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Serum Adiponectin and Type 2 Diabetes: A 6-Year Follow-Up Cohort Study

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Background: Studies on factors which may predict the risk of diabetes are scarce. This prospective cohort study was conducted to determine the association between adiponectin and type 2 diabetes among Korean men and women.
Methods: A total of 42,845 participants who visited one of seven health examination centers located in Seoul and Gyeonggi province, Republic of Korea between 2004 and 2008 were included in this study. The incidence rates of diabetes were determined through December 2011. To evaluate the effects of adiponectin on type 2 diabetes, the Cox proportional hazard model was used.
Results: Of the 40,005 participants, 959 developed type 2 diabetes during a 6-year follow-up. After the adjustment for age, body mass index (BMI), and waist circumference, the risks for type 2 diabetes in participants with normoglycemia had a 1.70-fold (95% confidence interval [CI], 1.21 to 2.38) increase in men and a 1.83-fold (95% CI, 1.17 to 2.86) increase in women with the lowest tertile of adiponectin when compared to the highest tertile of adiponectin. For participants with impaired fasting glucose (IFG), the risk for type 2 diabetes had a 1.46-fold (95% CI, 1.17 to 1.83) increase in men and a 2.52-fold (95% CI, 1.57 to 4.06) increase in women with the lowest tertile of adiponectin. Except for female participants with normoglycemia, all the risks remained significant after the adjustment for fasting glucose and other confounding variables. Surprisingly, BMI and waist circumference were not predictors of type 2 diabetes in men or women with IFG after adjustment for fasting glucose and other confounders.
Conclusion: A strong association between adiponectin and diabetes was observed. The use of adiponectin as a predictor of type 2 diabetes is considered to be useful.

Keywords: Adiponectin; Cohort studies; Diabetes mellitus; Impaired fasting glucose

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INTRODUCTION

With an increasing number of diabetic patients, the complication of diabetes has been deemed a social problem. The concerns toward the complication of diabetes have increased as recent studies have revealed significant associations with impaired fasting glucose (IFG), i.e., prediabetes, with cardiocerebrovascular disease during long-term follow-up [1,2].

Risk factors known to cause diabetes are obesity and genetic factors. Decreased levels of adiponectin secreted by adipose tissue could be a new predictor of diabetes. Adiponectin is a 244-amino acid protein that regulates the metabolism of lipids and glucose [3,4]. Adiponectin decreases insulin resistance and body weight by increasing lipid oxidation in muscles and other organs, such as the pancreas and liver [5]. Numerous cross-sectional studies and prospective cohort studies evaluated an inverse association between adiponectin and the risk of diabetes [6-8]. However, studies on whether adiponectin may predict the risk of diabetes among patients with IFG are not enough such studies. From a previous study among a Taiwanese population, about 3.2% of patients with IFG developed diabetes within 1 year [9]. This emphasizes the need for a predictor that can detect patients with IFG that could develop into diabetes.

Factors known to contribute to the development of diabetes from IFG are fasting glucose, body mass index (BMI), and waist circumference. Among these three factors, the strongest risk factor is believed to be fasting glucose. However, if adiponectin could be used to predict the development of diabetes despite an unchanged fasting glucose level, it could become very meaningful as a new biomarker.

As part of the Seoul Metabolic Syndrome Research Initiatives, this prospective cohort study was performed in a large-scale general population. The selected adiponectin levels were measured for the study population, and the incidence of diabetes was determined.

METHODS

Study population

Participants for this study were drawn from a pool of 185,510 participants who voluntarily underwent private health examinations in one of seven centers located in Seoul and Gyeonggi province in South Korea from 2004 to 2008. Among the 185,510 participants, 42,845 participants had reported adiponectin levels. Among the 42,845 participants, individuals having diabetes (n=2,380, 5.6%) and missing values of essential variables (n=460, 1.1%), such as fasting glucose, BMI, and waist circumference, were excluded. Finally, 34,856 participants (men, 21,766, 62.4%; women, 13,090, 37.6%) with normal fasting glucose levels (<100 mg/dL) and 5,149 participants (men, 4,101, 79.6%; women, 1,048, 20.4%) with IFG (100 to 125 mg/dL) were included in this study (Fig. 1). The incidence rates of diabetes were determined through December 2011.

Data collection and measurement of biomarkers

Each participant was interviewed through a structured questionnaire to collect information such as age, gender, cigarette smoking status (never smoker, ex-smoker, and current smokers), and alcohol intake status (never drinker and drinker). Waist circumference was measured midway between the lower rib and the iliac crest. Weight and height were measured while participants were wearing light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2).

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. Biomarkers, such as fasting glucose, were measured using the Histachi-7600 analyzer (Hitachi Ltd., Tokyo, Japan). For subjects with available serum, adiponectin level was measured using an enzyme-linked immunosorbent assay (Mesdia Co., Ltd., Seoul, Korea). The intra-assay and interassay variances for adiponectin were 6.3% to 7.4% and 4.5% to 8.6%, respectively.

Follow-up and outcome classification

The primary outcome variables were incident diabetes defined by outpatient treatment for diabetes (at least three visits for diabetes care within 365 days), hospitalization due to diabetes (at least one hospitalization for diabetes during the study period), and the use of prescription medication for diabetes management or treatment.

For fasting glucose in medical examination, participants who had IFG at baseline with ≥126 mg/dL fasting glucose level during follow-up through December 2010 were also defined as diabetic. Each hospital had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control.

For the prescription medication history for diabetes between 2004 and 2010, 15 diabetes-related medications and an insulin

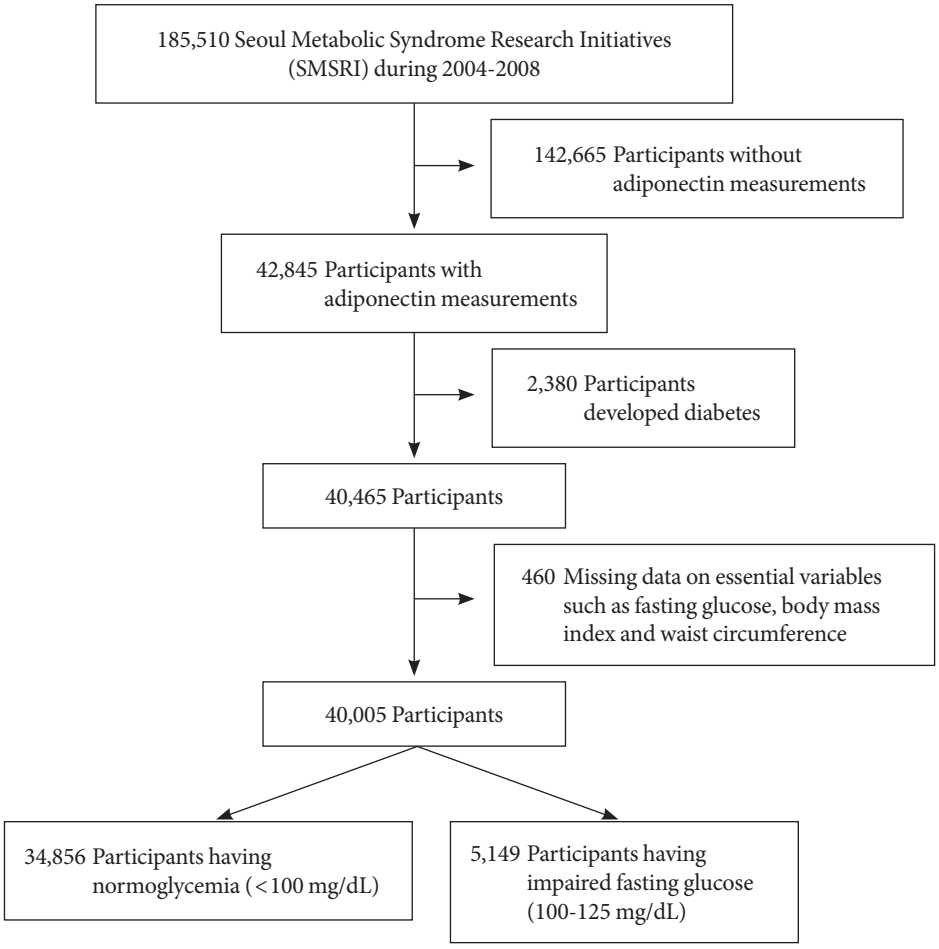

Fig. 1. Flow chart describing study population.

pump were listed in the medication database at the Health Insurance Review & Assessment Service. The medications included insulin, acarbose, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, repaglinide, nateglinide, metformin, voglibose, rosiglitazone, piglitazone, a combination of sulfonyl and metformin, and a combination of thiazolidinedione and metformin.

For outpatient visit and hospitalization, all the outpatient and hospitalization records from 2004 through 2011 were collected from the National Health Insurance Service. Outpatient treatment and hospitalization due to diabetes were defined according to the ICD-10 codes (E11 to E11x) and were mainly used to define type 2 diabetes.

Statistical analysis

For the incidence of type 2 diabetes, age-adjusted incidences of type 2 diabetes per 100 person-years (PY) were calculated. Adiponectin levels were also divided into tertiles as a categorical variable: for participants with normoglycemia, men, (T1) high, ≥7.24, (T2) middle, 4.61-7.23, (T3) low, <4.61 μg/mL, women, (T1) high, ≥11.84, (T2) middle, 7.44-11.83, (T3) low, <7.44 μg/mL; for participants with IFG, men, (T1) high, ≥6.24, (T2) middle, 3.91-6.23, (T3) low, <3.91 μg/mL, women, (T1) high, ≥9.42, (T2) middle, 5.99-9.41, (T3) low, <5.99 μg/mL; the highest tertile of adiponectin was a referent which was used to compare the effects of the other two groups in the association with diabetes. In multivariable models, age, BMI, and waist circumference were adjusted in model 1, whereas fasting serum glucose was additionally adjusted in model 2. Finally, hypertension, smoking status, alcohol intake, total cholesterol, and a family history of diabetes were additionally adjusted in model 3.

Cox proportional hazard models were used to evaluate the association between adiponectin and the risk for type 2 diabe-

tes. All the tested Cox proportional hazards models met the proportional hazards assumption. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the general characteristics of the study population.

For participants with normoglycemia, the mean age was similar in both men and women, while the mean BMI was higher in men than in women (men, 24.2 kg/m^2; women, 22.1 kg/m^2). The mean waist circumference was 83.7 cm in men and 73.1 cm in women. The mean adiponectin level was higher in women than in men (men, 6.6 μg/mL; women, 10.5 μg/mL). The mean levels of fasting glucose were similar in the genders (men, 85.8 mg/dL; women, 84.4 mg/dL). The rate of smoking was higher in men than in women.

For participants with IFG, the mean age was higher in women than in men (men, 45.2 years old; women, 47.7 years old), while the mean BMI was higher in men than in women (men, 25.2 kg/m^2; women, 24.1 kg/m^2). The mean waist circumference was 86.9 cm in men and 78.8 cm in women. The mean adiponectin level was higher in women than in men (men, 5.7 μg/mL; women, 8.6 μg/mL). The mean levels of fasting glucose were similar in the genders (men, 106.5 mg/dL; women, 105.5 mg/dL). The rates of smoking and alcohol consumption were higher in men than in women.

Among the 40,005 participants, 959 participants developed type 2 diabetes during a 6-year follow-up.

For normoglycemia, 360 of the 34,856 (1.03%) participants (21,766 men and 13,090 women) developed type 2 diabetes. Concretely, 99,609 PY were obtained when 21,766 men were followed, and 232 men (1.07%) developed type 2 diabetes (Table 2). When 13,090 women were followed, 61,535 PY were observed, and 128 women (0.98%) developed type 2 diabetes. The age-adjusted incidence rates of type 2 diabetes among participants having IFG were 0.29 per 100 PY for men and 0.32 per 100 PY for women (Table 3).

Also, among the 5,149 participants (4,101 men and 1,048 women) with IFG, 599 participants (11.63%) developed type 2

Table 1. General characteristics of the study participants

Characteristic	Men			Women		
	Normoglycemia[a] (*n*=21,766)	IFG[b] (*n*=4,101)	Diabetes[c] (*n*=1,895)	Normoglycemia[a] (*n*=13,090)	IFG[b] (*n*=1,048)	Diabetes[c] (*n*=485)
Age, yr	41.5±9.1	45.2±9.3	50.4±9.6	40.9±10.0	47.7±11.2	54.4±11.0
BMI, kg/m^2	24.2±2.9	25.2±2.8	25.3±3.0	22.1±2.9	24.1±3.5	24.8±3.3
Waist circumference, cm	83.7±8.9	86.9±7.4	87.6±7.8	73.1±7.8	78.8±8.9	81.9±8.8
SBP, mm Hg	120.7±12.7	126.4±13.7	127.2±14.3	112.1±13.9	121.8±15.7	125.4±16.1
DBP, mm Hg	76.3±9.9	79.6±10.6	80.1±19.9	70.6±9.7	75.3±11.0	76.6±11.3
Fasting serum glucose, mg/dL	85.8±7.6	106.5±6.1	141.3±44.5	84.4±7.4	105.5±5.4	128.2±43.9
Total cholesterol, mg/dL	189.6±31.7	197.8±33.5	194.0±36.9	181.3±31.7	198.2±34.6	196.8±39.3
HDL-C, mg/dL	48.7±8.6	48.3±10.0	47.3±9.3	57.2±10.9	55.0±11.5	51.7±11.0
Triglyceride, mg/dL	150.4±91.2	177.4±113.4	196.2±135.2	94.7±53.6	122.5±70.6	160.3±103.4
Adiponectin, μg/mL	6.6±3.7	5.7±3.3	5.7±3.8	10.5±5.5	8.6±5.0	8.9±6.0
HMW adiponectin, μg/mL	2.3±1.9	2.0±1.5	2.1±1.9	4.1±2.6	3.3±2.2	3.8±3.2
Smoking status, nonsmoker/ ex-smoker/current smoker (%)	27.7/28.3/44.0	25.1/35.3/39.6	20.9/37.7/41.4	93.0/3.0/4.0	95.0/2.1/2.9	96.7/1.8/1.5
Alcohol intake, no/yes (%)	29.0/71.0	30.3/69.7	37.3/62.7	58.3/41.7	64.1/35.9	79.2/20.8
Exercise, yes/no (%)	67.0/33.0	69.2/30.8	76.5/23.5	50.2/49.8	59.0/41.0	61.6/38.4

Values are presented as mean±standard deviation or percentage.
IFG, impaired fasting glucose; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HMW, high molecular weight.
[a]Normoglycemia (fasting serum glucose <100 mg/dL), [b]IFG (fasting serum glucose, 100 to 125 mg/dL), [c]Diabetes (fasting serum glucose ≥126 mg/dL or medication).

Table 2. Incidence rate per 100 person years of type 2 diabetes among Korean men

	Normoglycemia (n=21,766)			Impaired fasting glucose 100-125 (n=4,101)		
	PY	Incident diabetes	Incidence rate/100 PY	PY	Incident diabetes	Incidence rate/100 PY
20-29 yr	5,690	2	0.04 (0.03-0.04)[a]	390	3	0.77 (0.73-0.81)[a]
30-39 yr	40,733	43	0.11 (0.11-0.11)[a]	4,934	86	1.74 (1.73-1.75)[a]
40-49 yr	34,684	84	0.24 (0.24-0.24)[a]	7,393	191	2.58 (2.58-2.58)[a]
50-59 yr	14,245	69	0.48 (0.48-0.49)[a]	3,854	150	3.89 (3.88-3.99)[a]
60+ yr	4,257	34	0.80 (0.79-0.80)[a]	1,385	55	3.97 (3.94-4.00)[a]
Total	99,609	232		17,956	485	
Incidence						
Cumulative method[b]		1.07	-		11.83	-
Incidence density[c]		-	0.23		-	2.70
Age-adjusted incidence density[d]		-	0.29		-	2.39

PY, person years.
[a]95% confidence interval, [b]Cumulative method per 100 persons: 1.07=(232/21,766)×100; 11.83=(485/4,101)×100, [c]Incidence density per 100 PY: 0.23=(232/99,609)×100; 2.70=(485/17,956)×100, [d]Age-adjusted incidence density using the national population in 2005 as a standard population.

Table 3. Incidence rate per 100 person years of type 2 diabetes among Korean women

	Normoglycemia (n=13,090)			Impaired fasting glucose 100-125 (n=1,048)		
	PY	Incident diabetes	Incidence rate/100 PY	PY	Incident diabetes	Incidence rate/100 PY
20-29 yr	6,837	5	0.07 (0.07-0.07)[a]	221	3	1.35 (1.25-1.45)[a]
30-39 yr	23,397	26	0.11 (0.11-0.11)[a]	1,032	10	0.97 (0.95-0.99)[a]
40-49 yr	19,254	30	0.16 (0.16-0.16)[a]	1,475	31	2.10 (2.08-2.12)[a]
50-59 yr	8,775	38	0.43 (0.43-0.43)[a]	1,232	46	3.73 (3.70-3.76)[a]
60+ yr	3,272	29	0.89 (0.88-0.89)[a]	798	24	3.01 (2.97-3.05)[a]
Total	61,535	128		4,758	114	
Incidence						
Cumulative method[b]		0.98	-		10.88	-
Incidence density[c]		-	0.21		-	2.40
Age-adjusted incidence density[d]		-	0.32		-	2.11

PY, person years.
[a]95% confidence interval, [b]Cumulative method per 100 persons: 1.07=(232/21,766)×100; 11.83=(485/4,101)×100, [c]Incidence density per 100 PY: 0.23=(232/99,609)×100; 2.70=(485/17,956)×100, [d]Age-adjusted incidence density using the national population in 2005 as a standard population.

diabetes. Concretely, 17,956 PY were obtained when 4,101 men were followed, and 485 men (11.83%) developed type 2 diabetes (Table 2). When 1,048 women were followed, 4,758 PY were observed, and 114 women (10.88%) developed type 2 diabetes. The age-adjusted incidence rates of type 2 diabetes among participants having IFG were 2.39 per 100 PY for men and 2.11 per 100 PY for women (Table 3). In other words, when participants had IFG, the incidence rates of type 2 diabetes per year were higher in men (2.39%) than in women (2.11%).

Tables 4 and 5 display the association between adiponectin level and type 2 diabetes among male and female subjects us-

Table 4. Hazard ratios (95% confidence interval) for categorized adiponectin level on type 2 diabetes among Korean men

	Normoglycemia[a] (FSG <100 mg/dL)			Impaired fasting glucose[b] (FSG 100-125 mg/dL)		
	Model 1[c]	Model 2[d]	Model 3[e]	Model 1[c]	Model 2[d]	Model 3[e]
Serum adiponectin						
(T1) High	1.00	1.00	1.00	1.00	1.00	1.00
(T2) Middle	1.61 (1.15-2.26)	1.51 (1.07-2.12)	1.51 (1.05-2.17)	1.21 (0.96-1.53)	1.14 (0.90-1.44)	1.08 (0.83-1.39)
(T3) Low	1.70 (1.21-2.38)	1.51 (1.07-2.11)	1.54 (1.07-2.20)	1.46 (1.17-1.83)	1.39 (1.11-1.74)	1.27 (1.00-1.63)
Age, yr	1.07 (1.06-1.09)	1.07 (1.05-1.08)	1.06 (1.05-1.08)	1.04 (1.03-1.05)	1.03 (1.02-1.04)	1.03 (1.02-1.04)
BMI, kg/m^2	1.04 (1.03-1.06)	1.05 (1.03-1.06)	1.04 (1.03-1.06)	1.07 (1.00-1.13)	1.04 (0.98-1.11)	1.04 (0.97-1.11)
Waist circumference, cm	1.01 (1.00-1.01)	1.01 (1.00-1.01)	1.01 (1.00-1.01)	1.02 (1.00-1.04)	1.01 (0.99-1.04)	1.02 (0.99-1.04)
Fasting serum glucose, mg/dL		1.06 (1.04-1.08)	1.06 (1.04-1.08)		1.12 (1.11-1.13)	1.11 (1.09-1.12)
Hypertension			1.64 (1.22-2.20)			0.91 (0.73-1.13)
Total cholesterol, per 10 mg/dL			1.05 (1.01-1.10)			1.01 (0.99-1.04)
Smoking status						
Ex-smokers			0.97 (0.67-1.41)			1.03 (0.79-1.36)
Current smokers			1.48 (1.04-2.10)			1.30 (1.00-1.69)
Alcohol intake			0.92 (0.69-1.23)			1.00 (0.81-1.24)
Family history of diabetes			1.31 (0.89-1.95)			1.13 (0.88-1.46)

FSG, fasting serum glucose; BMI, body mass index.
[a]Normoglycemia group: high, ≥7.24, middle, 4.61-7.23, low, <4.61 μg/mL, [b]Impaired fasting glucose group: high, ≥6.24, middle, 3.91-6.23, low, <3.91 μg/mL, [c]Model 1, adjusted for age, body mass index, and waist circumference, [d]Model 2, model 1+additional adjustment for fasting glucose, [e]Model 3, model 2+additional adjustment for hypertension, total cholesterol, smoking status, alcohol intake, and family history of diabetes.

ing Cox proportional hazard modeling. The risks of type 2 diabetes were evaluated by dividing the adiponectin levels into tertiles as a categorical variable.

Compared to the highest tertile of adiponectin in participants with normoglycemia, the risk of type 2 diabetes with the lowest tertile had a 1.70-fold (95% confidence interval [CI], 1.21 to 2.38) increase in men (Table 4) and a 1.83-fold (95% CI, 1.17 to 2.86) increase in women (Table 5) after adjustment for age, BMI, and waist circumference.

For participants with IFG, the risk of type 2 diabetes increased by 1.46-fold (95% CI, 1.17 to 1.83) in men (Table 4) and by 2.52-fold (95% CI, 1.57 to 4.06) in women (Table 5) with the lowest tertile of adiponectin. All the risks, except for female participants with normoglycemia, remained significant after the adjustment for fasting glucose and other confounding variables.

Surprisingly, BMI and waist circumference were not predictors of type 2 diabetes in men or women with IFG after the adjustment for fasting glucose and other confounders.

After the age adjustment, the correlations of high molecular weight adiponectin with fasting glucose were -0.1467 (P=0.0006) for men and -0.1142 (P=0.1394) for women (data not shown).

Figs. 2 and 3 illustrate the Kaplan-Meier survival curve on the association between adiponectin and type 2 diabetes among subjects with normoglycemia and IFG during a 6-year follow-up. Participants having the lowest tertile of adiponectin had decreased survival rates compared to participants with the highest tertile of adiponectin. This trend was more apparent in women than in men.

DISCUSSION

This prospective cohort study consisted of 42,845 participants among the general population and involved a 6-year follow-up. In this study, adiponectin was found to be a predictor of type 2 diabetes among men with normoglycemia and among men and women with IFG. In particular, adiponectin was the strongest predictor among women. However, BMI and waist circumference were not predictors of diabetes among patients with IFG.

According to a systematic review of studies in 2007, BMI

Table 5. Hazard ratios (95% confidence interval) for categorized adiponectin level on type 2 diabetes among Korean women

	Normoglycemia[a] (FSG <100 mg/dL)			Impaired fasting glucose[b] (FSG 100-125 mg/dL)		
	Model 1[c]	Model 2[d]	Model 3[e]	Model 1[c]	Model 2[d]	Model 3[e]
Serum adiponectin						
(T1) High	1.00	1.00	1.00	1.00	1.00	1.00
(T2) Middle	1.11 (0.67-1.83)	1.08 (0.66-1.78)	1.07 (0.63-1.80)	1.06 (0.61-1.85)	1.16 (0.66-2.02)	0.95 (0.52-1.74)
(T3) Low	1.83 (1.17-2.86)	1.75 (1.12-2.74)	1.52 (0.94-2.46)	2.52 (1.57-4.06)	2.35 (1.45-3.79)	2.08 (1.25-3.46)
Age, yr	1.06 (1.04-1.07)	1.05 (1.04-1.07)	1.03 (1.01-1.06)	1.03(1.01-1.05)	1.03 (1.01-1.05)	1.03 (1.00-1.05)
BMI, kg/m^2	1.10 (1.01-1.21)	1.10 (1.00-1.21)	1.08 (0.98-1.19)	1.01 (0.92-1.12)	1.01 (0.91-1.12)	1.02 (0.91-1.14)
Waist circumference, cm	1.03 (0.99-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.08)	1.02 (0.98-1.06)	1.03 (0.98-1.07)
Fasting serum glucose, mg/dL		1.03 (1.00-1.05)	1.03 (1.00-1.06)		1.11 (1.08-1.14)	1.09 (1.06-1.12)
Hypertension			2.00 (1.28-3.12)			1.36 (0.88-2.11)
Total cholesterol, per 10 mg/dL			1.04 (0.98-1.10)			1.00 (0.94-1.05)
Smoking status						
Ex-smokers			1.19 (0.38-3.78)			0.82 (0.20-3.39)
Current smokers			0.62 (0.15-2.54)			1.36 (0.47-3.92)
Alcohol intake			0.91 (0.59-1.42)			1.22 (0.76-1.96)
Family history of diabetes			1.36 (0.84-2.19)			1.75 (1.11-2.76)

FSG, fasting serum glucose; BMI, body mass index.
[a]Normoglycemia group, high, ≥11.84, middle, 7.44-11.83, low, <7.44 μg/mL, [b]Impaired fasting glucose group, high, ≥9.42, middle, 5.99-9.41, low, <5.99 μg/mL, [c]Model 1, adjusted for age, body mass index, and waist circumference, [d]Model 2, model 1+additional adjustment for fasting glucose, [e]Model 3, model 2+additional adjustment for hypertension, total cholesterol, smoking status, alcohol intake, and family history of diabetes.

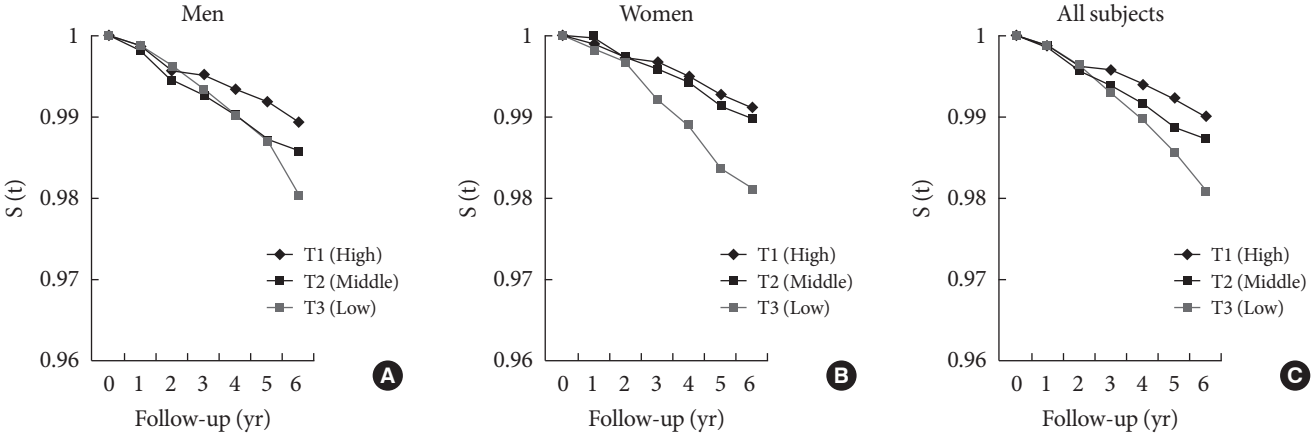

Fig. 2. The Kaplan-Meier survival curve demonstrating the association between adiponectin and type 2 diabetes among participants with normoglycemia during a 6-year follow-up (A) men, (B) women, (C) all subjects; adiponectin levels: men, (T1) high, ≥7.24, (T2) middle, 4.61-7.23, (T3) low, <4.61 μg/mL; women, (T1) high, ≥11.84, (T2) middle, 7.44-11.83, (T3) low, <7.44 μg/mL.

and waist circumference were found to be strongly related to type 2 diabetes [10]. In other words, waist circumference or abdominal obesity was strongly associated with type 2 diabetes. These findings were similar to the overall results from studies on the obesity index and the incidence of diabetes published in PubMed in 1966 to 2004. With an increase of 1 SD of waist circumference, the incidence of diabetes increased by 1.87 times. However, the study by Yoon et al. [6] on the associations of BMI, waist circumference, and serum adiponectin with diabetes among Koreans states that adiponectin was the only factor associated with the prevalence of diabetes. Although the study by Yoon et al. [6] was a cross-sectional study,

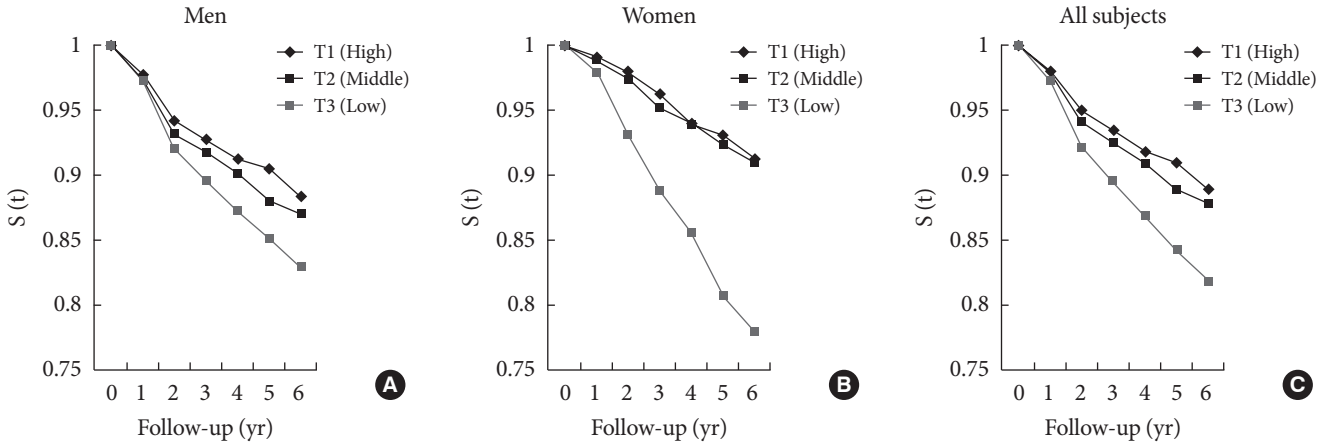

Fig. 3. The Kaplan-Meier survival curve demonstrating the association between adiponectin and type 2 diabetes among participants with impaired fasting glucose during a 6-year follow-up (A) men, (B) women, (C) all subjects; adiponectin levels: men, (T1) high, ≥6.24, (T2) middle, 3.91-6.23, (T3) low, <3.91 μg/mL; women, (T1) high, ≥9.42, (T2) middle, 5.99-9.41, (T3) low, <5.99 μg/mL.

it could have clinically significant meanings of diagnosis. In other words, despite the normal range of BMI and waist circumference, the risk of diabetes may be different based on adiponectin level.

In this study, adiponectin levels were higher in women than in men. Some of the aforementioned studies about adiponectin also mentioned higher levels of adiponectin in women compared to men [11,12], although another study showed that adiponectin levels were similar in men and women [13]. Cnop et al. [11] reported that different sizes and numbers of adipocytes in men and women may result in different levels of adiponectin in men and women. However, negative associations between adiponectin and estradiol were demonstrated by some studies. It is difficult to explain such differences between men and women because hormone replacement therapy was seldom carried out [14]. In addition, not many women are obese and are generally leaner than men. Therefore, adiponectin levels could be different for these reasons. In this present study, the BMI for men and women were 25.2 and 24.1 kg/m^2, respectively, while the waist circumferences of men and women were 86.9 and 78.8 cm, respectively. Between men and women, not much difference was observed in BMI as opposed to waist circumference. This indicates that differences in adiponectin level could be due to differences in waist circumference and not BMI.

Patients having IFG are known to have a greater chance of developing diabetes. From a previous study in a Taiwanese population, about 3.2% of patients having stage 2 IFG (110 to 125 mg/dL) developed diabetes within 1 year [9]. Previous results from our research group showed that adiponectin was independently associated with diabetes among participants with stage 2 IFG [15].

In the present findings, the age-adjusted incidence rates per 100 PY among patients with IFG (100 to 125 mg/dL) were 2.39 for men and 2.11 for women, i.e., the incidence rates of diabetes were 2.39% for men and 2.11% for women among participants who suffered from diabetes and visited clinics or hospitals more than one time a year for diabetic complications. These values were a bit lower than the study conducted in Taiwan. The difference may be explained by the age difference and the definitions of IFG between the two studies.

In patients with IFG, the predictive value of adiponectin was stronger in women than in men. The specific mechanisms are unknown, yet similar findings are still being observed in observational studies. In a cross-sectional study by Yoon et al. [6], the odds ratios for diabetes in the relationship with adiponectin after adjustments for age, smoking status, hypertension, alcohol intake, waist circumference, and BMI were 1.9 among men and 2.5 among women. This association was more apparent in women than in men [6].

Further research regarding the association of adiponectin with diabetes between men and women need to be done. To evaluate whether gender acts as an effect modifier, interaction analysis is necessary in the association of adiponectin with diabetes.

Adiponectin may exert its effects on glucose metabolism

through two distinct receptors termed adiponectin receptor 1 and adiponectin receptor 2 [8,16]. Previous animal studies show that adiponectin receptor 1 knocks out the results in the abrogation of adiponectin-induced activation of 5'-adenosine monophosphate-activated protein kinase and increases glucose production and insulin resistance [16,17]. The targeted disruption of adiponectin receptor 2 leads to a decrease in the activity of peroxisome proliferator-activated receptor α signaling pathways and insulin resistance [17]. Positive associations of adiponectin with insulin sensitivity were found in humans [18,19]. Some studies have associated variations in the adiponectin gene with insulin resistance and risk of type 2 diabetes [20,21].

This current study may have several limitations. Only a single measurement of adiponectin from all subjects had been followed till now. However, intraindividual adiponectin levels are reasonably stable over time [22]. In fact, Pischon et al. [22] reported that the intraclass correlation coefficient of 0.85 for adiponectin level was measured with the same participants 1 year apart. The advantage of this current study is that it is a prospective cohort study which may overcome the limitations of cross-sectional studies. Measured levels of adiponectin have been followed, and the incidence of diabetes has been evaluated according to the level of adiponectin. It is also very difficult to predict the occurrence of errors in the diagnosis of diabetes because diabetes has been defined by many means, including the changes of fasting glucose measurements, use of prescription medication for diabetes management and treatment, outpatient treatment for diabetes, and hospitalization due to diabetes. Although errors may occur in diagnosis of diabetes, this does not affect the relationship of adiponectin with diabetes. In other words, diagnostic errors could be counterbalanced according to adiponectin level, and the possibility of the association being affected by such errors is very low.

In conclusion, adiponectin is a strong predictor of type 2 diabetes, particularly among patients with IFG. Therefore, despite having the same levels of fasting glucose, the risk of type 2 diabetes can vary by adiponectin level, i.e., low levels of adiponectin were associated with increased risk of type 2 diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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