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The association between adiponectin and diabetes in the Korean population

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Abstract

As indicators of obesity, waist circumference (WC), body mass index (BMI), and adiponectin are well-known risk factors for diabetes mellitus. The objectives of this study were to measure the independent association between these obesity indicators and diabetes and to examine the combined effect of these indicators on diabetes in a Korean population. The WC, BMI, and serum adiponectin were measured in 4459 healthy Koreans and were classified into tertile groups for men and women. The independent and combined associations of the obesity indicators with diabetes were measured using logistic regression analyses. *Diabetes* was defined as fasting serum glucose greater than 126 mg/dL or taking medication. Levels of adiponectin were inversely associated with BMI and WC and directly associated with age and high-density lipoprotein (HDL) cholesterol ($P < .001$). After adjusting for age, BMI, WC, and other lifestyle factors, low levels of adiponectin were associated with an increased prevalence of diabetes. Further adjustment for HDL cholesterol and triglyceride attenuated this association in women but not men. The combined effects of WC and adiponectin on diabetes progressively increased; however, the interaction of these 2 variables was not statistically significant. The combined effect of BMI and adiponectin on diabetes showed similar results. These results suggest that adiponectin was associated with diabetes. The association was independent of BMI and WC and was partly modified by HDL and triglyceride. There were no effect modifications of adiponectin with WC and BMI on diabetes.

1. Introduction

Obesity is both a prevalent condition worldwide and a well-known, modifiable risk factor for various diseases, including diabetes. In a recent review article, waist circumference (WC) and body mass index (BMI) were reported as established risk factors for diabetes [1]. The pooled relative risks for incident diabetes were 1.87, 1.87, and 1.88 per standard deviation of BMI, WC, and waist-hip ratio, respectively, demonstrating that these 3 obesity indicators have similar associations with the incident of diabetes. Although the clinical perspective focusing on central obesity is appealing, further research is needed to determine the usefulness of either WC or waist-hip ratio over BMI.

Recently, adiponectin has also been reported as a new risk factor for developing diabetes. Adipose tissue exclusively secretes adiponectin, a 244–amino-acid protein that regulates the metabolism of lipids and glucose and circulates quite abundantly in plasma [2-6]. Adiponectin decreases insulin resistance and body weight by increasing lipid oxidation in muscle and other organs such as the pancreas and liver [7]. Hotta et al [8] showed that plasma adiponectin

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concentration was sex-dependent, higher among women than men, and reduced among individuals with obesity, diabetes mellitus, or coronary heart disease [8,9].

Although there are many studies on the independent associations of WC, BMI, and adiponectin on diabetes, the literature regarding the combined effect of these indicators on diabetes is sparse. Thus, the purpose of this study was to measure the independent association between these indicators and diabetes and to examine the combined effect of these indicators on diabetes in a Korean population. We hypothesized that lower levels of adiponectin may increase the risk of diabetes regardless of BMI and WC.

2. Materials and methods

2.1. Study subjects

The study population consisted of 6214 subjects who participated in the Korean Metabolic Syndrome Research Initiative and had routine health examinations at the Health Promotion Center in University Hospitals from January through December 2006. The purpose and contents of this research project were explained to these participants who volunteered to undergo the health examinations. Recruitment of these volunteered subjects only took place after obtaining informed consent from them. Participating hospitals are listed in the appendix. The analysis excluded subjects with missing information on WC, BMI, or adiponectin levels. Finally, 4459 subjects aged 24 to 87 years were selected for subsequent analysis. The Institutional Review Board of Human Research of Yonsei University approved the study, and written informed consent was obtained from all subjects.

2.2. Data collection

Each participant was interviewed using a structured questionnaire to collect histories of cigarette smoking (never smoked, ex-smoker, or current smoker) and alcohol consumption (nondrinker or drinker of any amount of alcohol) as well as other demographic characteristics such as age, sex, and family history of diabetes. Participants were asked if they do regular exercise, and results were divided into 2 groups: exercise and nonexercise. Waist circumference was measured midway between the lower rib and iliac crest. The participants' weights and heights were measured while wearing light clothing. Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters). Blood pressure was measured in a seated position by a registered nurse or blood pressure technician using a standard mercury sphygmomanometer or automatic manometer. Both systolic and diastolic blood pressures were measured after a 15-minute rest.

2.3. Measurement of biomarkers

For the clinical chemistry assay, serum was separated from peripheral venous blood samples that were obtained from each participant after 12 hours of fasting and was stored at −70°C for 2 hours. Metabolic syndrome biomarkers, such as fasting blood glucose, total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), were measured using the Hitachi-7600 analyzer (Hitachi, Tokyo, Japan). For subjects with available serum, adiponectin levels were measured using an enzyme-linked immunosorbent assay (Mesdia, Seoul, Korea). The intra- and interassay variances for the adiponectin were 6.3% to 7.4% and 4.5% to 8.6%, respectively. Data quality control was in accordance with the procedures of the Korean Association of Laboratory Quality Control.

2.4. Statistical analysis

All biomarkers were seen to have a normal distribution except adiponectin and TG. Therefore, log transformation was used for analyzing adiponectin and TG. The pairwise combined analyses of WC, BMI, and serum adiponectin concentration were conducted. We divided our study samples into 3 groups (tertiles) of WC (<82.0, 82.0-<88.5, and ≥88.5 cm for men; <71.0, 71.0-<77.5, and ≥77.5 cm for women), BMI (<23.5, 23.5-<25.7, and ≥25.7 kg/m^2 for men; <21.3, 21.3-<23.7, and ≥23.7 kg/m^2 for women), and adiponectin (<5.0, 5.0-<8.0, and ≥8.0 μg/mL for men; <7.6, 7.6-<12.4, and ≥12.4 μg/mL for women), respec-

Table 1
General characteristics of study population, 2006

n	Men	Women	Total
	2648	1811	4459
	Mean ± SD	Mean ± SD	Mean ± SD
Age (y)	46.4 ± 9.2	45.1 ± 9.4	45.8 ± 9.3
Waist (cm)	85.1 ± 7.4	74.7 ± 8.0	80.9 ± 9.2
BMI (kg/m^2)	24.7 ± 2.7	22.8 ± 2.9	23.9 ± 2.9
Adiponectin (μg/mL)	7.2 ± 4.1	10.8 ± 5.8	8.7 ± 5.2
Fasting blood glucose (mg/dL)	93.9 ± 19.1	86.9 ± 13.1	91.1 ± 17.3
Systolic blood pressure (mm Hg)	122.7 ± 13.9	114.7 ± 14.4	119.5 ± 14.6
Diastolic blood pressure (mm Hg)	79.2 ± 11.1	72.2 ± 10.7	76.3 ± 11.4
HDL-C (mg/dL)	52.5 ± 11.5	62.5 ± 13.7	56.6 ± 13.4
TG (mg/dL)	154.1 ± 103.0	98.7 ± 59.3	131.6 ± 92.0
	%	%	%
Smoking status			
Ex	37.7	2.9	23.6
Current	38.0	3.4	24.0
Diabetes [a]	7.1	2.5	5.3
Hypertension [b]	27.9	14.2	22.3
Family history of DM	17.6	18.0	17.8
Alcohol drinking	88.2	45.6	70.9
Exercise	29.3	40.6	32.9

DM indicates diabetes mellitus.

[a] Diabetes was defined as fasting serum glucose ≥126 mg/dL or medication.

[b] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or medication.

Table 2
Sex-adjusted Pearson correlation of study variables

	Adipo	Age	BMI	WC	SBP	DBP	HDL
Adipo	1.0						
Age	.100 **	1.0					
BMI	−.159 **	.133 **	1.0				
WC	−.196 **	.203 **	.857 **	1.0			
SBP	−.042 *	.186 **	.284 **	.282 **	1.0		
DBP	.002	.161 **	.254 **	.223 **	.723 **	1.0	
HDL	.287 **	−.053 **	−.279 **	−.300 **	−.065 **	−.017	1.0
TG	−.151 **	.074 **	.2664 **	.271 **	.134 **	.180 **	−.342 **

Adipo indicates adiponectin; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* $P < .01$.
** $P < .001$.

tively. Therefore, this stratification yielded 9 different groups of subjects defined by different levels of WC, BMI, and adiponectin.

To examine the association of these obesity indicators and diabetes, multiple logistic regression models were examined after adjusting for age and other potential confounding factors, including sex, smoking status, and alcohol consumption. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and analyses were performed separately for men and women. Multiple logistic regression models were also used to assess the modification of this association with interaction terms for BMI, WC, and adiponectin. All analyses were conducted using SAS statistical software, version 9.0 (SAS Institute, Cary, NC). All statistical tests were 2-sided, and statistical significance was determined as $P < .05$.

3. Results

As shown in Table 1, the mean age of men in the study population was 46.4 years; and 59.4% were middle-aged. The mean age of women in the study was 45.1 years, and 40.6% were middle-aged. The average WC was 85.1 and 74.7 cm for men and women, respectively. The average BMI was 24.8 and 23.6 kg/m^2 for men and women, respectively. Plasma adiponectin was about 33% higher in women (10.8 μg/mL) than men (7.2 μg/mL).

Levels of adiponectin were inversely associated with BMI, WC, and TG and directly associated with age and HDL-C ($P < .001$) (Table 2).

Next, separate models of each obesity indicator were conducted by sex. Among men, the OR (95% CI) of those with the highest tertile compared with those with the lowest tertile of these indicators, after adjusting for age and covariates, was 1.6 (1.1-2.3), 1.7 (1.1-2.6), and 2.1 (1.4-3.1), for WC, BMI, and adiponectin, respectively. The associations were much stronger in women; and the corresponding ORs (95% CI) were 6.2 (1.8-21.3), 3.0 (1.1-8.3), and 2.9 (1.3-6.3), respectively (data not shown). However, in one multivariate model with WC, BMI, and adiponectin among men after adjusting for age, hypertension, and other lifestyle factors, adiponectin was the only significant indicator among the 3 obesity indicators (OR [95% CI], 1.9 [1.3-2.9] for men [Table 3] and 2.5 [1.1-5.5] for women [Table 4]); and BMI and WC were no longer statistically significant predictors of diabetes. Further

Table 3
Multivariable-adjusted ORs for diabetes by tertile of waist, BMI, and adiponectin in men

Variables	Class	Diabetes case	Model 1		Model 2	
			OR	95% CI	OR	95% CI
WC (cm)	<82.0	40	1.0		1.0	
	82.0-<88.5	71	1.1	0.7-1.7	1.0	0.6-1.6
	≥88.5	77	1.2	0.7-2.1	1.1	0.6-2.0
BMI (kg/m^2)	<23.5	43	1.0		1.0	
	23.5-<25.7	73	1.5	0.9-2.4	1.5	0.9-2.4
	≥25.7	72	1.3	0.8-2.4	1.3	0.7-2.3
Adiponectin (μg/mL)	≥8.0	46	1.0		1.0	
	5.0-<8.0	60	1.4	0.9-2.1	1.3	0.8-1.9
	<5.0	82	1.9	1.3-2.9	1.7	1.1-2.6

Model 1: adjusted for WC, BMI, adiponectin, age, smoking, hypertension, alcohol drinking, and exercise. Model 2: adjusted for WC, BMI, adiponectin, age, smoking, hypertension, alcohol drinking, exercise, and HDL-C.

Table 4
Multivariable-adjusted ORs for diabetes by tertile of waist, BMI, and adiponectin in women

Variables	Class	Diabetes case	Model 1		Model 2	
			OR	95% CI	OR	95% CI
WC (cm)	<82.0	3	1.0		1.0	
	82.0-<88.5	12	2.4	0.6-10.3	2.2	0.5-9.4
	≥88.5	31	3.1	0.6-15.3	2.6	0.5-13.0
BMI (kg/m^2)	<23.5	5	1.0		1.0	
	23.5-<25.7	9	0.8	0.2-2.6	0.7	0.2-2.4
	≥25.7	32	1.3	0.3-4.9	1.2	0.3-4.4
Adiponectin (μg/mL)	≥8.0	10	1.0		1.0	
	5.0-<8.0	14	1.4	0.6-3.3	1.2	0.5-2.9
	<5.0	22	2.5	1.1-5.5	1.9	0.8-4.3

Model 1: adjusted for WC, BMI, adiponectin, age, smoking, hypertension, alcohol drinking, and exercise. Model 2: adjusted for WC, BMI, adiponectin, age, smoking, hypertension, alcohol drinking, exercise, and HDL-C.

Table 5
Combined effect of WC and BMI with adiponectin on diabetes in men

		Case	OR	95% CI
WC	Adiponectin			
<72.0	≥8.0	17	1.0	
<72.0	5.0-<8.0	12	1.1	0.5-2.3
<72.0	<5.0	11	1.4	0.6-3.1
82.0-<88.5	≥8.0	15	1.0	0.5-2.0
82.0-<88.5	5.0-<8.0	25	1.6	0.8-3.1
82.0-<88.5	<5.0	31	2.0	1.1-3.8
≥88.5	≥8.0	14	1.1	0.5-2.3
≥88.5	5.0-<8.0	23	1.6	0.8-3.2
≥88.5	<5.0	40	2.6	1.4-4.7
BMI	Adiponectin			
<23.5	≥8.0	14	1.0	
<23.5	5.0-<8.0	12	1.3	0.6-2.8
<23.5	<5.0	17	2.5	1.2-5.3
23.5-<25.7	≥8.0	17	1.7	0.8-3.6
23.5-<25.7	5.0-<8.0	26	2.5	1.3-5.0
23.5-<25.7	<5.0	30	3.1	1.6-6.1
≥25.7	≥8.0	15	1.7	0.8-3.8
≥25.7	5.0-<8.0	22	2.2	1.1-4.5
≥25.7	<5.0	35	3.1	1.6-6.0

Adjusted for age, smoking status, hypertension, alcohol drinking, and exercise.

adjustment for HDL-C and TG slightly attenuated this association in men and women, but adiponectin remained significantly associated with an increased risk of diabetes (OR, 1.7; 95% CI, 1.1-2.6) in men but not in women (OR, 1.9; 95% CI, 0.8-4.3).

Table 5 shows the combined analyses of (1) WC and adiponectin and (2) BMI and adiponectin on diabetes in men. Combined effects of both WC and BMI with adiponectin on diabetes progressively increased. Compared with the lowest tertile of WC and highest tertile of adiponectin, those in the highest tertile of WC and lowest tertile of adiponectin had a 2.6 times higher risk of diabetes. Similarly, for BMI and adiponectin, the OR (95% CI) was 3.1 (1.6-6.0). Results for women are not shown because of the small number of cases.

4. Discussion

Our study supports the findings of previous studies, demonstrating that lower levels of adiponectin were associated with an increased risk for diabetes. This association was independent of age, BMI, WC, and other covariates. High-density lipoprotein cholesterol and TG partly accounted for these associations. However, after adjustment for HDL-C and TG, low levels of adiponectin were still strongly associated with an increased diabetes risk in men; but the association for women was no longer statistically significant. We also showed that the diabetes risk increases among the combined group with the lowest tertile of adiponectin and the highest tertile of WC and BMI.

In a recent review article (2007) [1], BMI and WC were associated with type 2 diabetes mellitus. From a clinical perspective, central obesity (approximated by WC) is known to generate diabetogenic substances and should therefore be more informative than general obesity (BMI). Vazquez et al [1] conducted a meta-analysis based on published studies from 1966 to 2004, retrieved from a PubMed search, to compare associations of diabetes incidence with general and central obesity indicators. The pooled relative risks for incident diabetes were 1.87 (95% CI, 1.67-2.10) and 1.87 (95% CI, 1.58-2.20) per standard deviation of BMI and WC, respectively, demonstrating that these 2 obesity indicators have similar associations with incident diabetes. However, results from our present study showed that WC and BMI were no longer significant indicators for prevalent diabetes after adjusting for adiponectin levels in men and women. Although this finding was from a cross-sectional study design, these results have very important implications. For those who had low WC or BMI measurements, the probability of having diabetes varied according to the level of adiponectin in this study. Similarly, for those who had high WC or BMI measurements, the probability of having diabetes also varied according to the level of adiponectin. Further research is needed to determine the clinical and public health usefulness of adiponectin with WC and BMI.

Our data suggest that HDL-C might partly mediate the association between adiponectin and diabetes risk. Adiponectin was associated with substantially higher HDL-C [10], and HDL-C was associated with a borderline-significant reduced risk for diabetes [11]. The mechanisms by which adiponectin may affect HDL-C levels are largely unknown. Effects of adiponectin on hepatic lipase activity, which is increased in central obesity and insulin resistance, are suspected [12].

We observed a sex difference in adiponectin in this Korean population. Women had higher levels than men. Similar reports have been published by some authors [12,13], whereas a few others have failed to observe a sex difference [14]. Cnop et al [12] suggested that the possible explanation for sex differences in adiponectin levels might be due to the different numbers and sizes of fat cells attributed to the difference in sexes. In addition, Gavrila et al [15] reported that estradiol is negatively and independently associated with adiponectin. However, the population on hormone replacement therapy treatment was less than 5% of the present study population, which was very low. Apart from that, it could be a possible reason that the women in the present study population are relatively lean compared with the population of other Western ethnicities. The possible causes of adiponectin levels in sex differences need further research.

This study has several limitations. Because of the cross-sectional design, this study cannot elucidate mechanisms or determine the direction of causality. A single assessment of adiponectin levels may be susceptible to short-term variation, which would bias the results toward the null. However, Pischon et al [16] reported that intraindividual adiponectin levels are reasonably stable over time, with an intraclass correlation coefficient of 0.85 for adiponectin levels measured within the same participants 1 year apart. Because of the small sample size of female participants, the CIs of traits in female participants were much wider than those in men. Continuous study is needed for other possible causes other than using a small sample size. However, this factor is less effective for this research.

These results suggest that adiponectin is an independently associated risk factor for having diabetes and that this association is partly modified by HDL and TG. Our results suggest that the combined use of WC and BMI with adiponectin may help find subjects who are at greater risk of diabetes among healthy Koreans, particularly among younger populations. As a result, it provides a chance for risky individuals to prevent diabetes and for obese individuals to determine a more efficient way of weight control.

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Appendix A

List of participating hospitals in Korean Metabolic Syndrome Research Initiatives:

Severance Hospital, Yonsei University; Ewha Women's University; Seoul National University; and Korea University.

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