研究成果の刊行に関する一覧表

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Hypoadiponectinemia in Patients with Cerebral Infarction: Comparison with Other Atherosclerotic Disorders

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ABSTRACT: The present study was undertaken to determine serum adiponectin level in patients with cerebral infarction and to further analyze any difference in serum adiponectin levels among atherosclerotic disorders. One hundred fifty-two subjects with atherosclerotic disorders were enrolled, 110 males and 42 females, with the age of 67.0 ± 9.9 years (mean ± SD). They were divided into 62 patients with cerebral infarction, 48 patients with ischemic heart disease, and 42 patients with arteriosclerosis obliterans. Thirty-two subjects matched by age, gender, and body mass index served as controls. Serum adiponectin levels were 7.2 ± 0.6 μg/mL (mean ± SE) in the patients with cerebral infarction, 7.2 ± 0.8 μg/mL in those with ischemic heart disease, and 6.9 ± 0.9 μg/mL in those with arteriosclerosis obliterans. They were significantly less than the level of 12.6 ± 1.9 μg/mL in the control group ($P < 0.01$). However, there was no difference in serum adiponectin level among three groups of atherosclerotic disorders. In the patients with acute cerebral infarction, serum adiponectin level was temporarily reduced from 7.3 ± 0.9 to 6.2 ± 0.8 μg/mL 14 days after the hospitalization ($P < 0.01$), followed by recovery to the basal value. The present findings indicate that serum adiponectin levels are equivalently reduced in patients with atherosclerotic disorders, and that serum adiponectin is changeable under acute phase of cerebral infarction. **KEY INDEXING TERMS:** Cerebral infarction; Adiponectin. **[Am J Med Sci 2007;333(3):140–144.]**

Adipose tissue secretes a variety of biologically active molecules, including cytokines, growth factors, and complement factors, into the systemic circulation.[1–6] Adiponectin is the most abundant adipocytokine among them. Adiponectin is a 244 amino acid protein, and serum adiponectin concentration has an extremely high level in healthy subjects as compared with other circulatory cytokines.[7,8] The level is lower in men than in women.[9] Serum adiponectin levels change in several pathologic states; that is, serum adiponectin levels decrease in conditions of obesity, diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, and arteriosclerosis obliterans.[8,10–14] Adiponectin plays a crucial role in a cluster of these common disorders linked to metabolic syndrome. Adiponectin has various potential actions, including anti-inflammatory effect, antidiabetic effect, and antiatherogenic effect.[15,16] Also, adiponectin causes nitric oxide production and angiogenesis.[17,18]

Cerebral infarction is still a major disorder of atherosclerosis in Japan. Metabolic syndrome has a common risk factor for cerebral infarction, and there is fundamentally no difference among the atherosclerotic disorders. As mentioned earlier, serum adiponectin levels decline in each disorder of metabolic syndrome. There were reports that hypoadiponectinemia is associated with ischemic cerebrovascular disease and further increases the risk of 5-year mortality after first-ever ischemic stroke.[19,20] In the present study, we determined serum adiponectin levels in patients with cerebral infarction. Furthermore, we analyzed any difference in serum adiponectin levels among cerebral infarction, ischemic heart disease, and arteriosclerosis obliterans.

Subjects and Methods

Subjects

One hundred fifty-two patients with atherosclerotic disorders were enrolled between June 2003 and March 2005 in Jichi Medical University Omiya Medical Center and Chichibu Municipal Hospital. They were divided into three groups of cerebral infarction, ischemic heart disease, and arteriosclerosis obliterans. Sixty-two patients had cerebral infarction; 45 were male and 17 were

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females, with a mean age of 67.0 ± 10.9 years, ranging from 37 to 90 years. Twenty patients had been admitted to the hospital because of acute onset of stroke, and 42 patients had past history of cerebral infarction. The diagnosis of cerebral infarction was derived from the abnormality of neurologic findings and confirmed by brain computed tomography or magnetic resonance imaging. Thirty-one subjects had diabetes mellitus, 38 had hyperlipidemia, 49 had hypertension, 17 had simple obesity, and 37 had a smoking habit. In the second group, 48 patients had ischemic heart disease; 35 were male and 13 were female with a mean age of 66.8 ± 9.6 years, ranging from 38 to 87 years. The diagnosis of ischemic heart disease was dependent on coronary angiographic findings. Twenty subjects had diabetes mellitus, 29 had hyperlipidemia, 39 had hypertension, 15 had simple obesity, and 31 had a smoking behavior. In the third group, 42 patients had arteriosclerosis obliterans; 31 were male and 11 were female with a mean age of 67.2 ± 10.0 years, raging from 46 to 89 years. The diagnosis of arteriosclerosis obliterans was derived from an ankle brachial index of less than 0.90, and that arterial stenotic or obstructive change was confirmed by angiography. Twenty-eight subjects had diabetes mellitus, 24 had hyperlipidemia, 27 had hypertension, 9 had simple obesity, and 24 had a smoking habit. Thirty-five patients had had combined atherosclerotic disorder, and they were grouped into one of three groups based on the main disorder in the present occasion. Also, 32 subjects matched by age, gender, and body mass index served as a control group; 23 were male and 9 were female, with a mean age of 66.8 ± 8.4 years, ranging from 48 to 83 years. Twenty-two subjects had diabetes mellitus, 16 had hyperlipidemia, 15 had hypertension, 7 had simple obesity, and 13 had a smoking behavior. Subjects with advanced renal disease (serum creatinine levels more than 2.0 mg/dL) and those taking synthetic peroxisome proliferator-activated receptor-γ ligands were excluded. Blood samples were collected from patients in the supine position after an overnight fast to determine fasting plasma glucose, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and serum adiponectin levels at the time of hospitalization. In the patients with acute onset of cerebral infarction, blood was collected a day after the hospitalization. Risk factors for atherosclerosis were defined as follows: 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, a high-density lipoprotein cholesterol level of less than 40 mg/dL, and a triglyceride level of greater than 150 mg/dL, or the patient's having taken either statins or fibrates. Hypertension was defined as systolic blood pressure of greater than 140 mm Hg, diastolic pressure of greater than 90 mm Hg, or the patient's having taken antihypertensive agents. The present study was approved by the ethical committee of Jichi Medical University for human studies. We obtained informed consent from the subjects who joined the present protocol.

Measurement

Blood samples were collected into tubes and centrifuged at 3000 rpm at 4° C for 15 minutes. The supernatants were decanted and frozen at −80° C until assayed for adiponectin. Adiponectin was measured by enzyme-linked immunosorbent assay using Adiponectin ELISA kits (Otsuka Pharmaceutical, Osaka).

Statistical Analysis

All values are expressed as mean ± SEM. The values were analyzed by post hoc analysis of variance. Categorical data were analyzed by the χ^2 test. The statistical package of Social Science (SSPS for Windows, version 11.0) was employed for the present analysis. A *P*-value less than 0.05 was considered significant.

Results

Table 1 shows the clinical feature in the four groups of subjects. Because the control subjects were selected according to the match of age, sex, and body mass index, there were no differences in most of laboratory findings among the four groups. Only systolic blood pressure was significantly greater in the patients with cerebral infarction than in the control subjects. In the patients with cerebral infarction and ischemic heart disease, the incidence of hypertension was significantly higher than in the control subjects.

Figure 1 shows serum adiponectin level in the patients with cerebral infarction, ischemic heart disease, and arteriosclerosis obliterans and in the control subjects. Serum adiponectin level was 12.6 ± 1.9 μg/mL in the control group. Serum adiponectin levels in the patients with atherosclerotic disorders were significantly less than in the control subjects,

Table 1. Clinical Features of the Four Groups of Subjects

	Control	Cerebral Infarction	*P*-Value	Ischemic Heart Disease	*P*-Value	Arteriosclerosis Obliterans	*P*-Value
Subjects, n	32	62		48		42	
Age (y)	66.8 ± 8.4	67.0 ± 10.9		66.8 ± 9.6		67.2 ± 10.0	
Sex (M/F)	23/9	45/17		35/13		31/11	
Body mass index	23.4 ± 3.5	23.6 ± 4.0		23.9 ± 3.9		23.3 ± 2.7	
Diabetes mellitus, n (%)	22 (68.8)	31 (50.0)	0.129	20 (41.7)	0.032	28 (66.7)	0.850
Hyperlipidemia, n (%)	16 (50.0)	38 (61.3)	0.407	29 (60.4)	0.490	24 (57.1)	0.521
Hypertension, n (%)	15 (46.9)	49 (79.0)	0.003	39 (81.3)	0.003	27 (64.3)	0.207
Obesity, n (%)	7 (21.9)	17 (27.4)	0.738	15 (31.3)	0.506	9 (21.4)	0.963
Smoking, n (%)	13 (40.6)	37 (59.7)	0.125	31 (64.6)	0.060	24 (57.1)	0.241
Total cholesterol (mg/dL)	182.2 ± 6.3	186.8 ± 5.5	0.905	185.6 ± 5.9	0.964	197.6 ± 6.7	0.233
Triglyceride (mg/dL)	127.1 ± 12.5	117.3 ± 7.7	0.884	125.7 ± 11.3	1.000	161.3 ± 17.4	0.163
HDL cholesterol (mg/dL)	48.6 ± 5.6	46.9 ± 2.0	0.942	44.0 ± 2.1	0.552	42.6 ± 2.0	0.358
Low-density lipoprotein cholesterol (mg/dL)	102.5 ± 6.0	116.3 ± 5.8	0.208	115.0 ± 5.7	0.312	110.9 ± 4.5	0.637
Fasting plasma glucose (mg/dL)	144.3 ± 10.5	133.5 ± 6.9	0.642	150.6 ± 7.3	0.903	145.6 ± 7.9	0.999
HbA1c (%)	6.9 ± 1.8	6.5 ± 2.0	0.576	6.4 ± 1.4	0.516	6.8 ± 1.8	0.969
Systolic blood pressure (mm Hg)	135.8 ± 2.5	146.5 ± 3.5	0.047	136.6 ± 2.5	0.996	134.3 ± 2.7	0.978
Diastolic blood pressure (mm Hg)	76.2 ± 1.8	81.2 ± 2.0	0.163	77.0 ± 1.7	0.984	74.2 ± 1.6	0.812

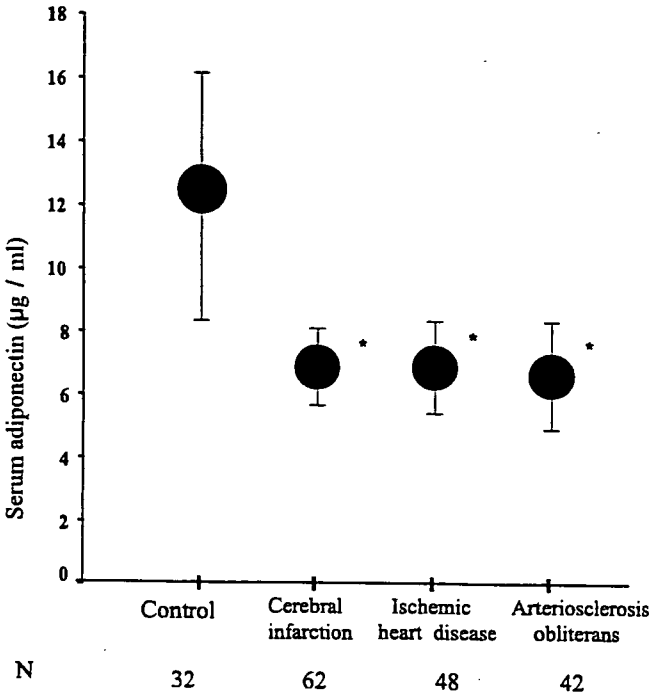

Figure 1. Serum adiponectin levels in the subjects with cerebral infarction, ischemic heart disease, and arteriosclerosis obliterans. Values are mean ± SEM. *$P < 0.01$ vs the control subjects.

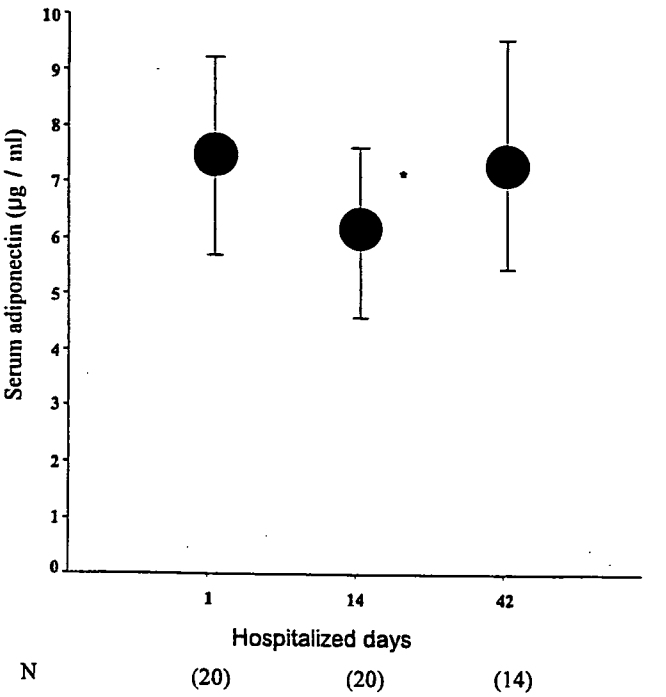

Figure 2. Alteration in serum adiponectin levels during the hospitalization in the subjects with acute cerebral infarction. Values are mean ± SEM. *$P < 0.01$ vs value at the admission.

as it was 7.2 ± 0.6 μg/mL in the patients with cerebral infarction, 7.2 ± 0.8 μg/mL in those with ischemic heart disease, and 6.9 ± 0.9 μg/mL in those with arteriosclerosis obliterans. However, there was no difference in serum adiponectin levels among the three groups of patients with atherosclerotic disorders. In addition, serum adiponectin was further reduced in the patients having more than two atherosclerotic disorders, as it was 6.6 ± 0.9 μg/mL in the patients with ischemic heart disease and arteriosclerosis obliterans (n = 25), and 6.3 ±1.1 μg/mL in those with all three atherosclerotic disorders (n = 5). In the patients with cerebral infarction, there was no difference in serum adiponectin levels between acute and old cerebral infarction (7.3 ± 0.7 vs. 7.1 ± 0.7 μg/mL; $P = 0.86$).

Because the incidence of hypertension was higher in the patients with cerebral infarction and ischemic heart disease (Table 1), we further analyzed serum adiponectin levels in the hypertensive control subjects (n = 15). Serum adiponectin levels were 12.1 ± 2.2 μg/mL in the hypertensive control subjects, and 13.1 ± 3.2 μg/mL in the normotensive control subjects (n = 17). In the patients with cerebral infarction and ischemic heart disease, serum adiponectin levels were still lower than in the hypertensive control subjects ($P < 0.05$).

Figure 2 shows an alteration in serum adiponectin levels during hospitalization in the 20 patients with acute cerebral infarction. Serum adiponectin level was 7.3 ± 0.9 μg/mL at the time of hospitalization. It further declined to 6.2 ± 0. 8 μg/mL 14 days after the hospitalization, a value significantly less than the value at the onset of stroke ($P < 0.05$). On the 42nd day of hospitalization, serum adiponectin level returned to its basal value.

Discussion

The present study demonstrated that serum adiponectin levels were equivalently decreased in patients with ischemic heart disease, arteriosclerosis obliterans, and cerebral infarction, as compared to levels in the control subjects. There were no differences in serum adiponectin levels among the disorders of atherosclerosis. Also, no difference was evident between the patients with acute onset and with their past history of cerebral infarction. Serum adiponectin level was further reduced in the subjects who had more than 2 atherosclerotic disorders. This means that a widespread change of atherosclerosis in systemic vessels could be related to a decrease in serum adiponectin level. It is of value that in the patients with acute onset of cerebral infarction serum adiponectin level was temporarily decreased 2 weeks after the onset, followed by a recovery to the basal level. As serum adiponectin rapidly accumulates in the subendothelial space of the injured human artery[21] and inhibits the atherogenic process,[10,16,22-24] adiponectin could be accumulated in the obstructive artery and may result in hypoadiponectinemia.[21] However, as mentioned earlier, there

was no alteration in serum adiponectin level in the patients with acute and old cerebral infarction. The present findings may indicate that hypoadiponectinemia proceeds simultaneously with the slow development of atherosclerotic disorders.

Basically, there is no difference in development of vascular derangement among the aforementioned disorders derived from atherosclerosis. The patients had multiple risk factors, including diabetes mellitus, hyperlipidemia, hypertension, obesity, and others. These risk factors affect serum adiponectin levels. It is known that serum adiponectin decreases in states of diabetes mellitus, hypertension, and obesity.[8,11,25–28] Particularly, there was significant difference in the rate of hypertension between the patients with cerebral infarction and ischemic heart disease and the control subjects. Hypertension per se could facilitate hypoadiponectinemia in the patients with atherosclerotic events.[29] In the present study, however, serum adiponectin levels did not decline in the hypertensive control subjects. Adiponectin has an anti-inflammatory and an anti-atherogenic action. There is a rapid accumulation of adiponectin locally in the atheromatous lesion of the obstructive artery.[21] In fact, the presence of risk factors could cause hypoadiponectinemia, which accounts for one of the multiple mechanisms for developing atherosclerosis. As atherosclerosis has developed slowly and progressively, the chronic process of inflammation and atherogenesis could become lost in the stimulatory signal of adiponectin production. It may indicate that hypoadiponectinemia and lesional accumulation of adiponectin are a successive phenomenon with the different phases under chronic inflammatory state of atherosclerosis.

In conclusion, hypoadiponectinemia was found in patients with the disorders of atherosclerosis. The levels were comparable among patients with cerebral infarction, ischemic heart disease, and arteriosclerosis obliterans. The patients had multiple risk factors of hyperlipidemia, hypertension, and diabetes mellitus, which all decrease serum adiponectin levels. Because there was no difference in serum adiponectin levels between the patients with acute and old cerebral infarction, hypoadiponectinemia may concomitantly proceed to the development of atherosclerotic disorders.

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