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Original Article

Adiponectin represents an independent risk factor for hypertension in middle aged Korean women

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Adiponectin, which is secreted specifically by adipose tissue, has been shown to act as an anti-atherosclerotic protein. Several studies have shown that adiponectin levels are lower in individuals with obesity, diabetes and cardiovascular disease. The present study investigated relationships between serum adiponectin levels and body mass index (BMI), waist-to-hip ratio (WHR), blood pressure (BP) and lipid profiles in 300 middle-aged Korean women (mean age 50.6 ± 6.2; BMI 25.8 ± 3.68 kg/m^2). The serum adiponectin level was positively associated with high density lipoprotein (HDL)-cholesterol (r = 0.29) and negatively associated with BMI, WHR, percent body fat, triglyceride (TG), systolic BP, and diastolic BP. Multivariable logistic regression analysis revealed that increasing concentrations of adiponectin were associated with lower risk of hypertension. In overall odds ratios (95% CIs) for hypertension, those in the second, third, and fourth (versus the first) quartile of adiponectin after adjustment for age were 0.59 (0.30 – 1.19), 0.47 (0.24 – 0.94), and 0.32 (0.16 – 0.65), respectively. Regardless of BMI, WHR and percent body fat, higher adiponectin was independently associated with a lower risk of hypertension. These findings suggest that the serum adiponectin level is decreased with atherogenic lipid phenotype including hypertriglyceridemia and low HDL-cholesterol. Furthermore, low serum adiponectin concentration may be an independent risk factor for hypertension in middle-aged Korean women.

Key Words: adiponectin, hypertension, blood pressure, middle-aged Korean women

Introduction

Adiponectin is an important adipokine, specifically secreted by the adipocytes, that circulates in abundance in the blood. Adiponectin is one of the key molecules linked to the metabolic syndrome and vascular disease.[1,2] Its concentration is decreased in obesity,[3,4] type-II diabetes,[5-7] and coronary artery disease.[8,9] Furthermore, adiponectin has been reported to be associated with lipid metabolism,[1,10,11] insulin resistance, [1,12] anti-inflammatory actions[13] and blood pressure.[14-16] Obesity is associated with low levels of the gene product of adiponectin, whereas weight loss increases adiponectin levels.[3,17,18] Yokota *et al.,*[19] reported that adiponectin inhibits pre-adipocyte differentiation and thus might contribute to the regulation of fat growth.

Hypertension is a major trigger of cardiovascular complications, and it is also a component of the metabolic syndrome. Hypertensive patients tend to have higher body mass index (BMI), increased triglyceride (TG) levels, and more insulin resistance compared with normotensive subjects.[20] A few studies have shown that there is an association between hypoadiponectinemia and hypertension in humans. Plasma adiponectin was significantly lower in patients with essential hypertension than in normotensive healthy subjects and a significant negative correlation was found between plasma adiponectin and blood pressure.[15] Furuhashi *et al.,*[21] reported that it is the hypertensive patients with insulin resistance who show lower adiponectin concentrations. However, Mallamaci *et al.,*[22] found that adiponectin concentration was increased in hypertensive patients with renal dysfunction. Young Japanese men (18-26 years) with high-normal blood pressure had lower serum adiponectin than those with optimal blood pressure.[14] Although adiponectin seems to be negatively associated with hypertension, several studies were of small number of subjects or did not adjuste for confounders. Since the effect of adiponectin on hypertension may differ with age, gender, and health status, the relationship should be investigated among subjects with specific conditions. Recently, Iwashima *et al.,*[23] reported that adiponectin independently affects the risk of hypertension after adjusting for age, BMI, TG, and high density lipoprotein (HDL)-cholesterol. Hypoadiponectinemia is a marker for predisposition to hypertension in men whose mean age is 58.4±0.4 years. However, the association between the plasma adiponectin concentration and hypertension in women has not been clearly elucidated.

Therefore, we examined the relationships between plasma adiponectin, anthropometric indices, and various

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metabolic factors, and tested whether low serum adiponectin concentration is a risk factor for hypertension among middle aged Korean women.

Subject and methods

Study participants and study design

The 1,007 free-living residents, aged over 30 years were randomly selected from 2 urban and 6 rural areas of Chuncheon city, Kangwon-Province, South Korea. They were recruited for a community assessment program. Data from 300 women aged 30-60 years were selected for this study. The participants provided their general characteristics during an interview using a structured questionnaire, and anthropometric measurements such as weight, height, waist and hip circumference were measured by the bioelectric impedance analysis (Inbody 3.0, Biospace Co., Korea). Blood pressure was measured with a standard mercury sphygmomanometer after the subjects had rested at least 10 min. Fasting blood samples were collected in plain tubes, placed on the container with ice packs, and returned to the laboratory within 24 hours. The blood sample was centrifuged, aliquoted into serum, and stored in -70°C until analysis.

Informed consent was obtained from each subject after full explanation of the purpose, procedures and risks of the study. The protocol was approved by the Institutional Review Board of the School of Public Health, Seoul National University.

Biochemical analysis

Fasting blood parameters, such as total cholesterol TG, HDL-cholesterol, were determined with standard colorimetric methods using the autoanalyzer (TBA 200FR, Japan). Serum adiponectin concentration was evaluated by using the commercially available ELISA kits (R&D system, USA).

Statistical analysis

Subjected were stratified into quartiles of serum adiponectin levels (< 4.51, < 7.52, < 10.8, and ≥ 10.8 μg/dl). The differences of anthropometric measurements and blood parameters across quartiles were tested with ANOVA. Pearson correlation coefficients were reported for relationships among variables. Linear regression was performed to determine parameter estimates and *p* values for the adiponectin concentrations in relation to the plasma lipids. Multiple logistic regression analysis was used to predict odds ratios of hypertension from serum adiponectin concentration adjusted for other risk factors such as cholesterol, TG, BMI, percent body fat, WHR, age, usual appetite, salty food preference, and menopause. *p* value less than 0.05 was considered to be statistically significant.

Table 1. Clinical characteristics of subjects

	N (%)
Menopause	
Menopausal women	164 (56.4)
Non-menopausal women	127 (43.6)
Body mass index (kg/m^2)	
< 25.0	136 (45.3)
25.0 - 27.5	130 (43.3)
≥27.5	34 (11.3)
Hypertension	
Hypertensive	159 (53.0)
Normotensive	141 (47.0)
Percent body fat	
≤ 28.0	50 (16.7)
> 28.0	250 (83.3)
Waist-to-hip ratio	
≤ 0.9	111 (37.0)
> 0.9	189 (63.0)

Results

Characteristics of the study participants are shown in Table 1. The percentage of menopausal women was 56.4%, and that of overweight or obese subjects (BMI ≥ 25) was 55.7%. About 83% of the subjects had over 28% of body fat and 63.0% had a WHR of 0.9. The Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg on repeated measurements, or receiving antihypertensive treatment.[24] Of the subjects, 53.0% were classified as being hypertensive.

Clinical characteristics are shown in Table 2. The means of plasma adiponectin concentration, BMI, WHR, and percent body fat were 8.38 ± 5.06 μg/mL, 25.78 ± 3.68kg/m^2, 0.92 ± 0.06, and 33.1 ± 5.54%, respectively. The means of total cholesterol, HDL-cholesterol, and TG concentrations were 204 ± 37.6mg/dL, 55.7 ± 12.5mg/dL, and 138±75.7 mg/dL, respectively. Compared with subjects in a high adiponectin quartile, subjects in the low adiponectin quartile were characterized by higher

Table 2. Characteristics of study subjects by quartiles of circulating adiponectin

		Quartiles of adiponectin			
Variable	All	1	2	3	4
Age (yr)	50.6 ± 6.2	50.2 ± 6^a	51.0 ± 6^a	50.5 ± 6.4^a	50.6 ± 6.5^a
Adiponectin (μg/dL)	8.38 ± 5.06	3.2 ± 1.2^a	6.3 ± 0.7^b	9.2 ± 0.9^c	14.9 ± 4.9^d
Body mass index (kg/m^2)	25.8 ± 3.68	27.1 ± 3.8^a	26.1 ± 3.1^{ab}	25.3 ± 3.8^{bc}	24.6 ± 3.4^c
Waist-to-hip ratio	0.92 ± 0.06	0.94 ± 0.05^a	0.93 ± 0.06^a	0.92 ± 0.07^{ab}	0.90 ± 0.06^b
Percent body fat (%)	33.1 ± 5.54	34.4 ± 5^a	33.5 ± 5^a	33.0 ± 5.8^{ab}	31.5 ± 6.1^b
Systolic blood pressure (mmHg)	128 ± 19.1	131 ± 17.5^a	132 ± 18.8^{ab}	127 ± 21.9^{ab}	125 ± 17.4^b
Diastolic blood pressure (mmHg)	84.9 ± 12.7	86.7 ± 12.5^a	86.9 ± 12.8^a	84.1 ± 12.8^{ab}	81.7 ± 12^b
Cholesterol (mg/dL)	204 ± 37.6	202 ± 31.7^a	202 ± 39.1^a	204 ± 42.9^a	207 ± 36.3^a
Triglyceride (mg/dL)	55.7 ± 12.5	49.4 ± 9.3^a	55.4 ± 12.7^b	56.4 ± 10.4^b	61.5 ± 14.3^c
HDL-cholesterol (mg/dL)	138 ± 75.7	170 ± 89.3^a	136 ± 75.9^b	124 ± 67.2^b	121 ± 59^b
Protein (mg/dL)	7.8 ± 0.4	7.8 ± 0.4	7.8 ± 0.5	7.8 ± 0.4	7.8 ± 0.4

Mean ± standard deviation
(a, b, c; Different letters in the same raw mean significant differences among groups at ANOVA)

Table 3. Correlations between several parameters and serum adiponectin

	Age	Adiponectin	BMI	WHR	Body fat percent	SBP	DBP	TC	HDL-C
Age									
Adiponetin	-0.010								
BMI	0.248^{***}	-0.237^{***}							
WHR	0.425^{***}	-0.200^{***}	0.896^{***}						
Body fat percent	0.324^{***}	-0.182^{**}	0.843^{***}	0.933^{***}					
SBP	0.323^{***}	-0.120^{*}	0.353^{***}	0.369^{***}	0.277^{***}				
DBP	0.302^{***}	-0.123^{*}	0.318^{***}	0.317^{***}	0.244^{***}	0.772^{***}			
TC	0.272^{***}	0.052	0.165^{**}	0.268^{***}	0.250^{***}	0.128^{*}	0.119^{*}		
HDL-C	-0.096	0.285^{***}	-0.251^{***}	-0.207^{***}	-0.212^{***}	-0.114^{*}	-0.102	0.221^{***}	
TG	0.187^{*}	-0.167^{**}	0.296^{***}	0.339^{***}	0.302^{***}	0.153^{**}	0.170^{**}	0.263^{***}	-0.40653^{***}

BMI; body mass index, WHR; Waist-to-hip ratio, SBP; systolic blood pressure, DBP; Diastolic blood pressure, TC; total cholesterol, HDL-C; high density lipoprotein cholesterol; $^{***}p < 0.001$ $^{**}p < 0.01$ $^{*}p < 0.05$ by Pearson's correlation

Table 4. Parameter estimates and p values for the adiponectin concentrations in relation to plasma lipids

	TC		HDL-C		TG	
	Estimate	p-value	Estimate	*p*-value	Estimate	*p*-value
All	0.404	0.330	0.704	<.001	-2.48	<.005
Blood pressure						
Hypertensive	0.672	0.280	0.661	<.001	-3.37	0.011
Normotensive	0.313	0.587	0.679	<.005	-1.34	0.227
BMI						
BMI < 25.0	0.770	0.173	0.714	<.001	-0.935	0.354
25 ≤ BMI < 27.5	-0.427	0.715	0.572	0.103	-3.70	0.110
BMI ≥ 27.5	0.053	0.489	0.418	0.100	-1.75	0.306
WHR						
WHR < 0.9	0.975	0.071	0.729	<.001	0.101	0.913
WHR ≥ 0.9	0.315	0.611	0.564	<.005	-3.28	0.011
Percent body fat						
Fat percent < 28.0	0.756	0.447	0.787	<.005	-3.29	0.046
Fat percent ≥ 28.0	0.425	0.353	0.619	<.001	-1.85	0.051

Adjusted for age

Table 5. Odd ratios of hypertension for adiponectin and obesity parameters

		Model 1			Model 2			Model 3			Model 4		
		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI	
Age		1.11	1.07	1.16	1.10	1.05	1.15	1.11	1.07	1.16	1.09	1.04	1.14
Adiponectin	q1	1.00			1.00			1.00			1.00		
	q2	0.59	0.30	1.19	0.64	0.32	1.29	0.59	0.29	1.18	0.63	0.31	1.26
	q3	0.47	0.24	0.94	0.57	0.28	1.15	0.46	0.23	0.93	0.54	0.27	1.09
	q4	0.32	0.16	0.65	0.40	0.19	0.82	0.32	0.16	0.64	0.36	0.18	0.74
BMI < 25.0					1.00								
25 ≤ BMI < 27.5					1.22	0.67	2.22						
BMI ≥ 27.5					2.35	1.26	4.37						
Fat percent < 28.0								1.00					
Fat percent ≥ 28.0								0.90	0.46	1.79			
WH ratio < 0.9											1.00		
WH ratio ≥ 0.9											2.23	1.30	3.83

Data are expressed as odds ratio and confidence interval. Usual appetite, salty food preference, lipid parameters, and menopause were not included since those are not significant variables in all models. Dependent variable is hypertension for all models, and independent variables are listed in the left column of the table.

HDL-cholesterol, where as there was no difference in total cholesterol. In addition, subjects in the low adiponectin quartile had a higher BMI, WHR, percent body fat, blood pressure, and TG.

In simple correlation analysis (Table 3), adiponectin was positively associated with HDL-cholesterol (r = 0.29). In contrast, adiponectin showed negative associations with BMI (r = -0.24), WHR (r = -0.20), percent body fat (r = -0.18), and TG (r = -0.17) although there were no associations with age and total cholesterol. There were also weak but significant associations with systolic BP and diastolic BP (both r = -0.12).

We used linear regression analysis to estimate the change in blood lipids required for an increase in adiponectin by 1μg/ml, adjusting for age (Table 4). A 1μg/ml increase in plasma adiponectin was associated with a 0.704 mg/dl increase in HDL-C and a 2.48 mg/dl decrease in TG. These associations remained significantly after dividing the subject into several subgroups by blood pressure, BMI, WHR, or percent body fat.

Based on these associations, we further assessed the role of adiponectin, BMI, WHR, and percent body fat as a determinant of hypertension and its independence by multivariable logistic regression analysis (Table 5). Increasing concentrations of adiponectin were found to be associated with lower risk of hypertension. Odds ratios (95% CIs) for hypertension, in the second, third, and fourth (versus the first) quartile of adiponectin after adjusting for age were 0.59 (CI 0.30 – 1.19), 0.47 CI 0.24 – 0.94), and 0.32 (CI 0.16 – 0.65), respectively (Model 1). When the BMI was introduced to the model 1, those with a BMI ≥ 27.5 were 2.35 times more likely to develop hypertension than those in the BMI < 25 (CI 1.26 – 4.37), and subjects with a BMI between 25 and 27.5 were 1.22 times more likely to have hypertension than those with a BMI < 25 (Model 2). When WHR was introduced to model 1, those with a WHR ≥ 0.9 were 2.23 times more likely to develop hypertension than those with a WHR < 0.9 (CI 1.30 – 3.83) (Model 4). The results showed that lower BMI and lower WHR were associated with a lower incidence of hypertension. In fact, the subjects within the highest adiponectin quartile still had a significantly lower odds ratio when BMI, WHR, percent body fat was introduced in model 2, 3, and 4. This implies that serum adiponectin concentration is independently negatively associated with hypertension regardless BMI, WHR or percent body fat.

Discussion

Most of the studies related to adiponectin examine the role of adiponectin in insulin resistance or diabetes, but not in hypertension. Our results show that blood pressure is significantly associated with adiponectin concentration which is consist with previous researches.[14,15,22] However, the causal association between hypoadiponectinemia, obesity, and hypertension has not yet been clearly elucidated. Thus, our study focused on whether or not hypertension risk is dependent on the adiponectin concentrations among middle aged women.

This study showed that adiponectin is negatively associated with blood pressures BMI, WHR, percent body fat and TG, but positively with HDL-cholesterol in middle aged Korean women. The multiple logistic regression analysis strongly supported that adiponectin is independently negatively associated with hypertension regardless BMI, WHR or percent body fat. Since blood pressure increased significantly with increasing aging and percent body fat, we adjusted age and indicator of obesity.[25-27] We found that serum adiponectin levels were negatively correlated with SBP and DBP, and that low serum adiponectin level was an independent risk factor for hypertension like others. Even though a few studies showed that adiponectin levels were not reduced in normotensives, non-insulin-resistant hypertensives or overweight subjects,[17,21,22] our multiple logistic results was very strong to prove our hypothesis.

For lipid profiles, individuals with a higher adiponectin level had higher HDL-cholesterol and lower TG concentrations. These results indicate that low risk factors of atherosclerosis such as high HDL and low TG may improve endothelial dysfunction to protect hypertension and 'adiponectin resistance', similar to concept of insulin resistance.[5,28] There is limited evidence to support our results that the negative correlation between hypertension and plasma adiponectin. Firstly, adiponectin was correlated to vasodilator response; secondly, adiponectin decreases high sensitive C-reactive protein; and thirdly, the rennin-angiotensin system may be induced with high fat mass by hypoadiponectinemia.[23,29,30]

In conclusion, this study showed that hypoadiponectinemia independently affects the hypertension risk – regardless of BMI, WHR or percent body fat - and is associated with hypertriglyceridemia and low HDL-cholesterol in middle aged Korean women. Therefore, adiponectin might improve endothelial pathogenic conditions such as hypertension, atherosclerosis and the metabolic syndrome.

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Original Article

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脂締素為韓國中年婦女罹患高血壓的獨立危險因子

脂締素由脂肪組織所分泌，是抗動脈粥狀腫的蛋白質。幾個研究指出在肥胖、糖尿病及心血管疾病患者身上其脂締素濃度較低。本研究探討 300 名韓國中年婦女(平均年齡 50.6±6.2；BMI 25.78±3.68 公斤/公尺^2)的血清脂締素含量與身體質量指數(BMI)、腰臀圍比(WHR)、血壓(BP)及血脂質之相關性。血清脂締素含量與高密度脂蛋白(HDL)-膽固醇呈正相關(r=0.29)，與BMI、WHR、體脂肪百分比、三酸甘油脂(TG)、收縮壓及舒張壓呈現負相關。多元羅吉斯迴歸分析顯示脂締素的濃度增加與較低的高血壓危險性有關。在校正年齡之後，其第二、第三及第四(與最低四分位相比)四分位的脂締素濃度的整體高血壓勝算比(95%信賴區間)分別為 0.59(0.30-1.19)、0.47(0.24-0.94)及 0.32(0.16-0.65)。不論BMI、WHR或是體脂肪百分比，較高的脂締素均是較低的高血壓危險性的獨立預測因子。這些結果指出粥狀腫脂質表現型，包含高三酸甘油脂血症及低HDL-膽固醇其血清脂締素含量較低。低血清脂締素濃度可能是韓國中年婦女高血壓的獨立危險因子。

關鍵字:脂締素、高血壓、血壓、韓國中年婦女。