Original Article

Adiponectin Levels Associated with the Development of Hypertension: A Prospective Study

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Adiponectin is a recently discovered protein that seems to be exclusively secreted by adipocytes and is the most abundant adipose tissue–derived protein. While some recent studies have demonstrated an association between adiponectin levels and hypertension, these studies were cross-sectional in design, and the results have been inconsistent. Therefore we performed a prospective study to elucidate the role of adiponectin in the development of hypertension. The results of this study showed that serum adiponectin levels were significantly lower in hypertensive subjects than in normotensive subjects. Moreover, in logistic regression analysis, the subjects in the lowest quartile had a 3.72-fold higher risk than those in the highest quartile. Even after adjusting for potential confounding factors, this association was found to be significant. Low serum adiponectin levels were found to be independently associated with a higher risk for the development of hypertension. Our results therefore suggest that hypoadiponectinemia is a novel predictor of hypertension. (*Hypertens Res* 2008; 31: 229–233)

***Key Words*: hypertension, adiponectin, prospective study, epidemiological study**

Introduction

The latest World Health Organization (WHO) projections indicate that approximately 1.6 billion adults (aged ≥15 years) are overweight and at least 400 million adults are obese. WHO further estimates that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. Because obese individuals are at risk of diabetes, hypertension, arteriosclerosis and other cardiovascular diseases, obesity and obesity-related diseases are a worldwide public health problem.

Adipose tissue is involved in regulating a variety of homeostatic processes as an endocrine organ that secretes many biologically active molecules. Adiponectin is a recently discovered protein that seems to be exclusively secreted by adipocytes and is the most abundant adipose tissue–derived protein (*1*, *2*). Plasma adiponectin levels in humans are lower in obese than in non-obese subjects, in patients with coronary artery disease and diabetes mellitus type 2 than in healthy subjects, higher in women than in men. A recent study reported that hypoadiponectinemia was significantly and independently associated with metabolic syndrome (*3*, *4*) and cardiovascular disease (*5–8*).

Hypertension is also a major trigger of cardiovascular complications and is associated with endothelial dysfunction and atherosclerosis. Though several cross-sectional studies have shown that adiponectin correlates negatively with blood pressure, the results of studies on the relation between adiponectin and hypertension have been inconsistent. Some recent studies have demonstrated an association between adiponectin levels and hypertension (*9–16*), but almost all these studies were

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Table 1. Baseline Demographic and Clinical Characteristics of Study Population Based on Serum Adiponectin Level Quartiles

Characteristics	Quartile 1 (n=93)	Quartile 2 (n=99)	Quartile 3 (n=100)	Quartile 4 (n=99)	p value
Follow-up period, years	4.2±0.6	4.1±0.5	4.2±0.5	4.2±0.6	0.46
Age, years	46.0±3.8	47.2±4.5	47.0±4.9	47.1±4.4	0.25
Smoking status, *n* (%)					
Non-smokers	28 (30.1)	28 (28.3)	17 (17.0)	28 (28.3)	0.37
Ex-smokers	9 (9.7)	10 (10.1)	8 (8.0)	9 (9.1)	
Current smokers	56 (60.2)	61 (61.6)	75 (75.0)	62 (62.6)	
Drinking status, *n* (%)					
Non-drinkers	12 (12.9)	8 (8.1)	13 (13.0)	15 (15.2)	0.81
Occasional drinkers	38 (40.9)	45 (45.5)	41 (41.0)	37 (37.4)	
Regular drinkers	43 (46.2)	46 (46.5)	46 (46.0)	47 (47.5)	
Body mass index, kg/m^2	24.8±2.5	23.6±2.6	22.8±2.6	21.4±2.6	<0.001
SBP, mmHg	122.7±10.2	120.4±10.9	118.5±11.3	119.0±10.9	<0.05
DBP, mmHg	76.7±8.9	76.0±8.6	73.4±9.1	72.9±9.0	<0.01

Data are expressed as mean±SD or *n* (%). SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Baseline Biochemical Characteristics of the Study Population Based on Serum Adiponectin Level Quartiles

Characteristics	Quartile 1 (n=93)	Quartile 2 (n=99)	Quartile 3 (n=100)	Quartile 4 (n=99)	p value
Serum adiponectin level, μg/mL					
Mean±SD	3.59±0.7	5.29±0.5	7.28±0.7	11.18±2.5	<0.001
Median (IQR)	3.70 (3.2–4.1)	5.30 (4.8–5.8)	7.20 (6.7–7.8)	10.60 (9.4–12.2)	
log-adiponectin level	1.27±0.2	1.66±0.1	1.98±0.1	2.39±0.2	<0.001
Triglyceride, mg/dL	288.63±159.2	191.64±159.2	137.64±66.3	132.65±277.8	
log-triglyceride	5.37±0.7	5.04±0.6	4.82±0.5	4.59±0.6	<0.001
Cholesterol level, mg/dL					
TC	206.28±35.9	200.92±34.1	197.76±36.0	195.04±31.9	0.13
LDL-C	109.24±28.8	107.72±28.6	109.94±31.2	103.72±26.9	0.43
HDL-C	50.86±8.7	56.78±12.7	61.11±15.5	69.99±14.2	<0.001
HbA1c, %	4.83±0.5	4.69±0.4	4.73±0.4	4.68±0.4	0.07

Data are expressed as mean±SD unless otherwise noted. IQR, interquartile range; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c.

small-sample clinical or case-control studies, and thus are not sufficient to establish a cause-effect relationship.

We therefore carried out a prospective study to elucidate the role of adiponectin in the development of hypertension.

Methods

Measurement

The study subjects were employees who belonged to health insurance society A in Fukuoka Prefecture, Japan. They received annual health check-ups in 2000. All the subjects were followed up at one of their health check-ups in the next 3 years: 53 subjects in 2003, 319 in 2004, and 122 in 2005.

Subjects with blood pressure ≥140/90 mmHg, and/or taking antihypertensive drugs (n=88), and/or with hemoglobin A1c (HbA1c) of ≥6.5% (n=15) at the time of the baseline data collection in 2000 were excluded. After these exclusions, 391 healthy men were included in this study.

Baseline adiponectin levels were determined in 2006 in archived serum samples that had been stored at −80°C. All of the subjects agreed to have their serum adiponectin levels measured. Height and weight were measured to calculate body mass index (BMI = weight in kg divided by the square of height in m). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured once using a standard mercury sphygmomanometer with the cuff on the right arm and the subjects in a sitting position. Hypertension was defined as an SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg and/or current use of antihypertensive medication. A questionnaire was used to obtain information on the subjects' smoking status and alcohol consumption.

Table 3. Crude and Adjusted Odds Ratios for Hypertension Based on Serum Adiponectin Level Quartiles

Variables	Normotensive *n* (%)	Hypertensive *n* (%)	Crude		Adjusted[a]	
			OR	95% CI	OR	95% CI
Serum adiponectin level						
>8.5 μg/mL	93 (26.9)	6 (13.3)	1.00	reference	1.00	reference
6.3–8.5 μg/mL	91 (26.3)	9 (20.0)	1.53	(0.52–4.48)	1.56	(0.52–4.68)
4.5–6.3 μg/mL	87 (25.1)	12 (26.7)	2.14	(0.77–5.94)	1.92	(0.66–5.63)
<4.5 μg/mL	75 (21.7)	18 (40.0)	3.72	(1.41–9.84)	3.42	(1.16–10.05)
			p for trend <0.01		p for trend 0.052	
Age (by 1 year)			1.01	(0.94–1.09)	1.03	(0.96–1.11)
Body mass index			1.10	(0.98–1.23)	1.04	(0.92–1.19)
Smoking status						
Non-smokers	87 (25.1)	14 (31.1)	1.00	reference	1.00	reference
Ex-smokers	31 (9.0)	5 (11.1)	1.00	(0.45–3.48)	0.81	(0.26–2.58)
Current-smokers	228 (65.9)	26 (57.8)	0.71	(0.35–1.42)	0.66	(0.32–1.36)
Drinking status						
Non-drinkers	45 (13.0)	3 (6.7)	1.00	reference	1.00	reference
Occasional drinkers	148 (42.8)	13 (28.9)	1.32	(0.36–4.83)	1.33	(0.36–4.99)
Regular drinkers	153 (44.2)	29 (64.4)	2.84	(0.83–9.77)	3.18	(0.90–11.26)

OR, odds ratio; CI, confidence interval. [a]Adjusted for age, body mass index, smoking status, drinking status.

Serum adiponectin levels were measured by a solid phase enzyme linked immunosorbent assay (ELISA) using a commercially available kit (adiponectin ELISA kit; Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan). Serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were measured enzymatically using commercial enzyme kits (Wako [Osaka, Japan] and Daiichi Kagaku [Tokyo, Japan], respectively). High-density lipoprotein cholesterol (HDL-C) was measured using the direct method. HbA1c was measured by latex agglutination using a commercially available kit (Fuji Rebio, Tokyo, Japan).

The study protocol was approved by the Ethics Committee of Fukuoka University and written informed consent was obtained from each participant.

Statistics

The characteristics of the subjects are presented as *n* (%), and geometric means and standard deviations. Variables with a skewed distribution were log-normal transformed for these analyses. Associations between adiponectin levels and various factors were analyzed by one-way analysis of variance (ANOVA) after organizing the data into quartiles according to adiponectin level. The χ^2 test was used for categorical data. Logistic regression analysis was used to assess the risk of development of hypertension in the quartiles of serum adiponectin. Results are presented as odds ratios (OR) together with their 95% confidence intervals (CI). A two-sided p value of <0.05 was considered to be statistically significant.

All analyses were performed using the Statistical Analysis System, Version 9.1 (SAS Institute, Cary, USA).

Results

In this study, serum adiponectin levels were divided into quartiles. The quartile cutoff points were 4.5, 6.3 and 8.5 μg/mL. Table 1 shows the basic characteristics of subjects by quartile at baseline. There were significant differences among the quartiles in BMI, SBP and DBP. By contrast, the differences in age, smoking status and drinking status were slight and not significant.

Table 2 shows that a low adiponectin level was significantly associated with high triglyceride levels ($p<0.001$). There was a significant tendency for HDL-C to increase with an increase in serum adiponectin levels ($p<0.001$).

Next, we carried out a logistic regression analysis to assess associations between the development of hypertension and potential risk factors. Forty-five subjects showed newly developed hypertension. As shown in Table 3, hypertensive subjects had lower serum adiponectin levels than normotensive subjects. Moreover, in logistic regression analysis, subjects in the bottom quartile had a significantly increased risk for new-onset hypertension compared to the top quartile (crude OR: 3.72; 95% CI: 1.41–9.84). This did not change with adjustment for potential confounding factors (adjusted OR: 3.42; 95% CI: 1.16–10.05). But adjusting for potential confounding factors attenuated the dose-response relationship between serum adiponectin level and the development of hypertension. The relationship was marginally significant (p for trend $=0.052$).

The logistic regression analysis showed that serum adiponectin levels were an independent factor associated with the development of hypertension.

Discussion

This prospective study assessed the association between serum adiponectin levels and hypertension. The results demonstrated that serum adiponectin levels were significantly lower in hypertensive subjects than in normotensive subjects. Moreover, in logistic regression analysis, subjects in the lowest quartile had a 3.72-fold greater risk of developing new-onset hypertension than those in the highest quartile. Even after adjusting for potential confounding factors, this association was significant. But the dose-response relationship between the development of hypertension and serum adiponectin levels was marginally significant.

The recently identified adiponectin is a novel peptide expressed specifically and abundantly in adipose tissue (*17*). Adiponectin levels in humans range from 0.5 to 30 μg/mL, which is 1,000-fold higher than the levels of other hormones, such as insulin and leptin (*18*). Some clinical and experimental studies have suggested that adiponectin may play a pivotal role in the development of vascular and metabolic diseases.

An association between hypertension and adiponectin levels has been reported by several groups. Kazumi *et al*. suggested that young Japanese men with high-normal blood pressure had lower adiponectin levels (*19*). Furuhashi *et al*. reported that adiponectin levels were significantly decreased in young, non-obese, normotensive men with a family history of essential hypertension (*20*). Lee *et al*. reported that higher adiponectin levels were independently associated with a lower risk of hypertension (*14*). Most recently, in a prospective study of a sample of the Chinese population, Chow *et al*. reported that normotensive subjects with baseline serum adiponectin levels in the lowest sex-specific tertile had a 2.76-fold higher risk of becoming hypertensive than those in the highest tertile (*15*). Our data are in line with the findings of the above-mentioned prospective study and also indicate that adiponectin plays an important role in the development of hypertension.

The mechanism by which adiponectin levels are lowered in patients with hypertension remains to be clarified, although there are several mechanisms that could account for the relationship. First, activation of the renin-angiotensin system (RAS) may be induced in adipose tissue by hypoadiponectinemia, resulting in an increase in fat mass and blood pressure (*21*). Furuhashi *et al*. reported that RAS blockade in essential hypertension increases adiponectin levels (*22*). Second, some studies have indicated that inflammation contributes to the pathogenesis of hypertension. Adiponectin seems to have several beneficial and protective effects, including anti-inflammatory, vasculoprotective and anti-diabetic effects. Adiponectin may play a key regulatory and anti-inflammatory role in the development of hypertension. Further study is therefore required.

The present study has certain limitations. First, the subjects were followed up to one of three different time points—*i.e.*, the health check-ups in 2003, 2004, and 2005—rather than to a single time point. However, each serum adiponectin quartile group had almost the same ratio of subjects participating and similar incidences of hypertension in each follow-up period. Second, because this study included only men, the findings cannot necessarily be extrapolated to women. Third, several important indicators of plasma adiponectin levels, such as body fat content and waist circumference, were not measured in our study. On the other hand, because longitudinal data was analyzed, this study may indicate a temporal relationship between lower serum adiponectin levels and the development of hypertension.

In conclusion, these findings show that a correlation exists between serum adiponectin levels and blood pressure. In addition, in logistic regression analysis, low adiponectin levels were associated with a higher risk of the development of hypertension. These results suggest that hypoadiponectinemia is a novel predictor of hypertension.

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