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Association between hypoadiponectinemia and cardiovascular risk factors in nonobese healthy adults

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Abstract

Adiponectin levels are significantly lower in obese adult patients with type 2 diabetes mellitus, essential hypertension, dyslipidemia, and cardiovascular disease. However, the role of hypoadiponectinemia in nonobese healthy adults has not been fully elucidated. In this study, we examined the association between hypoadiponectinemia and cardiovascular risk factors and estimated plasma adiponectin values in nonobese, apparently healthy adults. A total of 204 male and 214 female healthy individuals aged 20 to 80 years, with a body mass index (BMI) of less than 25 kg/m^2, were included in this study. We measured patients' plasma adiponectin levels, serum lipid profiles, high-sensitivity C-reactive protein (hs-CRP) levels, fasting glucose levels, and fasting insulin levels. Mean values of plasma adiponectin were 5.45 ± 3.3 μg/mL in male and 8.16 ± 4.6 μg/mL in female subjects. The hypoadiponectinemia group (<4.0 μg/mL) had significantly higher levels ($P < .01$) of BMI, fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and triglycerides, but lower levels of high-density lipoprotein cholesterol (HDL-C). In males, plasma adiponectin levels were inversely correlated with BMI ($r = -0.32$, $P < .01$), HOMA-IR ($r = -0.14$, $P < .05$), triglyceride levels ($r = -0.17$, $P < .05$), and hs-CRP levels ($r = -0.15$, $P < .05$), and positively correlated with HDL-C ($r = 0.24$, $P < .01$). In females, plasma adiponectin levels were negatively correlated with BMI ($r = -0.31$, $P < .01$), fasting glucose ($r = -0.18$, $P < .01$), fasting insulin ($r = -0.23$, $P < .01$), HOMA-IR ($r = -0.24$, $P < .01$), and triglyceride ($r = -0.18$, $P < .01$) levels, and positively correlated with HDL-C ($r = 0.37$, $P < .01$). Sex, age, BMI, and HDL-C ($P < .01$ for each) were found to be independent factors associated with plasma adiponectin levels in multivariate analysis. Hypoadiponectinemia is significantly associated with cardiovascular risk factors such as insulin resistance and atherogenic lipid profiles in nonobese, apparently healthy subjects.

1. Introduction

The recently identified adiponectin is a novel peptide expressed specifically and abundantly in adipose tissue [1]. Adiponectin has been associated with lipid metabolism [2,3], glucose metabolism [4], and insulin resistance [2,3,5]. Furthermore, adiponectin plays a role as an anti-inflammatory factor and is related to the development of atherosclerosis, hypertension, and coronary heart disease [6-9], which may directly contribute to the development of other obesity-related diseases [10,11]. Excess body fat, specifically abdominal visceral fat accumulation, is frequently accompanied by hypoadiponectinemia, a known mediator of the association between obesity and atherosclerotic vascular diseases [12].

Understanding the clinical implications of plasma adiponectin levels may be helpful in preventing the development of atherosclerotic vascular diseases. However, the role of hypoadiponectinemia in nonobese healthy adults has not been fully elucidated, and to our knowledge, plasma adiponectin levels and their association with cardiovascular risk factors have not been previously reported in nonobese healthy adults.

In this study, we examined the association between hypoadiponectinemia and cardiovascular risk factors such as insulin resistance, atherogenic lipid profiles, and high-sensitivity C-reactive protein (hs-CRP). Furthermore, we estimated plasma adiponectin values in nonobese, apparently healthy Korean adults.

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2. Subjects and methods

2.1. Subjects

Study participants were recruited from a health promotion center in a women's hospital in Seoul, South Korea. They visited the hospital for their periodic health examination, and no intervention of lifestyle modification was made for the subjects in this study. A total of 204 male and 214 female patients from 20 to 80 years of age and with body mass index (BMI) of less than 25 kg/m^2 were included in this study.

To recruit a healthy study population, we excluded patients with high blood pressure (mean systolic blood pressure >140 mm Hg or mean diastolic blood pressure > 90 mm Hg after 2 consecutive measurements), high fasting glucose levels (≥126 mg/dL), abnormal liver function tests (aspartate aminotransferase >35 IU/L or alanine aminotransferase >35 IU/L), or current illnesses (hypertension, diabetes mellitus, and liver disease).

2.2. Anthropometric evaluation

Body weight was measured to the nearest 0.1 kg on an electronic scale. Patients were weighed in light clothing without shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. BMI was calculated as the weight in kilograms divided by the square of height in meters.

2.3. Biochemical analyses

Biochemical tests were performed on blood samples collected after fasting for more than 12 hours. Venous blood was drawn, and after centrifugation, the serum and plasma were immediately frozen in a −80°C freezer. Serum levels of fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride were assayed using an ADVIA 1650 Chemistry system (Bayer, Tarrytown, NY). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula [13]. Fasting insulin was assayed by electrochemiluminescence immunoassay using an Elecsys 2010 (Roche, Indianapolis, IN). hs-CRP was measured by a latex-enhanced immunoturbidimetric assay using an ADVIA 1650 Chemistry system (Bayer), and the inter- and intra-assay variability was 2.70% ± 1.13% and 2.55% ± 1.0%, respectively. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index: [insulin (μIU/mL) × fasting blood glucose (mg/dL)/18]/22.5. Plasma adiponectin levels were measured by an enzyme immunoassay kit (AdipoGen, Seoul, Korea), and the inter- and intra-assay variability was 4.63% ± 0.82% and 2.72% ± 0.52%, respectively.

Table 1
Clinical and metabolic characteristics of study subjects

Characteristics	Male (n = 204)	Female (n = 214)	*P*
Age (y)	47.2 ± 14.3	45.5±14.2	.21
BMI (kg/m^2)	22.1 ± 1.94	21.8 ± 2.0	.06
Blood pressure (mm Hg)			
Systolic	120.3 ± 11.4	115.0 ± 11.7	<.01
Diastolic	72.5 ± 8.1	69.4 ± 8.9	<.01
Adiponectin (μg/mL)	5.45 ± 3.3	8.16 ± 4.6	<.01
<4.0[a]	81 (39.7)	48 (22.4)	<.01
≥4.0	123 (60.3)	166 (77.6)	
Glucose tolerance index			
Fasting glucose (mg/dL)	94.4 ± 9.4	90.0 ± 9.8	<.01
Fasting insulin (μIU/mL)	4.4 ± 2.6	4.2 ± 2.3	.52
HOMA-IR	1.04 ± 0.6	0.96 ± 0.6	.22
Lipid profile			
Total cholesterol (mg/dL)	176.0 ± 31.3	175.3 ± 28.9	.83
Triglyceride (mg/dL)	117.9 ± 60.7	90.6 ± 47.4	<.01
HDL-C (mg/dL)	51.4 ± 11.4	57.7 ± 12.1	<.01
LDL-C (mg/dL)	101.0 ± 27.6	99.5 ± 24.4	.56
hs-CRP (mg/mL)	0.1 ± 0.45	0.08 ± 0.28	.62

Data are shown as mean ± SD. *P* values are calculated by *t* test.

[a] Plasma adiponectin concentrations were classified into 2 categories: less than 4.0 μg/mL (hypoadiponectinemia) and 4.0 μg/mL or more.

Table 2
Plasma adiponectin values according to age and sex in nonobese male and female subjects

Sex	Age	Adiponectin (μg/mL)	
		n	Mean ± SD
Male*	20-29	33	6.41 ± 3.3
	30-39	39	3.96 ± 1.7
	40-49	41	4.98 ± 2.5
	50-59	40	5.04 ± 3.0
	60-69	37	6.52 ± 4.6
	≥70	14	7.05 ± 3.8
	Total	204	5.45 ± 3.3
Female	20-29	40	9.44 ± 5.1
	30-39	42	7.13 ± 4.3
	40-49	42	7.53 ± 4.4
	50-59	41	8.24 ± 4.8
	60-69	40	8.24 ± 4.4
	≥70	9	9.63 ± 4.9
	Total	214	8.16 ± 4.6

Data are shown as mean ± SD.

* $P < .05$ (plasma adiponectin levels in males were significantly different between age groups).

2.4. Statistical analyses

Data are expressed as mean ± SD. Variables such as plasma adiponectin, hs-CRP, fasting insulin, and HOMA-IR were logarithmically transformed before statistical analysis to approximate a normal distribution. Clinical characteristics and plasma adiponectin levels between sexes were compared using a *t* test for continuous variables. An analysis of variance was performed to assess the differences in adiponectin levels between age groups in both sexes. Plasma adiponectin concentrations were classified into 2 categories, less than 4.0 μg/mL (hypoadiponectinemia) and 4.0 μg/mL or more as previously described [7,14,15], and differences of clinical characteristics and study variables between the 2 groups were evaluated by *t* test. Pearson correlation coefficients were calculated to evaluate a relationship between plasma adiponectin levels and study variables such as age, blood pressure, lipid profiles, fasting glucose, BMI, hs-CRP, and HOMA-IR. Multiple linear regression analysis was used to determine the

Table 3
Clinical characteristics by adiponectin levels

Characteristics	Adiponectin			P
	All	<4.0[a] μg/mL	≥4.0 μg/mL	
	n = 418	n = 129	n = 289	
Age (y)	46.3 ± 14.2	45.3 ± 13.2	46.8 ± 14.7	.31
BMI (kg/m^2)	21.9 ± 2.0	22.6 ± 1.6	21.7 ± 2.0	<.01
Blood pressure (mm Hg)				
Systolic	117.6 ± 11.9	116.3 ± 11.7	118.1 ± 12.0	.15
Diastolic	70.9 ± 8.7	70.0 ± 8.2	71.3 ± 8.9	.17
Adiponectin (μg/mL)	6.8 ± 4.3	2.9 ± 0.7	8.6 ± 4.0	<.01
Glucose tolerance index				
Fasting glucose (mg/dL)	92.1 ± 9.9	94.5 ± 10.1	91.1 ± 9.6	<.01
Fasting insulin (μIU/mL)	4.3 ± 2.4	4.8 ± 2.2	4.1 ± 2.5	<.01
HOMA-IR	1.0 ± 0.6	1.14 ± 0.6	0.94 ± 0.6	<.01
Lipid profile				
Total cholesterol (mg/dL)	175.6 ± 30.1	174.6 ± 29.7	176.1 ± 30.2	.63
Triglyceride (mg/dL)	103.9 ± 56.0	116.5 ± 62.0	98.3 ± 52.1	<.01
HDL-C (mg/dL)	54.6 ± 12.2	49.6 ± 11.4	56.8 ± 11.9	<.01
LDL-C (mg/dL)	100.3 ± 26.0	101.6 ± 26.1	99.7 ± 26.0	.48
hs-CRP (mg/mL)	0.09 ± 0.38	0.08 ± 0.22	0.09 ± 0.43	.85

Data are shown as mean ± SD. *P* values are calculated by *t* test.
[a] Plasma adiponectin concentrations were classified into 2 categories: less than 4.0 μg/mL (hypoadiponectinemia) and 4.0 μg/mL or more.

interactions between plasma adiponectin levels and study variables. $P < .05$ was considered statistically significant. All calculations were performed using the Statistical Package for Social Sciences software, version 10.0 (SPSS, Chicago, IL).

3. Results

The clinical characteristics of male and female patients are shown in Table 1. There was no significant difference in mean age, BMI, fasting insulin, HOMA-IR, total cholesterol, LDL-C, or hs-CRP levels between the 2 subject groups. In contrast, blood pressure, fasting glucose, and triglyceride levels were significantly lower in females, but HDL-C was significantly higher in female compared with male subjects ($P < .01$ for all). Plasma adiponectin levels were significantly higher in females than in males (8.16 ± 4.6 and 5.45 ± 3.3 μg/mL, respectively; $P < .01$). Plasma adiponectin levels were highest in the second and lowest in the third decade of age in both sexes. In males, plasma adiponectin levels tended to increase with age after the third decade. Plasma adiponectin levels between age groups showed significant differences in males ($P < .05$), but not in females, as shown in Table 2.

The prevalence of hypoadiponectinemia (<4.0 μg/mL) was significantly higher in men than in women ($P < .01$). Subjects with hypoadiponectinemia had significantly higher levels of BMI, fasting glucose, fasting insulin, HOMA-IR, and triglyceride, but lower levels of HDL-C ($P < .01$, respectively) (Table 3).

In males, plasma adiponectin levels were inversely correlated with BMI ($r = -0.32$, $P < .01$), HOMA-IR ($r = -0.14$, $P < .05$), triglyceride levels ($r = -0.17$, $P < .05$), and hs-CRP levels ($r = -0.15$, $P < .05$), and positively correlated with HDL-C ($r = 0.24$, $P < .01$). In females, plasma adiponectin levels were negatively correlated with BMI ($r = -0.31$, $P < .01$), fasting glucose ($r = -0.18$,

Table 4
Correlations between adiponectin levels and various parameters

	Adiponectin			
	Male		Female	
	r	P	r	P
Age (y)	0.12	.09	0.03	.66
BMI (kg/m^2)	−0.32	<.01	−0.31	<.01
Blood pressure (mm Hg)				
Systolic	0.01	.99	0.13	.05
Diastolic	0.06	.36	0.13	.05
Glucose tolerance index				
Fasting glucose (mg/dL)	−0.07	.34	−0.18	<.01
Fasting insulin (uIU/mL)	−0.14	.05	−0.23	<.01
HOMA-IR	−0.14	<.05	−0.24	<.01
Lipid profile				
Cholesterol (mg/dL)	−0.09	.23	0.10	.14
Triglyceride (mg/dL)	−0.17	<.05	−0.18	<.01
HDL-C (mg/dL)	0.24	<.01	0.37	<.01
LDL-C (mg/dL)	−0.12	.08	0.01	.90
hs-CRP (mg/mL)	−0.15	<.05	−0.12	.09

Coefficients (*r*) and *P* values are calculated by Pearson correlation model.

Table 5
Multiple regression analysis[a] to assess independent relationships between adiponectin levels and clinical variables

Variables	Parameter estimate	SE	P
Sex	0.119	0.023	<.01
Age (y)	0.002	0.001	<.01
BMI (kg/m^2)	−0.030	0.006	<.01
HOMA-IR	−0.078	0.045	.08
HDL-C (mg/dL)	0.005	0.001	<.01
LDL-C (mg/dL)	−0.001	0.001	.22
hs-CRP (mg/mL)	−0.020	0.014	.15

[a] Calculated by multiple regression model using adiponectin as the dependent variable. $R^2 = 0.268$.

$P < .01$), fasting insulin ($r = -0.23$, $P < .01$), HOMA-IR ($r = -0.24$, $P < .01$), and triglyceride levels ($r = -0.18$, $P < .01$), and positively correlated with HDL-C ($r = 0.37$, $P < .01$), as shown in Table 4.

Sex, age, BMI, and HDL-C ($P < .01$, respectively) were found to be independent factors associated with plasma adiponectin levels in multivariate linear regression analysis as shown in Table 5.

4. Discussion

In the present study, we found that plasma adiponectin levels of nonobese male and female patients 20 to 80 years old were significantly higher in females than in males. Sex-based differences in plasma adiponectin levels are supported by previous studies [16-19] and could be explained by sex differences in body fat distributions [20]. However, sex differences could result from an additional independent factor (eg, androgen) that modulates adiponectin concentrations [18].

We found that plasma adiponectin levels between age groups were significantly different in males and tended to be higher in the elderly (≥60 years old) than in younger participants for both sexes. Previous studies [16,20,21] have reported a significant correlation of adiponectin concentrations with age. However, Nishizawa et al [18] and Ryan et al [22] have suggested that adiponectin concentrations may not differ by age. It is known that the concentration of adiponectin in the elderly is higher than in younger persons [20,23]. Investigations using mice revealed that androgens might inhibit the production of adiponectin [18], and that a decrease in sex hormones with aging might induce a sex difference in the presence of elevated adiponectin [24].

In our cohorts of Korean nonobese adults, the prevalence of hypoadiponectinemia (<4.0 μg/mL) was 40.7% in men and 22.0% in women, which was higher than in a previous report of Japanese patients [7]. Ryo et al [14] observed a prevalence of hypoadiponectinemia in Japanese adults of 22.8% in men and 8.8% in women. Given that the Japanese study included patients with obesity and metabolic diseases, the difference in the prevalence of hypoadiponectinemia in the general population might be much larger than reported by these 2 studies. The implications of this racial difference remain to be elucidated.

In this study, the hypoadiponectinemia group had significantly higher levels of BMI, fasting glucose, fasting insulin, HOMA-IR, and triglyceride, and lower levels of HDL-C than the normal group. This suggests that subjects with lower plasma adiponectin levels have a higher risk of cardiovascular disease in nonobese healthy adults. Tsukinoki et al [15] reported higher levels of BMI, blood pressure, total cholesterol, and fasting glucose, but lower levels of HDL-C in the hypoadiponectin group, which is consistent with the results of this study. Adiponectin levels can be linked to whole-body insulin sensitivity, and hypoadiponectinemia might play a causative role in the development of insulin resistance [25]. Hypoadiponectinemia may be directly linked to early atherosclerotic vascular damage and subsequent endothelial dysfunction [26]. Decreased plasma levels of adiponectin may serve as a marker of increased metabolic and inflammatory risk [27]. These data are in line with the prediction of insulin sensitivity for both glucose and lipid metabolism by plasma adiponectin levels [28].

We confirmed that plasma adiponectin levels were inversely correlated with levels of BMI, fasting glucose, fasting insulin, HOMA-IR, triglyceride, and LDL-C, but positively correlated with HDL-C. All of these results are in good agreement with previous reports. Shand et al [17] observed a direct correlation in both sexes between adiponectin levels and HDL-C, and age. Park et al [29] demonstrated that adiponectin levels were inversely correlated with levels of fasting insulin, HOMA-IR, triglyceride, and systolic blood pressure, but positively correlated with HDL-C. Yamamoto et al [30] reported that serum adiponectin levels were negatively correlated with HOMA-IR and positively correlated with HDL-C, independent of age, sex, and BMI in the Japanese population.

CRP is a sensitive marker of inflammation and is known to be independently associated with cardiovascular diseases and constituents of the metabolic syndrome [31-33]. In the present study, we found an inverse association between hs-CRP levels and adiponectin levels in male subjects. These results are consistent with some studies [27,34-36]. It is well known that adiponectin possesses anti-inflammatory and antiatherogenic properties. In vitro studies have shown that adiponectin inhibits monocyte adhesion to endothelial cells and suppresses macrophage to foam cell transformation. Furthermore, adiponectin attenuates the production and action of tumor necrosis factor α, which may influence interleukin 6 and CRP production. Considering these mechanisms, adiponectin may affect serum CRP levels through modulation of inflammatory cascades [6,37,38].

Because of the limitations inherent in cross-sectional studies, further prospective studies are necessary to clarify the relationship between hypoadiponectinemia and cardiovascular disease in nonobese subjects.

In conclusion, we estimated plasma adiponectin values in nonobese Korean males and females, and showed that there were age and sex differences in adiponectin level elevation. The present findings suggest that lower plasma adiponectin levels are significantly associated with cardiovascular risk factors such as insulin resistance and atherogenic lipid profiles in nonobese, healthy adults.

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