Acta Medica Okayama

Volume 63, *Issue* 6 2009 *Article* 3

DECEMBER 2009

Inverse Correlation between Adiponectin and the Risk of Metabolic Syndrome in Middle-aged Japanese Male Workers

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Abstract

Despite a close association between adiponectin and both hypertension and type 2 diabetes, the relationship between adiponectin and metabolic syndrome has not yet been well-investigated. To examine and evaluate the association between serum adiponectin levels and metabolic syndrome based on Japanese diagnostic criteria, we analyzed adiponectin and anthropometric parameters in 869 male employees aged 40-59 who belonged to a health insurance society in Fukuoka Prefecture and who underwent annual health check-ups from August 2006 to July 2007. Two hundred and thirty-two of the 869 subjects (26.7%) were diagnosed with metabolic syndrome. The serum adiponectin levels were significantly higher in the non-metabolic syndrome group. In a multiple logistic regression analysis, the subjects in the top quartile of serum adiponectin (adjusted odds ratio:0.36;95% confidence interval:0.21-0.63) and the second (adjusted odds ratio:0.51;95% confidence interval:0.31-0.84) quartile had a significantly decreased risk for metabolic syndrome in comparison to the bottom quartile. The dose-response relationship between serum adiponectin levels and metabolic syndrome was significant (p for trend 0.0001) after adjusting for age, body mass index, smoking status, and drinking status. The current findings suggest that hypoadiponectinemia is inversely correlated with the risk of metabolic syndrome in middle-aged Japanese male workers.

KEYWORDS: metabolic syndrome, epidemiology, adiponectin, body mass index, waist circumference

Acta Med. Okayama, 2009
Vol. 63, No. 6, pp. 325–330

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Inverse Correlation between Adiponectin and the Risk of Metabolic Syndrome in Middle-aged Japanese Male Workers

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Despite a close association between adiponectin and both hypertension and type 2 diabetes, the relationship between adiponectin and metabolic syndrome has not yet been well-investigated. To examine and evaluate the association between serum adiponectin levels and metabolic syndrome based on Japanese diagnostic criteria, we analyzed adiponectin and anthropometric parameters in 869 male employees aged 40–59 who belonged to a health insurance society in Fukuoka Prefecture and who underwent annual health check-ups from August 2006 to July 2007. Two hundred and thirty-two of the 869 subjects (26.7%) were diagnosed with metabolic syndrome. The serum adiponectin levels were significantly higher in the non-metabolic syndrome group. In a multiple logistic regression analysis, the subjects in the top quartile of serum adiponectin (adjusted odds ratio: 0.36; 95% confidence interval: 0.21–0.63) and the second (adjusted odds ratio: 0.51; 95% confidence interval: 0.31–0.84) quartile had a significantly decreased risk for metabolic syndrome in comparison to the bottom quartile. The dose-response relationship between serum adiponectin levels and metabolic syndrome was significant (p for trend < 0.0001) after adjusting for age, body mass index, smoking status, and drinking status. The current findings suggest that hypoadiponectinemia is inversely correlated with the risk of metabolic syndrome in middle-aged Japanese male workers.

Key words: metabolic syndrome, epidemiology, adiponectin, body mass index, waist circumference

The following factors, which cluster in individuals, are associated with an increased risk of developing diseases of the circulatory system: high blood pressure, low levels of high-density lipoprotein (HDL) cholesterol, high triglyceride levels, high plasma glucose concentrations, and obesity. These associated risk factors have together been called metabolic syndrome [1–3].

Received April 27, 2009; accepted July 9, 2009.
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The mechanisms underlying metabolic syndrome are still not fully known; however, recent studies have proposed an association between adipocyte-derived hormone and hypertension [4, 5], type 2 diabetes mellitus [6, 7], and dyslipidemia [8]. Adiponectin is a hormone that is specifically secreted by adipocytes and that acts as an antidiabetic and antiatherogenic adipocytokine [3, 9, 10]. Adiponectin exhibits various antiatherogenic effects on vascular cells, thereby suppressing the expression of adhesion molecules in vascular endothelial cells, the proliferation of smooth muscle cells, and cholesteryl-ester accumulation in

macrophages [10, 11].

Visceral fat accumulation is more strongly related to the induction of metabolic syndrome than subcutaneous fat accumulation [3]. Although both visceral fat and subcutaneous fat secrete peptides associated with insulin action in several systems, it appears that visceral fat and subcutaneous fat are biologically distinct because the gene expression of visceral and subcutaneous fat deposits tends to differ in young rats [12]. In addition, adiponectin expression is significantly lower in the visceral adipose tissue of genetically obese rats than in lean rats, but no differences have been observed when the subcutaneous adipose tissue specimens of the same animals are compared [13].

Serum adiponectin levels may therefore be a useful marker of visceral fat accumulation. However, few studies have attempted to determine precise relationships between adiponectin levels and the risk of metabolic syndrome in humans [14, 15]. In this context, the main aim of the present study was to examine and evaluate the association between serum adiponectin levels and metabolic syndrome.

Subjects and Methods

Subjects. The study subjects were recruited from male employees aged 40–59 who belonged to a health insurance society in Fukuoka Prefecture, Japan. From August 2006 to July 2007, we invited 1,430 male employees aged 40–59 who underwent annual health check-ups to participate in this study. Forty-seven (3.3%) did not agree to participate, and blood samples and a questionnaire were thus obtained from 1,383 participants.

A questionnaire was used to obtain information on the subjects' smoking status and alcohol consumption. 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. The waist circumference at the umbilical level was measured in the late exhalation phase when the subjects were in a standing position.

The 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). The serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) levels were measured enzymatically using commercial enzyme kits (Wako (Osaka, Japan) and Daiichi Kagaku (Tokyo, Japan), respectively). The high density lipoprotein cholesterol (HDL) was measured using the direct method.

The study protocol was approved by the Ethics Committee of Fukuoka University, and written informed consent was obtained from all participants.

Definition of metabolic syndrome. We defined metabolic syndrome based on the Japanese diagnostic criteria [2]. In addition to waist circumference ($\geq$85 cm in men), the presence of at least 2 of the following 3 abnormalities indicated metabolic syndrome:

1) Dyslipidemia: triglycerides $\geq$ 1.7 mmol/l and/or HDL cholesterol $<$ 1.0 mmol/l.
2) High blood pressure: systolic blood pressure $\geq$ 130 mm Hg and/or diastolic blood pressure $\geq$ 85 mm Hg.
3) Hyperglycemia: fasting plasma glucose $\geq$ 6.1 mmol/l.

Statistics. We excluded 510 participants because they had fasted for less than 8 h. For the statistical analysis, an additional 4 participants with missing data were excluded. Finally, 869 subjects were selected for the study. The subject characteristics are presented as n (%), and the means and standard deviations. The Student's *t*-test was used to compare the various parameters between the metabolic syndrome group and the non-metabolic syndrome group. The χ^2 test was used for categorical data. A logistic regression analysis was used to assess the risk of metabolic syndrome in the quartiles of serum adiponectin. For comparative purposes, the odds ratios were calculated by a crude analysis and with adjustments for age (by one year), body mass index (by 1 kg/m^2), smoking status (non-smokers, ex-smokers, current-smokers), drinking status (non-drinkers, occasional drinkers, regular drinkers). The results are presented as the odds ratios (OR) together with their 95% confidence intervals (95% 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, NC, USA).

Results

The subject characteristics are shown in Table 1. In this study, the serum adiponectin levels were divided into quartiles. The quartile cutoff points were 4.5, 6.3, and 8.5μg/ml. Two hundred and thirty-two subjects (26.7%) were thus diagnosed as having metabolic syndrome. No significant differences in age, smoking, drinking habit, and serum LDL cholesterol levels between the metabolic syndrome and non-metabolic syndrome subjects were observed. A significant difference was observed in the waist circumference, SBP, DBP, fasting plasma glucose, serum total cholesterol, HDL, serum triglyceride, and serum adiponectin levels between the metabolic syndrome and non-metabolic syndrome subjects.

The subjects with metabolic syndrome had lower serum adiponectin levels than those without metabolic syndrome. The proportion of subjects with serum adiponectin levels below 4.7 (μg/ml) in the metabolic syndrome group and non-metabolic syndrome group were 41.4% (96/232) and 20.4% (130/637), respectively. The average of serum adiponectin was clearly larger in the non-metabolic syndrome group than in the metabolic syndrome group. The proportion of subjects decreased as serum adiponectin levels rose in the metabolic syndrome group, but the proportion conversely increased as serum adiponectin levels rose in the non-metabolic syndrome group.

Next, we carried out a logistic regression analysis to assess the associations between metabolic syndrome and potential risk factors. As shown in Table 2, the subjects in the top (crude OR: 0.19; 95% CI: 0.12–0.31), third (crude OR: 0.34; 95% CI: 0.22–0.52), and second (crude OR: 0.61; 95% CI: 0.41–0.91) quartiles had a significantly decreased risk for metabolic syndrome in comparison to the bottom quartile based on a logistic regression analysis.

The dose-response relationship between serum adiponectin levels and metabolic syndrome was significant (p for trend < 0.0001) for both a univariate and a multivariate analysis. However, adjusting for poten-

Table 1 Characteristics of the subjects

	Metabolic syndrome (+)	Metabolic syndrome (−)	p-value
Number of subjects	232	637	
Age (years)	49.2 ± 5.1	49.7 ± 5.5	0.230
BMI (kg/m^2)	26.8 ± 2.9	23.2 ± 2.9	$p < 0.001$
Waist circumference (cm)	93.4 ± 6.7	84.2 ± 7.6	$p < 0.001$
Systolic blood pressure (mmHg)	147.3 ± 19.2	129.9 ± 17.4	$p < 0.001$
Diastolic blood pressure (mmHg)	91.4 ± 12.4	80.6 ± 12.1	$p < 0.001$
Fasting plasma glucose (mmol/l)	6.3 ± 1.9	5.4 ± 1.2	$p < 0.001$
Serum total cholesterol (mmol/l)	5.6 ± 0.9	5.3 ± 0.9	$p < 0.001$
Serum HDL cholesterol (mmol/l)	1.3 ± 0.3	1.5 ± 0.3	$p < 0.001$
Serum LDL cholesterol (mmol/l)	3.2 ± 0.8	3.1 ± 0.8	0.091
Serum triglyceride (mmol/l)	2.5 ± 1.5	1.4 ± 0.9	$p < 0.001$
Serum adiponectin (μg/ml)			
Average	5.6 ± 2.3	7.3 ± 3.5	$p < 0.001$
< 4.7	96 (41.4%)	130 (20.4%)	$p < 0.001$
4.7–6.3	66 (28.4%)	146 (22.9%)	
6.2–8.5	43 (18.5%)	172 (27.0%)	
> 8.5	27 (11.6%)	189 (29.7%)	
Smoking status			
Non-smokers	50 (50.9%)	159 (53.1%)	0.196
Ex-smokers	64 (27.6%)	140 (22.0%)	
Current-smokers	118 (21.6%)	338 (25.0%)	
Drinking status			
Non-drinkers	130 (56.0%)	350 (54.9%)	0.558
Occasional drinkers	64 (27.6%)	163 (25.6%)	
Regular drinkers	38 (16.4%)	124 (19.5%)	

Data are the means ± SD. BMI, body mass index.

Table 2 Crude and adjusted odds ratios for metabolic syndrome based on the adiponectin level quartiles

Variables	Crude		Adjusted[a]	
	OR	95% CI	OR	95% CI
Serum adiponectin level (μg/mL)				
< 4.7	(reference)		(reference)	
4.7–6.3	0.61	(0.41–0.91)	0.78	(0.49–1.24)
6.2–8.5	0.34	(0.22–0.52)	0.51	(0.31–0.84)
> 8.5	0.19	(0.12–0.31)	0.36	(0.21–0.63)
	p for trend < 0.0001		p for trend < 0.0001	
Age (by one year)	0.98	(0.96–1.01)	1.03	(0.99–1.06)
Body mass index (by 1 kg/m²)	1.54	(1.44–1.66)	1.53	(1.43–1.65)
Smoking status				
Non-smokers	(reference)		(reference)	
Ex-smokers	1.45	(0.94–2.24)	1.46	(0.87–2.44)
Current-smokers	1.11	(0.76–1.62)	1.39	(0.88–2.19)
Drinking status				
Non-drinkers	(reference)		(reference)	
Occasional drinkers	1.33	(0.84–2.10)	1.61	(0.87–2.44)
Regular drinkers	1.28	(0.85–1.93)	1.94	(0.88–2.19)

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

tial confounding factors attenuated the dose-response relationship between serum adiponectin levels and metabolic syndrome. The logistic regression analysis showed the serum adiponectin levels to demonstrate an inverse correlation with the risk of metabolic syndrome.

Discussion

This study assessed the association between serum adiponectin levels and metabolic syndrome according to a definition based on Japanese diagnostic criteria [2]. BMI was positively associated with the risk of metabolic syndrome, and the risk of metabolic syndrome for subjects with lower serum adiponectin levels was significantly high after adjusting for the BMI. BMI is an important confounding factor when evaluating the association between serum adiponectin levels and metabolic syndrome because the BMI has been reported to inversely correlate with adiponectin levels [10, 16]. In this study, the definition of metabolic syndrome includes waist circumference but no BMI. The present results show low serum adiponectin levels to be associated with metabolic syndrome after adjusting for the BMI.

The odds ratios for both smoking and drinking status were not significantly correlated with metabolic syndrome in this study. The association between current smoking and metabolic syndrome is confounded by certain factors that increase the circulating white blood cell count in Japanese women, as in men. [17, 18] Smoking is a potential confounding factor for the association between adiponectin and metabolic syndrome because plasma adiponectin levels are significantly lower in current smokers than in never-smokers [19].

The relationship between drinking habits and metabolic syndrome remains controversial. While a positive association [20] and no significant association [21] have been reported, a lower prevalence of metabolic syndrome is associated with mild to moderate alcohol consumption [22–25]. In addition, smoking has been reported to decrease [19], while moderate alcohol consumption has been reported to increase the circulating adiponectin concentrations [7, 25]. Smoking and drinking are confounding factors regarding the relationship between adiponectin levels and metabolic syndrome.

These results demonstrate that serum adiponectin levels are significantly lower in subjects with metabolic syndrome than in those without metabolic syndrome based on a univariate analysis. Moreover, in a logistic regression analysis, the subjects in the lowest quartile had a fivefold greater risk of metabolic syndrome than those in the highest quartile. Even after adjusting for potential confounding factors, this association remained significant. In addition, the dose-response relationship between the risk of metabolic syndrome and the serum adiponectin levels was significant.

An association between adiponectin and hypertension [4], type 2 diabetes mellitus [6, 7], and dyslipidemia [8] has been reported. Our data are consistent with the findings of the above-mentioned study and also indicate that adiponectin plays an important role in metabolic syndrome. Adiponectin exhibits various antiatherogenic effects on vascular cells, thereby suppressing the expression of adhesion molecules in vascular endothelial cells, the proliferation of smooth muscle cells, and cholesteryl-ester accumulation in macrophages [10, 11]. However, details regarding the mechanisms underlying the inverse association between adiponectin and metabolic syndrome are not yet clear and remain to be elucidated.

This study has certain limitations. First, it was a cross-sectional study. Decreased secretion of adiponectin occurs earlier than metabolic syndrome because adiponectin levels are positively correlated with the insulin sensitivity [24] and an inverse relationship between serum adiponectin levels and insulin resistance [7] has been reported. However, the serum adiponectin concentrations do not show any correlations with the homeostasis model assessment index for either non-obese or obese normoglycemic subjects [26]. We cannot rule out the probability that the presence of metabolic syndrome decreases the secretion of adiponectin. Therefore, the temporality of such a causal relationship cannot be inferred. A prospective study with a larger sample size is thus required to clarify this issue.

Next, the subjects of this study were middle-aged Japanese male workers. Most of the subjects of studies regarding the relationship between adiponectin levels and hypertension [4], type 2 diabetes mellitus [6, 7] and dyslipidemia [8], and life style factors [16] have been male. A few studies have also analyzed the relationships between adiponectin levels and the risk of metabolic syndrome for women [14, 24]. However, the number of subjects evaluated in these studies has not been large. As such, further study is necessary to determine whether or not the results of this study can be applied to females.

In conclusion, we have shown herein that in middle-aged Japanese male workers, adiponectin levels are inversely correlated with the risk of metabolic syndrome after adjusting for potential confounding factors. Clarifying whether adiponectin may have a predictive value in the natural course of metabolic syndrome and whether lifestyle factors may alter the risk of metabolic syndrome awaits further investigation.

Acknowledgments. This study was supported in part by a Grant-in-Aid for Scientific Research (20590619), without conflicts of interest.

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