Plasma adiponectin as a predictive factor of survival after a bypass operation for peripheral arterial disease

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Objective: **We investigated an association between adiponectin and long-term survival in patients requiring an arterial bypass operation for peripheral arterial disease.**

Methods: **An enzyme-linked immunosorbent assay kit was used to measure plasma adiponectin levels in 49 patients (38 men, 11 women) before they underwent an arterial bypass operation. Median patient age was 70 years (range, 49-90 years). The study excluded patients with hemodialysis requirement, heart failure, malignant neoplasm, or collagen disease. The symptoms at the first visit were severe intermittent claudication in 27 patients (55%) and critical limb ischemia with rest pain or ulcer, or both, in 22 (45%).**

Results: **Plasma adiponectin levels were a mean 7.8 ± 5.3 μg/mL (range, 1.0-25.2 μg/mL). Multiple regression analyses revealed that plasma adiponectin was positively correlated with age ($r = 0.49$, $P = .0003$) and negatively correlated with body mass index ($r = -0.51$, $P = .0002$) and systolic blood pressure ($r = -0.41$, $P = .0059$). The Cox proportional hazards model revealed that plasma adiponectin (hazard ratio, 1.30; $P = .03$) and critical limb ischemia (hazard ratio, 16.67; $P = .047$) were significant independent predictors of patient survival after a bypass operation.**

Conclusion: **Plasma adiponectin could be indicative of mortality after a bypass operation for patients with advanced peripheral arterial disease. (J Vasc Surg 2009;50:95-9.)**

Peripheral arterial disease (PAD) is a progressive atherosclerotic condition that affects approximately 27 million people in North America and Europe; however, its mechanism of progression is not fully understood. The reported risk factors for atherosclerosis are diabetes mellitus, hypertension, dyslipidemia, and smoking, but prognostic factors for patients with PAD have not been clearly determined. Lipid-related metabolism was recently shown to be strongly associated with the prognosis of atherosclerosis. During a 24-month period, outcome events of PAD occurred more frequently in patients with metabolic syndrome or obesity than in patients without these diagnoses.[1] Waist circumference was an independent predictor of the likelihood of PAD outcome events in claudicant patients.[1]

Adiponectin is a fat-derived secreted protein that is abundantly present in human plasma.[2,3] Adiponectin contains a collagen-repeat domain at the N terminus and a globular domain at the C terminus, with a sequence homology to collagens VIII and X, and compliment factor C1q. Adiponectin levels are negatively regulated by accumulation of body fat.[4] In this regard, plasma adiponectin levels are low in obese individuals.[5] Hypoadiponectinemia has been clinically identified as a risk factor for the development of type 2 diabetes mellitus,[6] coronary artery disease,[7] and hypertension.[8] Increasing evidence from experimental studies indicates that adiponectin protects against the development of diabetes mellitus, hypertension, and cardiovascular disease.

Thus, adiponectin could act as a key molecule for clarifying the pathogenesis of obesity-linked disorders. Recent prospective studies demonstrated that low adiponectin levels are an independent predictor of death in patients with stroke.[9] Conversely, high plasma adiponectin levels were a positive predictor of death in patients with chronic heart failure.[10]

Plasma adiponectin was reported to be significantly lower in patients with early-stage PAD than in patients without PAD and was independently associated with the ankle-brachial index (ABI).[1,11] However, the relationship between adiponectin level and the prognosis of PAD patients has not been fully investigated. Here, we investigated the association of plasma adiponectin with the survival of PAD patients requiring an arterial bypass operation. We hypothesized that plasma adiponectin could be a determinant factor of patients' long-term survival after a bypass operation for PAD, which represents one of the end-stage conditions of generalized atherosclerosis.

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Table I. Clinical characteristics of the 49 study participants

Variable	*No. or mean ± SD*
Age, y	70.2 ± 8.7
Sex	
Male	38
Female	11
Body mass index, kg/m^2	22.4 ± 3.8
Diabetes mellitus	28
Hypertension	38
Dyslipidemia	17
Ischemic heart disease	20
Cerebrovascular disease	12
Systolic blood pressure, mm Hg	140 ± 19
Total cholesterol, mg/dL	194.1 ± 37.0
Triglyceride, mg/dL	129.7 ± 83.2
Creatinine, mg/dL	1.1 ± 0.8

MATERIALS AND METHODS

The study enrolled 50 consecutive patients with PAD who underwent an arterial bypass operation at Saiseikai Wakayama Hospital. They were diagnosed with PAD by peripheral arteriography and their clinical symptoms. One patient was lost to follow-up at an early stage; thus, 49 patients (38 men, 11 women) were finally analyzed. The patients were a median age of 70 years (range, 49-90 years). The study excluded hemodialysis patients and those with heart failure, malignant neoplasm, or collagen disease because these comorbidities are known to affect plasma adiponectin levels.

The symptoms at the first visit to our hospital were severe intermittent claudication in 27 patients (55%) and critical limb ischemia with rest pain or ulcer, or both, in 22 (45%), noted as Fontaine 2 in 27, Fontaine 3 in four, and Fontaine 4 in 18. The concomitant diseases were type 2 diabetes mellitus in 28 patients (57%), hypertension in 38 (78%), dyslipidemia in 17 (35%), ischemic heart disease in 20 (41%), and symptomatic cerebrovascular disease in 12 (24%) (Table I).

Diabetes mellitus was defined according to the World Health Organization criteria. Hypertension was defined as systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg on repeated measurements, or receiving antihypertensive treatment. Dyslipidemia was defined as levels of total cholesterol ≥220 mg/dL or triglyceride ≥150 mg/dL, or receiving lipid-lowering therapy. Ischemic heart disease was diagnosed by the existence of significant stenosis or occlusion in preoperative coronary angiography.

All patients underwent peripheral artery bypass grafting. An artificial graft was used in 22 patients, and an autologous vein was used in 27. The operations comprised an aortobifemoral bypass in 8 patients, a femorofemoral crossover bypass in 7, a femoropopliteal bypass in 17, and a tibial bypass in 17.

Routine laboratory results and body mass index (BMI) was recorded. After patients provided informed consent, venous blood samples were obtained before the operation, and the plasma adiponectin levels were determined using an adiponectin enzyme-linked immunosorbent (ELISA) kit (Otsuka Pharmaceutical Co Ltd, Tokyo, Japan).

Table II. Adiponectin level in subgroups

Subgroup	*Adiponectin level*[a]	P
Gender		.17
Male	7.3 ± 4.3	
Female	9.8 ± 7.7	
Severity of leg ischemia		.20
Claudication	7.0 ± 4.6	
Critical limb ischemia	8.9 ± 5.9	
Diabetes mellitus		.33
Yes	7.2 ± 5.5	
No	8.7 ± 4.9	
Hypertension		.82
Yes	7.9 ± 5.6	
No	7.5 ± 3.9	
Dyslipidemia		.17
Yes	6.4 ± 4.1	
No	8.6 ± 5.7	
Ischemic heart disease		.61
Yes	7.1 ± 4.7	
No	7.8 ± 5.0	
Cerebrovascular disease		.66
Yes	7.3 ± 6.1	
No	8.0 ± 5.0	
History of tobacco smoking		.14
Yes	7.2 ± 4.4	
No	9.7 ± 7.1	

[a]Data are presented as the mean μg/mL ± standard deviation.

After the operation, the patients were followed up at our outpatient clinic at intervals of 3 to 6 months. Antithrombotic treatment was prescribed in all patients postoperatively with one or a combination of following agents: aspirin, cilostazol, eicosapentaenoic acid, and iloprost. Six patients were prescribed lipid-lowering agents and 15 received angiotensin-converting enzyme inhibitors.

The results were expressed as the mean ± standard deviation (SD). The plasma adiponectin levels were compared among subgroups using a *t* test for unpaired variables. The correlations between plasma adiponectin and the indicated parameters were examined by multiple regression analyses. The survival rate was calculated with the Kaplan-Meier method. A survival analysis was performed with the multivariable Cox proportional hazards model. Differences were considered to be significant at $P < .05$.

RESULTS

Plasma adiponectin levels in PAD patients. The clinical characteristics of the patients are summarized in Table I. The mean plasma adiponectin level was 7.8 ± 5.3 μg/mL (range, 1.0-25.2 μg/mL) and did not differ according to gender; symptoms of leg ischemia (claudication or critical limb ischemia); presence of diabetes mellitus, hypertension, dyslipidemia, or ischemic heart disease; and history of cerebral vascular disease or tobacco smoking (Table II). The plasma adiponectin levels were not corre-

Table III. Adiponectin level and clinical parameters

Variable	*r*	P
Age	0.49	.0003
Body mass index	−0.51	.0002
Systolic blood pressure	−0.41	.0059
Total cholesterol	−0.02	.89
Triglyceride	−0.19	.20
Serum creatinine	0.23	.11

Table IV. Mortality during follow-up analyzed with multivariable Cox proportional hazard analysis

Variable	*HR (95% CI)*	P
Age	0.96 (0.83-1.12)	.624
Body mass index	1.06 (0.69-1.64)	.783
Systolic blood pressure	1.03 (0.96-1.10)	.379
Severity of leg ischemia (CLI)	16.7 (1.03-271)	.047
Diabetes mellitus (yes)	1.34 (0.18-9.09)	.794
Ischemic heart disease (yes)	2.78 (0.34-25)	.339
History of tobacco smoking (yes)	3.59 (0.07-25)	.814
Adiponectin	1.30 (1.03-1.66)	.030
Total cholesterol	0.99 (0.96-1.03)	.737
Triglyceride	0.99 (0.96-1.01)	.226

CI, Confidence interval; *CLI,* critical limb ischemia; *HR,* hazard ratio.

lated with total cholesterol, triglyceride, or serum creatinine, but were positively correlated with age ($r = 0.49$, $P = .0003$) and negatively correlated with BMI ($r = -0.51$, $P = .0002$) and systolic blood pressure ($r = -0.41$, $P = .0059$; Table III).

Plasma adiponectin levels and prognosis of the bypass graft. During the mean follow-up of 3.3 years, graft occlusion occurred in 20 patients. The primary graft patency rate was 61.2%, and the secondary patency rate was 74.8% for 3 years. To determine independent predictors of graft patency, the Cox proportional hazards model was used to analyze plasma adiponectin, age, BMI, systolic blood pressure, serum creatinine, total cholesterol, triglyceride, symptoms of leg ischemia, association of diabetes mellitus or ischemic heart disease, history of tobacco smoking, and type of operation, the number of patent tibial run-off vessels. None of these factors was significantly associated with the primary or secondary patency rate.

Plasma adiponectin levels and survival. A total of 12 patients died during the follow-up period. Perioperative mortality was not different among the different type of operation (data not shown). Cox proportional hazards model analysis of plasma adiponectin, age, BMI, systolic blood pressure, serum creatinine, total cholesterol, triglyceride, symptoms of leg ischemia, association of diabetes or ischemic heart disease, and history of tobacco smoking revealed that plasma adiponectin (hazard ratio, 1.30; $P = .03$) and critical limb ischemia (hazard ratio, 16.67; $P = .047$) were significant independent predictors of survival of PAD patients after a bypass operation (Table IV). The Fig shows the survival curves of patients with plasma adiponectin levels of the first (<4.0 μg/mL; n = 11), the second (4.0 to ≤6.0 μg/mL; n =11), the third (6.0 to ≤10.7 μg/mL; n = 15), and the fourth quartile (≥10.7 μg/mL; n = 12). The survival rate of patients in the fourth quartile was significantly worse than in the other three quartiles ($P = .042$) according to Kaplan-Meier analysis and the Mantel-Cox test.

DISCUSSION

The present study is the first, to our knowledge, to examine the association between plasma adiponectin and death in PAD patients after a bypass operation. In this study, high plasma adiponectin levels were independently associated with an increased risk of death in PAD patients who underwent a bypass operation.

Adiponectin is generally reported to act in an anti-inflammatory, antidiabetic, and antiatherogenic fashion. The plasma adiponectin levels did not differ between patients with claudication and those with critical limb ischemia. Furthermore, no significant differences were noted for the associated atherosclerotic risk factors. We speculate that these findings resulted because we recruited patients with relatively severe PAD. Specifically, our indications for a bypass operation are so restricted that the symptoms were quite severe even in patients with claudication.

Several studies have investigated adiponectin levels in PAD patients. Golledge et al[1] reported that serum adiponectin was positively correlated with the ABI, maximum walking distance, and initial claudication distance. Their participants were limited to patients with claudication. Iwashima et al[11] reported a positive correlation of plasma adiponectin with the ABI and a negative correlation with the Fontaine stage; however, few of their participants appeared to have critical limb ischemia. Their average ABI was 0.61, and the average Fontaine stage was 1.8, whereas 45% of our participants had critical limb ischemia and all of our patients required a bypass operation.

It may be true that plasma adiponectin is negatively correlated with the severity of PAD in the early stage of the disease, but this may not be the case in more severely affected patients. Plasma adiponectin was positively correlated with age and negatively correlated with BMI and systolic blood pressure in our study, consistent with many previous reports and supporting the validity of our data set.

Because adiponectin plays a favorable role in the remodeling of endothelial function[12] and acts in an anti-inflammatory fashion,[13] the plasma adiponectin level may affect the prognosis of graft patency. We found no relationship between the initial plasma adiponectin level and the fate of the graft. On the other hand, a high level of plasma adiponectin was an independent predictor of all causes of death after a bypass operation. A positive correlation between plasma adiponectin and a poor survival rate was observed, and patients with plasma adiponectin levels lower than the third quartile had a better prognosis than those higher than the fourth quartile. Thus, adiponectin represents a useful biomarker for assessment of death in patients with severe PAD who undergo bypass surgery.

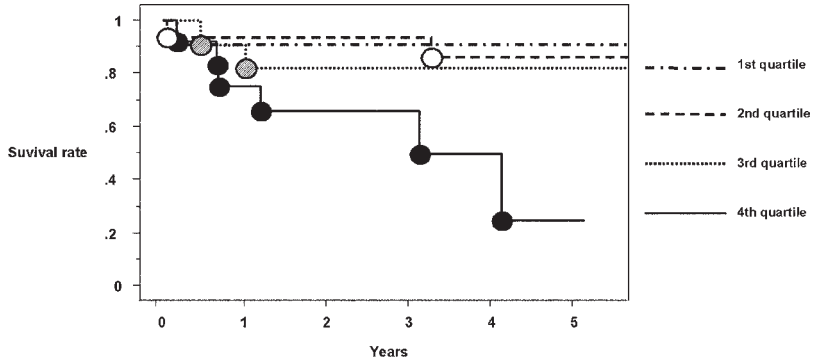

Fig. Survival curves are shown for patients with plasma adiponectin levels of the first (<4.0 mg/mL, n = 11), the second (4.0 to <6.0 mg/mL, n = 11), the third (6.0 to <10.7 mg/mL, n = 15) and the fourth quartile (≥10.7 mg/mL, n = 12). Survival rate of patients in the fourth quartile was significantly worse than in the other three quartiles ($P = .042$) according to Kaplan-Meier analysis and the Mantel-Cox test.

These results appear to be counterintuitive, however, considering the anti-inflammatory, antidiabetic, and antiatherosclerotic properties of adiponectin. In patients with established chronic heart failure (CHF), high serum adiponectin levels were independently predictive of death. Tsutamoto et al[14] suggested that higher adiponectin levels could be a marker of the wasting process in CHF, based on the finding that weight loss increases plasma adiponectin. Kistorp et al[10] found the same relationship between adiponectin and survival of patients with advanced CHF. Similar results were obtained by George et al,[15] who speculated that high adiponectin levels may represent an expression of high energy expenditure.

High adiponectin levels were a determinant factor of death in patients presenting with chest pain,[16] and the authors suggested that high adiponectin levels might reflect counter-regulatory or compensatory increases, or occur as a consequence of resistance at the adiponectin receptor level. PAD patients who require a bypass operation likely have elevated energy waste to maintain the whole body condition against the progress of atherosclerosis. It is also possible that clearance of adiponectin is impaired in severe PAD, presumably due to downregulation or dysfunction of adiponectin receptors and that at this stage, adiponectin no longer has vascular protective actions due to decreased sensitivity of adiponectin to the vasculature or reduced levels of the functionally active form of adiponectin. Irrespective of the possible explanations, however, the mechanism of how high levels of adiponectin are associated with death in PAD patients is still unknown. Because our results are obtained from an observational study, future studies will be needed to explain why patients with higher levels of a seemingly protective factor show a higher rate of death.

The present study has several limitations. The sample size was relatively small. Adiponectin levels did not correlate with graft outcomes, although the graft patency rate was not excellent. It might not be reasonable to estimate graft-related outcomes from such disparate patient groups.

The magnitude of the hazard ratio was higher for ischemic heart disease or diabetes mellitus, but we could not find statistical significance for these variables, which could be a strong predictor for survival after bypass operation.[17] Future prospective studies involving larger populations with homogeneous patients are therefore required.

Some agents that may increase the plasma adiponectin level, such as antidiabetic[18] and antihyperlipidemic drugs,[19] were used in the present study and may have affected the results.

Finally, we intentionally excluded patients with end-stage renal failure who required hemodialysis. PAD with hemodialysis is the most serious condition associated with this disease and has the worst survival,[20] although a recent improvement in graft patency was reported.[21,22] The contribution of adiponectin to the mortality rate of hemodialysis patients remains to be elucidated in future studies.

CONCLUSION

High plasma adiponectin levels are independently associated with an increased risk of death in PAD patients who undergo a bypass operation. In the high-risk population, adiponectin, an antiatherosclerotic protein by nature, adversely predicted patient survival, similar to the case for CHF patients and patients presenting with chest pain.

AUTHOR CONTRIBUTIONS

Conception and design: HK, RS, MJ, KM, NO, TM
Analysis and interpretation: HK
Data collection: HK, RS, MJ
Writing the article: HK
Critical revision of the article: HK, RS, MJ, KM, NO, TM
Final approval of the article: HK, RS, MJ, KM, NO, TM
Statistical analysis: HK, RS, KM
Obtained funding: RS, TM
Overall responsibility: HK, RS

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