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Close association of hypoadiponectinemia with arteriosclerosis obliterans and ischemic heart disease

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Abstract

Adiponectin is an adipose-derived cytokine, and it is suggested that hypoadiponectinemia increases the prevalence of ischemic heart disease (IHD). The present study was undertaken to determine serum adiponectin levels in patients with arteriosclerosis obliterans (ASO) and IHD. Forty-nine patients with ASO and 49 age-, sex-, and body mass index–matched control subjects were examined. The diagnosis of ASO was derived from an ankle brachial index of less than 0.90 and stenotic or obstructive change in angiogram. Ischemic heart disease was diagnosed by ischemic or stenotic change in ECG, treadmill, or coronary angiogram. Serum adiponectin level was 8.6 ± 0.9 μg/mL in the patients with ASO, a value significantly less than that of 12.4 ± 1.0 μg/mL in the control subjects ($P < .01$). Next, we subgrouped the subjects into 4 groups according to the presence of ASO and IHD. Serum adiponectin levels were 9.4 ± 1.5 and 10.2 ± 1.6 μg/mL in the subjects with ASO (n =23) and those with IHD (n = 13), respectively. It was further reduced to 7.9 ± 1.2 μg/mL in the subjects having both ASO and IHD (n = 26), a value significantly less than that of 13.2 ± 1.4 μg/ml in the control subjects (n = 36; $P < .05$). Serum high-density lipoprotein cholesterol was significantly less in the subjects with ASO than in the control subjects (42.1 ± 1.7 vs 48.5 ± 2.0 mg/dL; $P < .05$), but there were no differences in blood pressure, total cholesterol, low-density lipoprotein cholesterol, triglyceride, and uric acid levels. The present results indicate that a reduction in serum adiponectin level is associated with the prevalence and magnitude of systemic atherosclerosis including IHD and ASO.

1. Introduction

Adiponectin is an adipose tissue–derived cytokine that was identified in the human adipose tissue cDNA library [1-3]. Serum adiponectin level is measurable by enzyme-linked immunosorbent assay (ELISA), and its level is unexpectedly a high concentration in healthy subjects [4]. The level is lower in men than in women [5]. Clinically, serum adiponectin levels are reduced in varying pathological states including obesity, diabetes mellitus, and ischemic heart disease (IHD) [4,6-9]. Kumada et al [8] have demonstrated that hypoadiponectinemia increases the prevalence of IHD by 2-fold. However, the clinical significance of hypoadiponectinemia in IHD has not been fully elucidated.

Arteriosclerosis obliterans (ASO) is another typical disorder of atherosclerosis, in which arterial obstruction occurs in arteries supplying blood in lower extremities. Risk factors of ASO are fundamentally not distinct from those of IHD. In the present study, we determined serum adiponectin levels in patients with ASO, as compared with age-, sex-, and body mass index (BMI)–matched subjects. Furthermore, we analyzed any difference in serum adiponectin levels among subjects having ASO, IHD, or both.

2. Subjects and methods

2.1. Subjects

Forty-nine patients with ASO were examined between June 2003 and February 2004. They were 40 men and 9 women, with the age of 66.0 ± 9.8 years (mean ± SD), ranging from 40 to 83 years. They were admitted to the

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Cardiovascular and Metabolic Ward of the Jichi Medical School Omiya Medical Center because of intermittent claudication. Ankle brachial index and arterial angiogram were carried out to determine the site and degree of arterial obstruction. The diagnosis of ASO was derived from an ankle brachial index of less than 0.90 and when arterial stenotic or obstructive change was confirmed by angiogram. Thirty-three subjects had diabetes mellitus, 10 had hyperlipidemia, 31 had hypertension, and 26 had IHD. Also, 49 age-,sex-, and BMI-matched control subjects served as a control group. They were 40 men and 9 women, with the age of 66.1 ± 8.2 years, ranging from 49 to 83 years. In the control subjects, 32 subjects had diabetes mellitus, 16 had hyperlipidemia, 21 had hypertension, and 13 had IHD. Subjects with advanced renal disease having a serum creatinine level higher than 2 mg/dL and those taking synthetic peroxisome proliferator–activated receptor (PPAR) γ ligands were excluded [10,11]. Blood collections were made after an overnight fast to determine fasting plasma glucose, hemoglobin A1c, serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, uric acid, and serum adiponectin levels. Risk factors for atherosclerosis were defined as follows: hypertension was defined as systolic blood pressure of greater than 140 mm Hg, diastolic pressure of greater than 90 mm Hg, or having taken antihypertensive drugs. Diabetes mellitus was defined according to the criteria of the World Health Organization. Dyslipidemia was defined as a total cholesterol concentration of greater than 220 mg/dL, an HDL-C level of less than 40 mg/dL, and a triglyceride level of greater than 150 mg/dL. The present study was approved by the Ethical Committee of the Jichi Medical School for human studies. We obtained informed consent from all the subjects who joined the present protocol.

Table 1
Clinical features of subjects with ASO and control subjects

	Control subjects	ASO subjects	*P*
n	49	49	
Age (y)	66.1 ± 1.1	66.0 ± 1.4	.982
Sex (male/female)	40:9	40:9	
BMI	23.3 ± 3.2	22.5 ± 2.7	.125
Diabetes mellitus (n)	32	33	
Hypertension (n)	21	31	
Hyperlipidemia (n)	16	10	
IHD (n)	13	26	
Cigarette smoking (Yes/Previously/No)	17/5/25	18/15/16	
Fasting plasma glucose (mg/dL)	141 ± 7.6	150.1 ± 7.7	.405
Total cholesterol (mg/dL)	190.8 ± 5.9	189.8 ± 5.9	.898
HDL-C (mg/dL)	48.5 ± 2.0	42.5 ± 1.7	.015
Low-density lipoprotein cholesterol (mg/dL)	107.8 ± 4.5	116.9 ± 4.6	.164
Triglyceride (mg/dL)	129.6 ± 9.8	148.0 ± 14.2	.287
Uric acid (mg/dL)	5.6 ± 0.2	5.9 ± 0.2	.260
Hemoglobin A1c (%)	7.2 ± 0.3	6.6 ± 0.2	.089
Systolic blood pressure (mm Hg)	134 ± 2	136 ± 3	.577
Diastolic blood pressure (mm Hg)	78 ± 2	76 ± 2	.534

Values are means ± SEM.

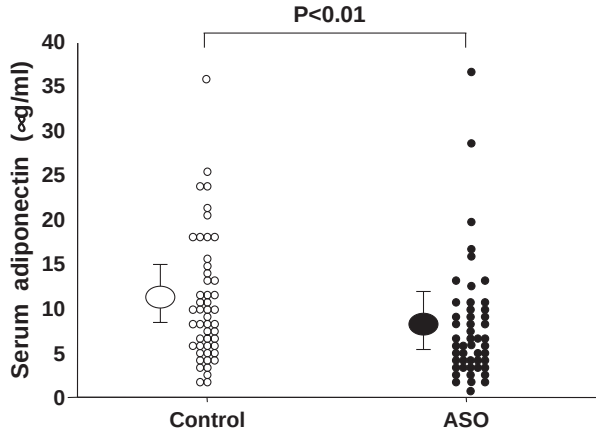

Fig. 1. Serum adiponectin levels in the subjects with ASO (n = 49) and in the control subjects (n = 49). Values are means ± SEM.

2.2. Measurements

Blood was collected in tubes and centrifuged at 3000 rpm at 4 °C for 15 minutes. The supernatants were decanted and frozen at −80 °C until assayed for serum adiponectin. Adiponectin was measured by ELISA using Adiponectin ELISA kits (Otsuka Pharmaceutical Co, Osaka, Japan).

2.3. Statistical analysis

All values are expressed as means ± SEM. The values were analyzed by the Fisher *t* test to compare differences. Single linear regression analysis was performed to calculate correlations. The statistical package of StatView for

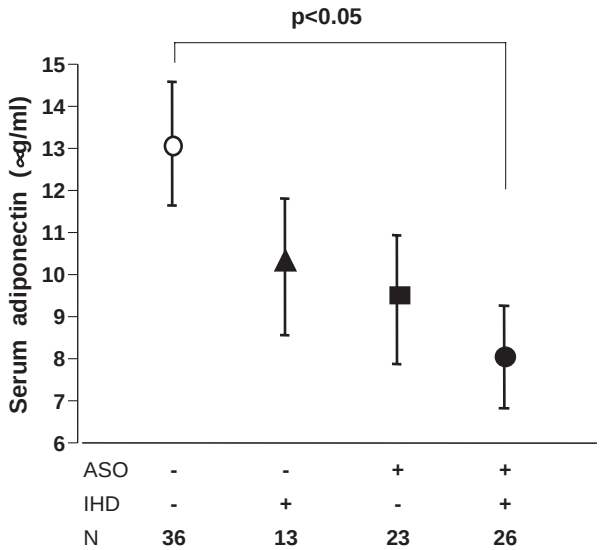

Fig. 2. Serum adiponectin levels in the subjects with ASO, IHD, or both. Values are means ± SEM.

Macintosh version 5.0 (Abacus Concepts, Berkeley, Calif) was used for the present analysis. A P value less than .05 was considered significant.

3. Results

We compared clinical features in the 2 groups of subjects (Table 1). Because the subjects were collected according to the match of age, sex, and BMI, there were no differences in most of categories in the 2 groups of subjects. The BMI was 22.5 ± 2.7 in the subjects with ASO, which was comparable with that in the control subjects. The number of subjects having hypertension or IHD was markedly increased in the subjects with ASO, as compared with that in the control subjects. Serum HDL-C was significantly less in the subjects with ASO than in the control subjects ($P < .05$).

Fig. 1 shows serum adiponectin levels in the subjects with ASO and the control subjects. Serum adiponectin level was 12.4 ± 1.0 μg/mL in the control subjects. It was reduced to 8.6 ± 0.9 μg/mL in the subjects with ASO, a value significantly less than that in the control subjects ($P < .01$).

Fig. 2 shows serum adiponectin levels in the subjects who had ASO, IHD, or both. Serum adiponectin levels were 9.4 ± 1.5 and 10.2 ± 1.6 μg/mL in the subjects with ASO and IHD, respectively. It was further decreased to 7.9 ± 1.2 μg/mL in the subjects having both ASO and IHD, a value significantly less than that of 13.2 ± 1.4 μg/mL in the subjects having neither IHD nor ASO ($P < .05$).

Table 2 shows the relationship of serum adiponectin level with varying parameters in the subjects with ASO and the control subjects. Among the various parameters, serum adiponectin seemed likely to have a correlation with BMI in the control subjects ($P = .06$), but this was not a case in the subjects with ASO. Otherwise, no correlation was found in both the control subjects and those with ASO except for the significant correlation between serum adiponectin and serum HDL-C in the control subjects.

Table 2
Linear regression analysis of serum adiponectin levels with varying parameters in the subjects with ASO and the control subjects

	Control subjects		ASO subjects	
	r	P	r	P
Adiponectin vs BMI	−0.320	.060	−0.005	.978
Adiponectin vs age	0.072	.685	−0.167	.327
Adiponectin vs total cholesterol	0.051	.775	−0.062	.715
Adiponectin vs triglyceride	−0.328	.053	−0.209	.216
Adiponectin vs low-density lipoprotein cholesterol	0.063	.719	0.017	.922
Adiponectin vs HDL-C	0.353	.037	−0.037	.828
Adiponectin vs uric acid	−0.086	.624	0.139	.415
Adiponectin vs systolic blood pressure	0.114	.518	0.053	.756
Adiponectin vs diastolic blood pressure	−0.146	.405	0.032	.851
Adiponectin vs hemoglobin A1c	−0.151	.388	−0.099	.562
Adiponectin vs fasting plasma glucose	−0.216	.215	0.176	.299

4. Discussion

The present study clearly demonstrated that serum adiponectin levels were significantly decreased in the subjects with ASO compared with the age-, sex-, and BMI-matched control subjects. The reduction in serum adiponectin levels was comparable in the subjects with ASO and those with IHD. Serum adiponectin level was further decreased in the subjects who had both IHD and ASO. We confirmed that hypoadiponectinemia was also found in ASO, in addition to IHD [8,9]; this is the first report to note hypoadiponectinemia in ASO.

There are 2 phases in the atherogenic process. Namely, atherosclerosis develops slowly and progressively in widespread arteries year by year. It is well known that the inflammatory, vulnerable plaque of the atheroma may fall into rupture, resulting in acute obstruction of culprit coronary artery [12-14]. There is no difference in the atherogenic process between IHD and ASO. As adiponectin acts as modulator of anti-inflammatory response in the vascular wall [15,16], hypoadiponectinemia may cause an excessive inflammatory event. At the present time, there are 2 possibilities with regard to the pathological role of hypoadiponectinemia in atherosclerosis. First, hypoadiponectinemia accelerates the development of atherosclerosis. Second, as serum adiponectin rapidly accumulates in the subendothelial space of the injured human artery [16] and inhibits the atherogenic process [15,17,18], adiponectin is accumulated locally as an anti-atherogenic action in the lesion of the atheromatous plaque in the obstructive artery and probably results in hypoadiponectinemia [6,8]. However, these hypotheses cannot be simply determined from the cross-sectional study design; further studies will be necessary to elucidate the exact mechanism of hypoadiponectinemia.

The subjects had multiple risk factors including diabetes mellitus, dyslipidemia, hypertension, smoking, and others. These factors may affect serum adiponectin levels [4,7,19]. It is known that serum adiponectin levels have a negative correlation with BMI in healthy subjects [4]. As shown in Table 2, the correlation seemed likely to be kept in the control subjects ($P = .06$); however, it disappeared when the factor of ASO was added. In addition, as compared with the subjects with IHD, BMI seemed likely to be lower in the subjects with ASO (24.6 ± 0.8 vs 22.2 ± 0.4). Because hypoadiponectinemia was comparable in 2 groups of subjects with IHD and ASO, a decrease in serum adiponectin levels could be much remarkable in the subjects with ASO. When serum HDL-C was removed from the analysis, the statistical significance of the difference in serum adiponectin levels between the subjects with ASO and the control subjects was reduced ($P = .0625$). These findings may indicate that serum adiponectin levels are partially underlain on low serum HDL-C and that hypoadiponectinemia is strongly linked to the development of atherosclerosis in the subjects with ASO.

In conclusion, hypoadiponectinemia was found in the subjects with ASO, a degree comparable with those with IHD. The decrement in serum adiponectin levels was the

greatest in the subjects with both IHD and ASO who had severe widespread atherosclerosis. The present study indicates that hypoadiponectinemia is associated with the prevalence and magnitude of systemic atherosclerosis including IHD and ASO.

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