride levels (r = - 0.128), waist circumference (r = - 0.208), BMI (r = - 0.094), hsCRP (r = - 0.113), fasting insulin (r = - 0.110), glucose (r = - 0.064), and HOMA-IR (r =

Table 4. Odds Ratio for Metabolic Syndrome Defined by ATP III and IDF Criteria According to Adiponectin

Adiponectin (μg/mL)	Model 1 OR (95% CI)	*p* value	Model 2 OR (95% CI)	*p* value	Model 3 OR (95% CI)	*p* value	Model 4 OR (95% CI)	*p* value
ATP III in men								
1st quartile (< 5.18)	1.0[reference]		1.0[reference]		1.0[reference]		1.0[reference]	
2nd quartile (5.18 - 7.48)	0.49 (0.39 - 0.62)	< 0.001	0.51 (0.40 - 0.65)	< 0.001	0.51 (0.40 - 0.65)	< 0.001	0.51 (0.40 - 0.67)	< 0.001
3rd quartile (7.48 - 10.74)	0.46 (0.35 - 0.61)	< 0.001	0.47 (0.35 - 0.62)	< 0.001	0.47 (0.35 - 0.62)	< 0.001	0.58 (0.43 - 0.80)	0.001
4th quartile (≥ 10.74)	0.23 (0.15 - 0.34)	< 0.001	0.22 (0.14 - 0.33)	< 0.001	0.21 (0.14 - 0.32)	< 0.001	0.32 (0.20 - 0.50)	< 0.001
IDF in men								
1st quartile (< 5.18)	1.0[reference]		1.0[reference]		1.0[reference]		1.0[reference]	
2nd quartile (5.18 - 7.48)	0.47 (0.37 - 0.60)	< 0.001	0.49 (0.38 - 0.64)	< 0.001	0.50 (0.38 - 0.65)	< 0.001	0.52 (0.40 - 0.67)	< 0.001
3rd quartile (7.48 - 10.74)	0.55 (0.42 - 0.73)	< 0.001	0.56 (0.42 - 0.77)	< 0.001	0.57 (0.42 - 0.77)	< 0.001	0.62 (0.46 - 0.85)	0.003
4th quartile (≥ 10.74)	0.18 (0.11 - 0.29)	< 0.001	0.17 (0.10 - 0.28)	< 0.001	0.17 (0.10 - 0.28)	< 0.001	0.21 (0.13 - 0.34)	< 0.001
ATP III in women								
1st quartile (< 8.21)	1.0[reference]		1.0[reference]		1.0[reference]		1.0[reference]	
2nd quartile (8.21 - 11.19)	0.98 (0.76 - 1.25)	0.853	1.09 (0.85 - 1.41)	0.504	1.09 (0.85 - 1.41)	0.846	1.02 (0.77 - 1.36)	0.869
3rd quartile (11.19 - 14.62)	0.59 (0.46 - 0.75)	< 0.001	0.65 (0.50 - 0.83)	0.001	0.65 (0.50 - 0.83)	0.001	0.72 (0.54 - 0.94)	0.017
4th quartile (≥ 14.62)	0.39 (0.31 - 0.50)	< 0.001	0.45 (0.35 - 0.58)	< 0.001	0.45 (0.35 - 0.58)	< 0.001	0.57 (0.43 - 0.76)	< 0.001
IDF in women								
1st quartile (< 8.21)	1.0[reference]		1.0[reference]		1.0[reference]		1.0[reference]	
2nd quartile (8.21 - 11.19)	0.92 (0.72 - 1.12)	0.507	1.01 (0.78 - 1.32)	0.910	1.02 (0.78 - 1.32)	0.901	0.99 (0.77 - 1.23)	0.972
3rd quartile (11.19 - 14.62)	0.61 (0.49 - 0.77)	< 0.001	0.67 (0.52 - 0.86)	0.001	0.67 (0.52 - 0.86)	0.002	0.70 (0.54 - 0.90)	0.006
4th quartile (≥ 14.62)	0.34 (0.27 - 0.43)	< 0.001	0.38 (0.29 - 0.49)	< 0.001	0.38 (0.29 - 0.49)	< 0.001	0.42 (0.32 - 0.55)	< 0.001

Model 1: adjusted for age; Model 2: adjusted for age, BMI and smoke; Model 3: adjusted for age, BMI, smoke and CRP; Model 4: adjusted for age, BMI, smoke, CRP, total cholesterol and HDL-cholesterol.
ATP III, National Cholesterol Education Program Adult Treatment Panel III report; IDF, International Diabetes Federation; OR, odds ratio; CI, confidence intervals.

- 0.133), and positively correlated with HDL cholesterol (r = 0.169), and age (r = 0.187). However, there was no significant relationship between LDL cholesterol and systolic or diastolic blood pressure in women.

Table 4 shows ORs of MetS as a dependant variable, defined by the ATP III and IDF, across quartiles of adiponectin. Full adjustment (age, BMI, smoking, CRP, and cholesterol levels) ORs for MetS in men were 0.51 (95% CI 0.40-0.67), 0.58 (95% CI 0.43-0.80), and 0.32 (95% CI 0.20-0.50), respectively, by ATP III criteria, whereas 0.52 (95% CI 0.40-0.67), 0.62 (95% CI 0.46-0.85), and 0.21 (95% CI 0.13-0.34), respectively, by IDF criteria. In the case of women, full adjustment ORs for MetS were 1.02 (95% CI 0.77-1.36), 0.72 (95% CI 0.54-0.94), and 0.57 (95% CI 0.43-0.76), respectively, by ATP III criteria, whereas 0.99 (95% CI 0.77-1.23), 0.70 (95% CI 0.54-0.90), and 0.42 (95% CI 0.32-

0.55), respectively, by IDF criteria.

DISCUSSION

We performed a large-scale cross-sectional study in an Asian non-diabetic sample to determine the relationships between serum adiponectin levels and MetS as well as its components. Our results clearly showed that serum adiponectin is strongly associated with the MetS phenotype, and correlated with MetS components. Furthermore, serum adiponectin is an independent protective adipokine for MetS in men and women under both ATP III and IDF criteria.

The adipocytes are active endocrine secretory cells that release adipokines including tumor necrosis factor (TNF)-α, interleukins (IL), leptin, visfatin, and adiponectin.[9] Adiponectin is the most abundant adipokine secreted by adipose cells that may regulator of insulin sensitivity. Adiponectin itself is also regulated by metabolic stress as well as a number of hormones, such as catecholamines, glucocorticoids, IL-6, TNF-α, growth hormone, thiazolidinediones and androgens.[10] Therefore, adiponectin is closely related obesity with metabolic derangement including insulin resistance.

In the present study, data were analyzed according to gender because mean serum adiponectin levels in men were typically lower than those in women (8.41 vs. 11.88 μg/mL, $p < 0.001$), despite higher prevalence of MetS in women. Such gender differences in adiponectin levels have been previously reported.[11-13] Androgen levels may play a role in gender differences, because androgens appear to have an inhibitory effect on adiponectin.[14] Thus, it has been suggested that one cause of higher incidence of atherosclerotic disease in men is decreased adiponectin concentration, since adiponectin is an anti-atherogenic protein.

In the present study, circulating adiponectin levels were found to be associated significantly with the individual components of MetS, CRP, and HOMA-IR. These results support the insulin-sensitizing, anti-inflammatory, and anti-dyslipidemic activities for adiponectin, consistent with reports from other investigators.[11-13,15] On the other hand, systolic and diastolic blood pressures were clearly not associated with serum adiponectin levels. In recent animal studies, adiponectin-KO mice on a high salt diet developed hypertension, which was ameliorated by adiponectin replenishment. These results suggest that hypoadiponectinemia contributes to the development of obesity-related hypertension.[16] However, studies of the relationship between adiponectin levels and hypertension have produced conflicting results in clinical settings.[12,17-20] Adamczak, et al.[17] reported that adiponectin levels are reduced in those with hypertension compared to BMI matched normotensive controls. In contrast, however, some studies found that adiponectin levels per se are not associated with systolic and diastolic blood pressure,[12,20] and that higher adiponectin concentrations are also found in hypertensive patients.[19] Epidemiologic data suggest that five components responsible for MetS are clustered in various age and ethnic groups.[12,21-23] Our present cohort showed a clustering of waist circumference, HDL-cholesterol, triglyceride, and adiponectin levels and insulin resistance. However, blood pressure levels clustered into a separate factor of MetS, consistent with the results of the epidemiologic studies of Meigs, et al.[23] and Mohan, et al.[12] Thus, the relationship between adiponectin and blood pressure warrants further study with samples drawn from other populations.

Another significant finding of the present study is that mean adiponectin levels were found to decrease significantly with increasing numbers of MetS components in both men and women ($p < 0.0001$). In the WOSCOPS study, risk increased as the number of metabolic abnormalities rose up to 3.7-fold for risk of coronary heart disease (CHD) risk and 24-fold for diabetes in men with four or more baseline abnormalities.[24] In the NHANES II survey, when those with no MetS risk factors were used as a reference group, the hazard ratios for CHD mortality were 2.10 (95% CI, 1.05 to 4.19) for those with one to two MetS risk factors and 3.51 (95% CI, 1.81 to 6.81) for those with MetS.[25] The results of those large cohort studies indicate that the hazard ratios of coronary artery disease, diabetes and CHD mortality increase as the number of MetS components increase. Therefore, adiponectin might be a valid surrogate marker to expand traditional risk-factor-based treatment strategy.

Recent studies have shown that adiponectin levels have an inverse association with new onset type 2 diabetes in population-based studies. Adiponectin concentrations in the top tertile had a 60% lower risk of incident type 2 in caucacian.[26] In addition, the link between adiponectin levels and new onset diabetes was stronger in obese men and women.[27]

While there are strong associations with low adiponectin levels and elevated risk of diabetes, controversies exist on the associations between adiponectin levels and vascular events. The initial data that higher adiponectin predisposes individuals to lower vascular risk has now been challenged.[28] High adiponectin levels have been linked to high rates of all-cause and cardiovascular mortality in prospective stud-

ies.[29,30] The roles of adiponectin in vascular outcome are currently not clear and further studies are needed.

Therefore, the present cohort study (KGRC cohort), which was based on 10,000 rural Korean individuals, could define prognostic or additional values for adiponectin to predict a hard endpoint for cardiovascular disease in the future.

Several limitations of the present study must be considered. First, this study was cross-sectional in design and was not intended to assess a cause-and-effect relationship between serum adiponectin and MetS or its components. However, the strength of our results was the fact that this study was based on a large population from representative rural regions of Korea. Second, the study included only one biologically homogeneous east Asian sample. Nevertheless, we believe that these data are likely to be applied to other east Asian populations, because studies with other ethnic groups have linked circulating adiponectin to MetS in clinical settings.[12,31]

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