

CLINICAL STUDY

Serum adiponectin is associated with family history of diabetes independently of obesity and insulin resistance in healthy Korean men and women

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Abstract

Background: Adiponectin has been reported as a new risk factor for the development of diabetes. However, it is not clear whether adiponectin levels are associated with family history of diabetes (FHD). **Objective:** The objective of this study was to measure the independent association of serum adiponectin with FHD in relation to insulin resistance and obesity.

Methods: In 2006, a cross-sectional study was conducted in which waist circumference (WC), body mass index (BMI), and serum adiponectin were measured in 5919 healthy Korean men and women. Multiple linear regression models were used to assess the association of serum adiponectin levels with FHD. The population was classified into two groups according to median values for each of the following variables: WC, BMI, and homeostasis model assessment of insulin resistance (HOMA-IR).

Results: The positive FHD group had higher HOMA-IR and lower adiponectin levels in both men and women than those without FHD. Adiponectin levels were significantly associated with FHD in men and women respectively, after adjusting for age, BMI, and alcohol consumption ($P=0.0123$ and 0.0004). The relationship between adiponectin and FHD was similar between the high and low insulin resistance, BMI, and WC groups in male non-smokers and in all Korean women.

Conclusion: These results confirm that adiponectin levels are associated with FHD. These data also suggest that the association of serum adiponectin with FHD may be independent of obesity and insulin resistance.

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Introduction

Adiponectin has been reported as a new risk factor for the development of diabetes. Exclusively secreted by adipose tissue, ADIPOQ is a 244-amino acid protein that regulates the metabolism of lipids and glucose, and circulates quite abundantly in plasma (1–5). ADIPOQ decreases insulin resistance and body weight by increasing lipid oxidation in muscle and other organs such as the pancreas and liver (6). Plasma ADIPOQ concentrations are also reduced in individuals with obesity, diabetes mellitus, or coronary heart disease (7, 8).

Family history of diabetes (FHD) has been associated with hypoadiponectinemia in some (9–13) but not all studies (14–16). However, previous studies generally had small sample sizes that may explain the inconsistencies in findings. The underlying mechanisms of association between FHD and ADIPOQ levels are not yet fully understood. Because ADIPOQ levels can be used to predict increased insulin sensitivity (14), the inverse

association between ADIPOQ and FHD may be due to insulin resistance (14, 17). However, the literature on the association of serum ADIPOQ levels with FHD independently of insulin resistance is sparse. Thus, the purpose of this study was to see whether the association between FHD and ADIPOQ levels in relation to insulin resistance and obesity is independent.

Materials and methods

Study subjects

The study population comprised 6551 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 to December 2006. The objective and contents of this research project were explained to participants who volunteered to undergo the health examinations. Recruitment of these

volunteered subjects took place only after informed consent had been obtained. Participating hospitals are listed in the appendix (18). The analysis excluded subjects with missing information on waist circumference (WC), body mass index (BMI), or ADIPOQ levels, and those who had a history of cancer, cardiovascular disease, stroke, or diabetes ($n=292$). We also excluded those who had been on medication for diabetes and subjects with a fasting blood sugar >110 mg/dl ($n=340$). Finally, 5919 subjects, aged between 24 and 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.

Data collection

Each participant was interviewed using a structured questionnaire to collect the history of cigarette smoking (never smoked, ex-smoker, or current smoker) and alcohol consumption (non-drinker or drinker of any amount of alcohol), as well as other demographic characteristics such as age, gender, and FHD. FHD was defined as subjects with at least one first-degree relative with diabetes (parent or sibling). Both current and ex-smokers were asked to report the average number of cigarettes they smoke or had smoked per day. WC was measured midway between the lower rib and the iliac crest. Weight and height were measured while the participants were wearing light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2). Blood pressure was measured for the patient 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-min rest.

Measurement of biomarkers

For the clinical chemistry assay, serum was separated from peripheral venous blood samples that were obtained from each participant after 12 h of fasting, and was stored at -70°C for 2 h. Metabolic syndrome biomarkers such as fasting blood glucose, total cholesterol (TC), triglycerides (TG), and high density lipoprotein cholesterol (HDL-C) were measured using the Hitachi-7600 analyzer (Hitachi Ltd). For subjects with serum available, ADIPOQ levels were measured using an ELISA (Mesdia Co., Ltd, Seoul, Republic of Korea) (18). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR). HOMA indices were calculated as follows: $\text{HOMA} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/l)} / 22.5$. The intra- and interassay variances for the ADIPOQ were 6.3–7.4% and 4.5–8.6% respectively. Data quality control was performed in accordance with the procedures of the Korean Association of Laboratory Quality Control.

Statistical analysis

All biomarkers except ADIPOQ were found to have a normal distribution. Therefore, ADIPOQ levels are presented as median interquartile range and were log-transformed in the multivariate analyses. The independent *t*-test was used to analyze the statistical differences among the characteristics of the study participants. The mean serum ADIPOQ level was calculated for each category of FHD. Multiple linear regression models were used to assess the associations of serum ADIPOQ levels with FHD. Current smokers were further divided into two groups of 1–10 and 10 and more cigarettes per day. Analyses were adjusted for age at enrollment (continuous variable), BMI, and smoking status.

To examine the association between FHD and ADIPOQ stratified by insulin resistance (HOMA-IR), BMI, and WC, we divided our study samples into two groups (by median values) of HOMA-IR (<0.795 and ≥ 0.795), BMI (<24.48 and ≥ 24.48), and WC (<85 and ≥ 8) for men and HOMA-IR (<0.705 and ≥ 0.705), BMI (<22.3 and ≥ 22.3), and WC (<74.5 and ≥ 74.5) for women. All analyses were conducted using SAS statistical software, version 9.0 (SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided, and statistical significance was determined as $P < 0.05$.

Results

The characteristics of participants in relation to their FHD are shown for Korean men in Table 1. Male subjects with FHD were on average younger than those without FHD. In general, those with FHD had higher WC, BMI, FBS, TC, HOMA, and insulin levels, and had lower ADIPOQ levels. However, HDL cholesterol, C-reactive protein (CRP), and smoking status were similar for the two groups. For women, subjects with FHD were also on average younger than those without FHD (Table 2). Those with FHD generally had higher FBS and HOMA levels, and women with FHD had lower ADIPOQ levels. However, WC, BMI, HDL cholesterol, and CRP measurements were similar for the two groups (Table 2).

Using the age-adjusted Pearson correlation test, levels of ADIPOQ were found to be inversely associated with BMI, WC, and TG, and directly associated with HDL cholesterol ($P < 0.001$). However, the correlation between CRP and ADIPOQ was not significant ($P = 0.3228$; data not shown). ADIPOQ levels were significantly associated with FHD in men and women respectively, after adjusting for age, BMI, and alcohol drinking ($P = 0.0123$ and 0.0004 ; Table 3). When HOMA index was added as a covariate, the association didn't change much in men and women ($P = 0.0177$ and 0.0004 ; data not shown).

To control for potential confounding by insulin resistance and obesity, data were further stratified by BMI, WC, and HOMA (Table 4). For men, the relationship between ADIPOQ and FHD was statistically significant in

Table 1 General characteristics of healthy Korean men according to family history of diabetes.

N	Family history of diabetes		P value
	Negative (N=2825) Mean ± s.d.	Positive (N=503) Mean ± s.d.	
Age (year)	45.7 ± 9.3	43.4 ± 7.3	<0.0001
WC (cm)	84.9 ± 7.2	86.0 ± 7.4	0.0022
BMI (kg/m ²)	24.5 ± 2.6	24.9 ± 2.8	0.0038
ADIPOQ ^a (µg/ml)	6.20 ± 4.7	5.65 ± 4.1	0.0005
Log ADIPOQ ^a	2.52 ± 0.8	2.42 ± 0.7	0.0006
FBS (mg/dl)	90.5 ± 8.3	92.6 ± 8.5	<0.0001
SBP (mmHg)	123.0 ± 13.6	123.5 ± 11.9	0.4353
DBP (mmHg)	77.9 ± 10.8	77.6 ± 10.4	0.6599
Total cholesterol (mg/dl)	186.8 ± 30.2	191.0 ± 30.9	0.0046
HDL cholesterol (mg/dl)	49.9 ± 11.0	49.6 ± 10.9	0.5934
LDL cholesterol (mg/dl)	115.5 ± 28.2	117.5 ± 28.2	0.2117
Triglyceride (mg/dl)	142.1 ± 92.3	149.6 ± 101.9	0.1004
C-reactive protein (mg/dl)	0.16 ± 0.3	0.16 ± 0.3	0.9726
HOMA	0.93 ± 0.7	1.02 ± 0.7	0.0067
Insulin (µIU/ml)	4.12 ± 2.9	4.41 ± 2.8	0.0316
Smoking status (%)			
Ex	34.8	33.2	0.3663
Current	40.0	38.6	
Alcohol drinking (%)	88.5	89.5	0.5433

P values refer to differences between groups as determined by t-test and χ²-test for continuous and categorical variables respectively. FBS, fasting plasma glucose; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; HDL, high density lipoprotein; LDL, low density lipoprotein.

^aMedian ± interquartile range (IQR).

subjects with BMI < 24.48, in those with WC ≥ 85 and in non-smokers, while this relationship was not significant in the other groups (Table 4). However, when the analyses were performed only on non-smokers and light smokers, ADIPOQ levels were significantly associated with FHD in both BMI groups. The WC and HOMA groups also showed similar associations of ADIPOQ levels with FHD.

For women, ADIPOQ levels in the FHD group were significantly lower among those with HOMA < 0.705 (P value = 0.0377) and with HOMA ≥ 0.705 (P value = 0.0036) respectively, compared with the non-FHD group (Table 4). Similar associations of ADIPOQ levels with FHD were seen in the BMI and WC groups.

Discussion

Our study demonstrates that FHD is associated with hypoadiponectinemia that supports findings of previous studies (9, 10). In a recent study, in 64-year-old women in Sweden, mean ADIPOQ levels were lower (11.4 vs 13.9) in those with FHD than those without FHD (10). In another study in male subjects in Sweden, first-degree relatives of type 2 diabetic patients also had significantly lower ADIPOQ levels (9). The present study showed an inverse relationship between FHD and ADIPOQ levels in Korean men and women. For men, the association was stronger in non-smokers which

Table 2 General characteristics of healthy Korean women according to family history of diabetes.

N	Family history of diabetes		P value
	Negative (N=2141) Mean ± s.d.	Positive (N=450) Mean ± s.d.	
Age (year)	44.4 ± 9.5	43.2 ± 7.9	0.0033
Waist (cm)	74.9 ± 7.8	75.3 ± 7.9	0.3777
BMI (kg/m ²)	22.7 ± 2.9	22.8 ± 2.8	0.5237
ADIPOQ ^a (µg/ml)	10.0 ± 7.4	8.7 ± 6.7	0.0001
Log ADIPOQ ^a	3.0 ± 0.7	2.9 ± 0.7	<0.0001
FBS (mg/dl)	86.6 ± 7.9	89.2 ± 8.3	<0.0001
SBP (mmHg)	115.2 ± 13.8	116.1 ± 14.6	0.2343
DBP (mmHg)	71.7 ± 10.2	71.6 ± 10.5	0.9820
Total cholesterol (mg/dl)	182.3 ± 32.9	181.6 ± 30.3	0.6440
HDL cholesterol (mg/dl)	59.5 ± 13.0	58.8 ± 12.2	0.2755
LDL cholesterol (mg/dl)	108.5 ± 30.4	105.7 ± 27.5	0.0597
Triglyceride (mg/dl)	90.6 ± 52.7	89.3 ± 51.1	0.6369
C-reactive protein (mg/dl)	0.12 ± 0.2	0.11 ± 0.2	0.6152
HOMA	0.81 ± 0.6	0.88 ± 0.6	0.0386
Insulin (µIU/ml)	3.75 ± 2.6	3.93 ± 2.5	0.1795
Smoking status (%)			
Ex	2.5	1.8	0.1034
Current	4.1	2.2	
Alcohol drinking (%)	51.2	52.8	0.5124

P values refer to differences between groups as determined by t-test and χ²-test for continuous and categorical variables respectively. FBS, fasting plasma glucose; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; HDL, high density lipoprotein; LDL, low density lipoprotein.

^aMedian ± interquartile range (IQR).

implies that smoking is a confounding factor. Moreover, in male non-smokers and in Korean women, the relationship remained even when performing subgroup analyses of the HOMA-IR, BMI, and WC categories, suggesting that the association of serum ADIPOQ with FHD is independent of obesity and insulin resistance.

The present study was performed with a larger sample size than that of other studies, and like these previous

Table 3 Multiple linear regression model of mean log ADIPOQ in healthy Korean men and women.

Variables	Model 1		Model 2	
	β	P value	β	P value
Men				
Age (year)	0.007	<0.0001	0.005	<0.0001
Family history of diabetes	-0.077	0.0042	-0.066	0.0123
BMI (kg/m ²)			-0.040	<0.0001
Smoking status				
Ex			-0.007	0.7881
Current			-0.076	0.0017
Women				
Age (year)	0.005	0.0001	0.009	<0.0001
Family history of diabetes	-0.113	0.0001	-0.103	0.0004
BMI (kg/m ²)			-0.037	<0.0001
Smoking status				
Ex			0.104	0.1511
Current			0.037	0.5274

Table 4 Multiple linear regression model^a of mean log ADIPOQ for family history of diabetes (yes) by BMI, WC, and HOMA in healthy Korean men and women.

Variables	Subgroups	All men FHD (yes)			Non or light smoking men FHD (yes)			All women FHD (yes)		
		N	β	P value	N	β	P value	N	β	P value
BMI (kg/m ²)	<24.48	1666	-0.083	0.0359	549	-0.140	0.0225	1292	-0.122	0.0036
	≥24.48	1662	-0.054	0.1308	488	-0.134	0.0384	1299	-0.084	0.0375
WC (cm)	<85	1574	-0.046	0.2502	525	-0.114	0.0436	1334	-0.066	0.1070
	≥85	1754	-0.072	0.0427	512	-0.140	0.0308	1257	-0.143	0.0006
HOMA	<0.795	1664	-0.057	0.1450	534	-0.156	0.0170	1297	-0.090	0.0377
	≥0.795	1664	-0.065	0.0704	503	-0.101	0.0934	1294	-0.115	0.0036

Adjusted for age, BMI, and alcohol drinking. BMI, body mass index; WC, waist circumference; HOMA, homeostasis model assessment; FHD, family history of diabetes; light smokers, subjects who smoke <10 cigarettes per day.

^aReference group: no family history of diabetes groups.

studies, we also found that lower serum ADIPOQ concentrations in FHD groups were not dependent on insulin resistance status or obesity. Because ADIPOQ predicts increased insulin sensitivity (14), the inverse association between ADIPOQ and obesity, T2DM, or FHD may to a large extent, be explained by the parallel occurrence of insulin resistance (14, 17). However, a recent cross-sectional study in Sweden reported that a FHD was associated with low serum ADIPOQ concentrations independently of obesity, glycemia, or insulin sensitivity, although the study was limited by the fact that all of the study subjects were 64-year-old women (10). Two other studies have reported that ADIPOQ levels are reduced in lean offspring of type 2 diabetes subjects maintaining that the inverse association of ADIPOQ levels with FHD is independent of BMI (9, 12).

We observed a sex difference in the association of ADIPOQ with FHD in this Korean population. Women showed a stronger association of ADIPOQ with FHD than did men. One of the possible reasons of the difference is a clear difference in TG concentration between men and women in the present study. Serum triglyceride levels were much higher in men than in women. However, mean TG levels were significantly lower in male non-smokers than in male current smokers (119.2 and 151.3 mg/dl; data not shown). When the analyses were performed according to smoking status in men, the association of ADIPOQ with FHD appeared stronger in non-smokers. This observation along with recent studies which have reported that smoking status is associated with lower levels of ADIPOQ (19–21), suggests that smoking is a possible confounder in the association between ADIPOQ and FHD. The possible causes of sex differences in the association of ADIPOQ levels with FHD should be investigated further.

This study has several limitations. Due to its cross-sectional design, this study cannot elucidate mechanisms or determine the direction of causality of the relationship between ADIPOQ and FHD. A single assessment of ADIPOQ levels may be susceptible to short-term variation, which would bias the results toward the null. However, Pischon *et al.* reported that intra-individual ADIPOQ levels are reasonably stable over time, with an intra-class correlation coefficient of

0.85 for ADIPOQ levels measured within the same participants 1 year apart (22). Another limitation of this study is the classification of FHD. We did not classify the types of diabetes. However, type 2 diabetes is the most common type of diabetes in the Republic of Korea, while the incidence rate of type 1 diabetes in the country is among the lowest reported in the world. During the period 1995–2000, the age-adjusted incidence of type 1 diabetes was 1.36 per 100 000/year (23, 24).

In summary, these results confirm that ADIPOQ concentrations are lower in first-degree relatives of diabetic patients, and suggest that the association may not be due to the concomitant presence of insulin resistance and obesity. Further studies should be performed in other populations to confirm the association between ADIPOQ and FHD regardless of insulin resistance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Appendix

List of participating hospitals in Korean Metabolic Syndrome Research Initiatives: Severance Hospital, Yonsei University; Ewha Women's University; Seoul National University; Korea University.

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