Association Between Adiponectin Production in Coronary Circulation and Future Cardiovascular Events in Patients With Coronary Artery Disease

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Summary

Adiponectin has antiatherosclerotic properties and is also produced in the local coronary circulation. We previously reported that significantly less adiponectin was produced in the coronary circulation of patients with than without coronary artery disease (CAD). The goal of this study was to determine whether adiponectin production in the coronary circulation could predict future cardiovascular events in patients with CAD.

Forty-eight CAD patients whose left anterior descending coronary arteries required percutaneous coronary intervention (PCI) were enrolled. The amount of adiponectin production in the coronary circulation was defined as the plasma adiponectin level at the great cardiac vein minus that at the orifice of the left coronary artery. All patients were divided by adiponectin production level in the coronary circulation into the adiponectin-positive production group (> 0 μg/mL) and adiponectin-negative production group (≤ 0 μg/mL). Median follow-up period was 66 months (maximum, 108 months). The primary endpoint was the combined occurrence of major adverse cardiovascular events (MACE), including rehospitalization due to unstable angina, heart failure, nonfatal myocardial infarction, revascularization with PCI or coronary artery bypass grafting, ischemic stroke, and cardiovascular death.

Sixteen MACE occurred. The incidence of MACE was significantly higher in the adiponectin-negative production group than in the adiponectin-positive production group ($P = 0.02$). In multivariate analysis, adiponectin-negative production was a predictor of MACE ($P = 0.03$). Kaplan-Meier analysis revealed that the MACE-free rate was significantly lower in the adiponectin-negative production group than in the adiponectin-positive production group.

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Key words: MACE

Adiponectin is one of several adipocytokines and has antiatherosclerotic properties that are linked to coronary artery disease (CAD).[1,2] Systemic hypoadiponectinemia is closely associated with obesity,[3] type 2 diabetes,[4] CAD,[5] and coronary plaque volume;[6] thus, low plasma adiponectin levels have been suggested to increase the risk of cardiovascular disease.

Recently, several studies have reported an association between circulating plasma adiponectin levels and major adverse cardiovascular events (MACE) in patients with or without CAD.[7-10] Prospective studies have shown that high plasma adiponectin levels are associated with a low risk of myocardial infarction in healthy men [11] and with a moderately decreased CAD risk in diabetic men.[12] However, recently, the paradoxical association of high adiponectin levels with adverse outcomes was reported in high-risk patients such as those with severe CAD and heart failure. Adiponectin seems to play a paradoxical role in patients with manifest CAD, and the results of these studies are controversial.

We previously reported that adiponectin is locally produced in the coronary circulation and might participate in modulating the coronary circulation in individuals with normal coronary arteries.[13] We also reported that significantly less adiponectin was produced locally in the coronary circulation of patients with than without CAD.[14] These findings suggested that lower adiponectin production in the coronary circulation is related to the progression of coronary atherosclerosis; however, there is uncertainty about the association of adiponectin production levels in the coronary circulation with CAD and MACE. The goal of this study was to determine whether the amount of adiponectin production in the coronary circulation could predict future cardiovascular events in patients with CAD.

METHODS

Patients: Forty-eight CAD patients whose left anterior descending coronary arteries required percutaneous coronary intervention (PCI) because of severe stenosis associated with stress-induced ischemia were enrolled from June 2005 to July 2008. The study population comprised 30 men and 18 women with a mean age of 69 years (range, 45 to 83 years) (Table I).

Adiponectin production in coronary circulation: Blood samples were simultaneously collected from the orifice of the left coronary artery (LCA) and the great cardiac vein (GCV) before PCI. We measured the plasma levels of adiponectin in the blood samples. The production of adiponectin in the coronary circulation was defined as venous-arterial differences in the coronary circulation, that is, the plasma adiponectin level at GCV minus that at the orifice of LCA. All patients were divided by adiponectin production level in the coronary circulation into an adiponectin-positive production group and an adiponectin-negative production group. The adiponectin-positive production group was defined as having a plasma level of adiponectin at GCV – plasma level of adiponectin at LCA of > 0 μg/mL, and the adiponectin-negative production group was defined as having a plasma level of adiponectin at GCV – plasma level of adiponectin at LCA of ≤ 0 μg/mL.

Follow-up for endpoints: The primary endpoint was the combined occurrence of MACE, including rehospitalization due to unstable angina, heart failure, nonfatal myocardial infarction, revascularization with PCI or coronary artery bypass grafting, ischemic stroke, and cardiovascular death. Using their medical records, we examined retrospectively whether MACE had occurred before March 1, 2012.

Nonfatal myocardial infarction was defined by a rise of cardiac troponin T with ischemic symptoms and/or characteristic electrocardiographic changes. Ischemic stroke was defined as the presence of a neurological deficit lasting for at least 24 hours with definite evidence of a cerebrovascular accident verified by either magnetic resonance imaging or computed tomography.

This protocol was approved by the ethics committee of Miyazaki University School of Medicine and all subjects enrolled provided written informed consent.

Measurement of adiponectin: Plasma adiponectin levels were measured using sandwich ELISA (adiponectin ELISA kit; Otsuka Pharmaceutical Co Ltd (Tokyo) as previously reported.[3]

Statistical analysis: Data are expressed as the mean ± SD for numeric variables and as a number (percent) for categorical variables. Continuous variables between groups were compared by Student's t-test. Comparisons of categorical variables between groups were assessed by the chi-square test. Kaplan-Meier curves of MACE-free survival among the two groups were compared using the log-rank test. All data were analyzed using the JMP (Kyoto, Japan) statistical package, version 7.0. A P value of < 0.05 was considered significant.

RESULTS

The median follow-up period was 66 months (range, 4-108 months). Table I shows a comparison of the adiponectin-positive production group and adiponectin-negative production

Table I. Comparison of Adiponectin-Positive Production and -Negative Production Groups

	Adiponectin-positive production group ($n = 37$)	Adiponectin-negative production group ($n = 11$)	P
Age (years)	65 ± 11	69 ± 11	0.33
Male (n (%))	22 (59)	8 (72)	0.42
Body mass index	23 ± 3	24 ± 3	0.77
Hypertension (n (%))	14 (88)	29 (91)	0.74
Diabetes mellitus (n (%))	15 (41)	6 (55)	0.54
Myocardial infarction (n (%))	4 (11)	1 (9)	0.87
Atrial fibrillation (n (%))	1 (3)	1 (9)	0.35
Hospitalization due to heart failure (n (%))	3 (8)	2 (18)	0.34
Stroke/transient ischemic attack (n (%))	1 (3)	1 (9)	0.35
Smoking (n (%))	11 (30)	5 (45)	0.33
Systolic blood pressure (mmHg)	136 ± 17	132 ± 16	0.44
Diastolic blood pressure (mmHg)	76 ± 12	77 ± 16	0.92
B-blocker use (n (%))	12 (32)	1 (9)	0.08
ACEI/ARB use (n (%))	22 (59)	8 (73)	0.42
Statin use (n (%))	12 (32)	3 (27)	0.66
Sulfonylurea use (n (%))	6 (12)	3 (27)	0.45
Adiponectin in great cardiac vein (μg/mL)	7.60 ± 3.58	9.08 ± 6.07	0.31
Adiponectin in left coronary artery (μg/mL)	6.81 ± 3.31	9.26 ± 6.10	0.08
Triglycerides (mg/dL)	123 ± 52	111 ± 40	0.51
Total cholesterol (mg/dL)	176 ± 28	196 ± 37	0.05
Fasting glucose (mg/dL)	107 ± 26	109 ± 17	0.97
Creatine (mg/dL)	1.03 ± 0.25	0.96 ± 0.27	0.48
Brain natriuretic peotide (pg/mL)	49.7 ± 53.2	8.9 ± 3.0	0.15
C-reactive protein (mg/dL)	0.14 ± 0.17	0.29 ± 0.40	0.24
Left ventricular ejection fraction (%)	65 ± 9	61 ± 917	0.29

ACEI indicates angiotensin-converting enzyme inhibitor and ARB, angiotensin II receptor blocker. Values are expressed as the mean ± SD or numbers.

group. There was no significant difference between the two groups.

Sixteen MACE occurred, including one cardiovascular death, one case of unstable angina, one case of heart failure, 6 cases of PCI, one case of coronary artery bypass grafting, two cases of nonfatal myocardial infarction, and 4 cases of ischemic stroke (Table II). The incidence of MACE was significantly higher in the adiponectin-negative production group (7/11 patients) than in the adiponectin-positive production group (9/37 patients) ($P = 0.02$) (Table III). In multivariate analysis, adiponectin-negative production was a predictive factor for MACE ($P = 0.03$) (Table IV). Kaplan-Meier analysis revealed that the MACE-free rate was significantly lower in the adiponectin-negative production group than in the adiponectin-positive production group (Figure).
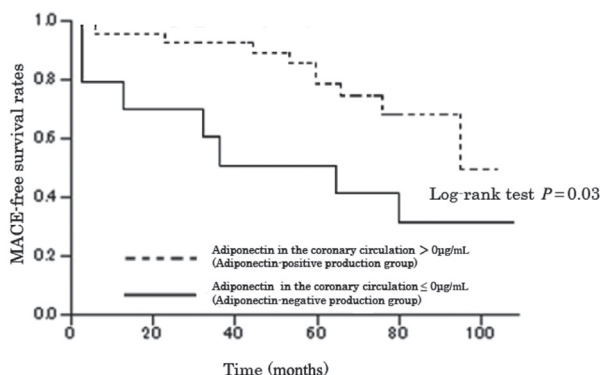

Figure. Kaplan-Meier survival curves stratified by plasma adiponectin levels in the coronary circulation. Patients in the adiponectin-negative production group had a reduced event-free survival rate.

Table II. List of 16 Patients With MACE

No	age	gender	Adiponectin in the coronary circulation (µg/mL)	Adiponectin in LCA (µg/mL)	Adiponectin in GCV (µg/mL)	Follow (months)	MACE
1	49	M	-0.2	3.4	3.2	33	UAP
2	69	M	-0.5	7.2	6.7	4	PCI
3	73	M	0.9	11	11.9	24	PCI
4	61	M	0.2	8.1	8.3	45	MI
5	80	F	0.6	11	11.6	7	PCI
6	65	F	0.2	3.9	4.1	45	CVA
7	78	M	-0.9	16	15.1	66	CVA
8	68	M	-0.3	7.6	7.3	4	CVA
9	79	M	-0.1	24.5	24.4	55	CV death
10	68	M	-0.1	9.2	9.1	14	PCI
11	62	M	0.7	4.8	5.5	60	CABG
12	56	M	0.5	4.5	5	54	PCI
13	79	F	2.1	14.6	16.7	86	CHF
14	63	M	1.2	9.4	10.6	95	PCI
15	70	M	0	6.8	6.8	80	CVA
16	77	F	1	10.5	12.1	44	MI

MACE indicates major adverse cardiac events; LCA, left coronary artery; GCV, great cardiac vein; CHF, chronic heart failure; UAP, unstable angina pectoris; PCI, percutaneous coronary intervention; CABG, coronary bypass grafting; MI, myocardial infarction; CVA, cerebrovascular attack; and CV death, cardiovascular death.

Table III. Comparison of the Incidence of MACE Between Adiponectin-Positive Production Group and Adiponectin-Negative Production Group

	Adiponectin-positive production group $n = 37$	Adiponectin-negative production group $n = 11$	P
MACE (n (%))	9 (24)	7 (64)	0.02

MACE indicates major adverse cardiovascular events.

Table IV. Univariate and Multivariate Analysis of the Predictive Factor for MACE

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age (over 70 years old)	0.53	0.16 ~ 1.79	0.31	0.82	0.20 ~ 3.32	0.78
Gender (male)	1.94	0.55 ~ 6.88	0.3	3.21	0.69 ~ -14.93	0.14
Adiponectin-negative production group	5.44	1.29 ~ -22.97	0.02	5.25	1.12 ~ -24.46	0.03
Total cholesterol (180 mg/dL over)	2.78	0.80 ~ -9.59	0.11	5.5	0.68 ~ -13.67	0.14

MACE indicates major adverse cardiovascular events.

DISCUSSION

In the present study, adiponectin production in the coronary circulation was defined as the difference between the adiponectin level at GCV and that at LCA. In other words, the amount of adiponectin production in the coronary circulation is the sum of production and consumption in the coronary circulation. Based on this definition, we showed that CAD patients with adiponectin-negative production, that is, less adiponectin production and/or more adiponectin consumption in the coronary circulation, may have an increased risk of MACE, including cardiovascular and cerebrovascular events. This suggests that an atherosclerotic lesion is more developed in not only the coronary artery but also the cerebral/carotid artery in the adiponectin-negative production group. Our findings may for the first time indicate an association between adiponectin production and/or adiponectin consumption in the coronary circulation and MACE.

Table II shows a lower incidence of stroke in the adiponectin-positive production group (one patient) than the adiponectin-negative production group (3 patients); however, the difference between the two groups was not statistically significant. Additionally, there were no differences in the risk factors for stroke, such as previous stroke/TIA, smoking, atrial fibrillation, and CRP between the two groups (Table I). Taken together, the overall incidence of stroke and cardiac events was significantly higher in the adiponectin-negative production group than the adiponectin-positive production group.

The relationship between the systemic adiponectin level and MACE is controversial. Prospective studies have shown that high plasma adiponectin levels are associated with a low risk of myocardial infarction in healthy men [11] and with a moderately decreased CAD risk in diabetic men.[12] On the other hand, recently, the paradoxical association of high adiponectin levels with adverse outcomes was reported in high-risk patients such as those with severe CAD and heart failure. Adiponectin seems to play a paradoxical role in patients with manifest CAD.[15,16] In this study, Table 1 shows a higher mean value of adiponectin at LCA in the adiponectin-negative production group than the adiponectin-positive production group. However, there is no statistical difference between the two groups, possibly because of the wide deviation of the value. Although we did not measure adiponectin in the peripheral vein, the adiponectin level in LCA blood might substitute for systemic adiponectin. The adiponectin level in LCA was not associated with MACE. Adiponectin-positive production may be more sensitive for MACE than systemic adiponectin. The difference in the adiponectin level between GCV and LCA is the sum of production and consumption in the coronary circulation. Adiponectin could be incorporated into the vascular intima and the atherosclerotic lesion. Adiponectin has the ability to bind to collagens I, II, and V, which are abundant in the vascular intima, and to accumulate in the vascular subendothelial space when the endothelial barrier is damaged.[17] It has also been suggested that adiponectin targets injured atherosclerotic plaque, resulting in its consumption in the circulating plasma.[18] Thus, we speculate that the transcardiac extraction of adiponectin, at least partly, results from incorporation into atherosclerotic plaque in the coronary artery.

The main production site of adiponectin in the coronary circulation is thought to be epicardial adipose tissue, because adiponectin is exclusively secreted from adipocytes,[1] and epicardial adipose tissue and the myocardium share the same blood supply, namely, the coronary circulation.[19] We previously reported that adiponectin is locally produced in the coronary circulation and might participate in modulating the coronary circulation in individuals with normal coronary arteries.[13] We speculate that adiponectin secreted from epicardial fat directly affects the coronary artery in a vasocrine or paracrine manner.[20] We also reported that patients with CAD had lower adiponectin production in the coronary circulation than non-CAD patients;[14] however, in some patients with CAD, adiponectin in GCV was lower than in LCA, namely the adiponectin-negative production group in the present study. The adiponectin-negative production group was a predictive factor of MACE and had a lower MACE-free rate in this study. Adiponectin level in the coronary circulation is determined by the net balance between the production and uptake of adiponectin. We speculate that patients with adiponectin-negative production could have extensively developed atherosclerotic lesions of not only a coronary artery but also a cerebral artery. This may partially contribute to the higher risk of MACE.

In conclusion, our results suggest that the amount of adiponectin production in the coronary circulation may be able to predict future cardiovascular events in CAD patients.

Limitations: The present study had several limitations. First, it was a retrospective and small study. Second, there were no adiponectin data for peripheral blood. Third, the association between MACE and change of adiponectin in the coronary circulation during the follow-up period was unclear. Further investigations are needed to elucidate in more detail the association between MACE and adiponectin in the coronary circulation.

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