J Tokyo Wom Med Univ
78 (10・11) 461～467 (2008)

Original

Adiponectin and Atherosclerosis in Chronic Hemodialysis Patients

Asuka AOKI[1], **Kan KIKUCHI**[2], **Misao TSUKADA**[1], **Takashi AKIBA**[2] and **Kosaku NITTA**[1]

[1]Department of Internal Medicine IV, Tokyo Women's Medical University, School of Medicine
[2]Department of Blood Purification, Tokyo Women's Medical University, School of Medicine

(Accepted Sep. 8, 2008)

Atherosclerosis is a serious complication in patients undergoing chronic hemodialysis. The serum levels of adiponectin to the risk of development of arterial sclerosis and its treatment have not yet been fully clarified in hemodialysis patients.

The present study was undertaken to examine the relationship between atherosclerosis and the serum levels of adiponectin in hemodialysis patients. The subjects were 25 males and 24 females who had been undergoing chronic hemodialysis at our facility.

Simple regression analysis revealed a significantly negative correlation between the brachial ankle pulse wave velocity (baPWV) and the serum adiponectin level ($r = -0.43$, $p = 0.003$). Stepwise multiple regression analysis revealed the serum adiponectin level and age as major factors determining the baPWV. To analyze the relationship between the serum levels of adiponectin and various parameters of atherosclerosis, the serum adiponectin levels in the patients were divided into tertiles, low group, medium group, and high group. Observation of the changes of the baPWV over one year revealed that the value increased significantly in the low group as compared with that in the patients with values in the high group and medium group. Development of cardiovascular disease was observed only in the patients with serum adiponectin levels in the low group.

The results of this study indicate that serum adiponectin are important factors determining the rate of progression of atherosclerosis in chronic hemodialysis patients.

Key words: hemodialysis, adiponectin, atherosclerosis, pulse wave velocity

Introduction

It has been shown that the multiple risk factor syndrome, characterized by the coexistence of multiple risk factors (abnormal glucose tolerance, hyperlipidemia, hypertension, etc.), plays a significant role in the onset of atherosclerotic diseases. The National Cholesterol Education Program (NECP) and WHO concepts of metabolic syndrome were proposed for use in diagnosing this condition, and also have proposed criteria for the diagnosis of this condition[1)2)]. This syndrome is not simply an incidental accumulation of multiple factors, but has rather been shown to involve visceral fat accumulation in the upstream pathway[3)4)].

Metabolic syndrome serves as a firm basis for atherosclerosis because accumulation of visceral fat causes not only the coexistence of multiple risk factors but also secretion of adipocytokines related directly to the onset of atherosclerotic disease[5)].

Adiponectin is an adipocytokine of fat-cell origin which exerts anti-atherosclerotic and antidiabetic activities, whose level decreases with visceral fat accumulation[6)]. Adiponectin exerts anti-atherosclerotic activity through its direct actions on the blood vessels. Adiponectin is also known to be involved in ameliorating resistance to insulin, and to exhibit anti-inflammatory activity and antihypertensive activity through stimulation of tissue fat catabolism[7)~9)]. It has been reported that healthy individuals with high serum adiponectin levels are sig-

nificantly less likely to die of future cardiovascular diseases[10][11]. Atherosclerosis is a serious complication in patients undergoing hemodialysis[12][13]. Cerebrovascular and coronary artery diseases are leading causes of death in hemodialysis patients, although the serum adiponectin levels are higher in these patients than in healthy individuals[14]. However, the relationships of visceral fat accumulation and the serum adiponectin levels to the risk of development of arterial sclerosis and its treatment have not yet been fully clarified in hemodialysis patients in the multiple arteriosclerotic disease developing prior to the introduction of hemodialysis.

The present study was undertaken to examine the relationship between atherosclerosis and the serum adiponectin levels and between the serum adiponectin levels and visceral fat area in hemodialysis patients.

Subjects and Methods

1. Subjects

The subjects of this study were 49 patients undergoing chronic hemodialysis at the Kidney Center of Tokyo Women's Medical University. The patient characteristics are shown in Table 1.

2. Methods

Assessment of the background factors, measurement of abdominal circumference, blood pressure and visceral fat area, assessment of atherosclerosis, and collection of blood samples were conducted for each subject.

The blood samples were collected before the first dialysis session of a week, 6 hours or more after the last meal, for measurement of adiponectin, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglycerides (TG) and high sensitivity CRP (hsCRP), and blood glucose.

After completion of each dialysis session, the dry weight (DW) of the patients was measured, and the abdominal circumference was measured around the umbilicus with the subject in the standing position. Patients with polycystic kidney disease as the underlying disease were excluded from the abdominal circumference measurement.

The mean of 13 measurements of blood pressure during a month (each conducted before a dialysis session on a given day) was adopted as the blood pressure level for a given patient.

The visceral and subcutaneous fat areas were measured on transverse abdominal CT scans obtained at the umbilical level. Imaging was performed at the terminal expiratory phase. The visceral and subcutaneous fat areas were measured on the basis of the CT number of fat tissue.

The brachial ankle pulse wave velocity (baPWV) was measured as a marker of atherosclerosis using a blood pressure and pulse wave measuring device (Form PWV/ABI, Omron Colin, Kyoto, Japan). And the all patients were measured the baPWV after one year again.

Serum adiponectin was measured by ELISA (Human Adiponectin ELISA Kit, Otsuka Pharmaceutical, Tokyo, Japan).

Each parameter was expressed as the mean ± SD. Statistical analysis was performed using JMP Version 5.1 (SAS for Windows, Cart, NC, USA). In all tests, $p<0.05$ was regarded as denoting statistical significance.

Results

Table 1 shows the background variables of the patients. The underlying disease was chronic glomerulonephritis in 30 cases (61.2%), polycystic kidney disease in 6 (12.2%), diabetic nephropathy in 5 (10.2%), other diseases(Alport's syndrome, toxemia of pregnancy, gout-kidney disease and neurogenic bladder) in 4 (8.2%), and unknown in 4 (8.2%). The adiponectin level was significantly higher in the female (28.3 ± 16.2 μg/ml) than in the male (19.3 ± 11.1 μg/ml) patients ($p = 0.02$).

Simple regression analysis revealed a significant negative correlation between baPWV and ADPN ($r=-0.43$, $p=0.003$) (Fig. 1).

Step-wise multiple regression analysis was carried out using baPWV as a dependent variable, and age, duration of dialysis, serum adiponectin, hsCRP, TC, TG, visceral fat area and the calcium-phosphorus product as independent variables. Serum adiponectin (F value=14.8, $p=0.0005$) and age (F value=4.9, $p=0.03$) were identified as significant independent variables for the baPWV (Table 2).

Simple regression analysis revealed a significant

Table 1 Clinical characteristics of patients

	Male	Female	p value
Number	25	24	-
Age (years)	54.6 ± 14.0	54.0 ± 14.0	0.89
Hemodialysis duration (years)	10.3 ± 9.3	16.4 ± 9.6	0.03
Waist circumference (cm)	82.6 ± 7.1	76.4 ± 12.9	0.05
Visceral fat area (cm^2)	103.1 ± 54.8	75.2 ± 60.8	0.11
Body mass index (kg/m^2)	21.2 ± 2.6	20.7 ± 4.4	0.60
Systolic blood pressure (mmHg)	137.6 ± 17.0	135.3 ± 18.9	0.66
Diastolic blood pressure (mmHg)	72.7 ± 12.2	68.1 ± 14.7	0.24
Hemoglobin (g/dl)	10.7 ± 0.9	10.1 ± 0.9	0.02
Serum albumin (g/dl)	3.9 ± 0.3	3.8 ± 0.3	0.19
Serum urea nitrogen (mg/dl)	70.9 ± 15.3	76.5 ± 17.7	0.24
Serum creatinine (mg/dl)	12.7 ± 2.1	10.4 ± 1.7	0.01
Ca (mg/dl)	9.2 ± 0.7	9.2 ± 0.9	0.85
P (mg/dl)	5.4 ± 0.3	5.5 ± 0.3	0.74
Total cholesterol (mg/dl)	153.1 ± 29.9	167.3 ± 30.7	0.11
Triglycerides (mg/dl)	109.1 ± 66.1	79.8 ± 30.5	0.05
LDL cholesterol (mg/dl)	87.1 ± 19.1	84.7 ± 22.3	0.69
HDL cholesterol (mg/dl)	46.1 ± 17.0	62.6 ± 18.5	0.01
hsCRP (mg/dl)	2,766 ± 4,974	2,214 ± 4,722	0.70
FBS (mg/dl)	94.4 ± 18.7	91.8 ± 31.1	0.72
Adiponectin (μg/ml)	19.3 ± 11.1	28.3 ± 16.2	0.02

FBS: fasting blood sugar, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, Ca: calcium, P: phosphorous.

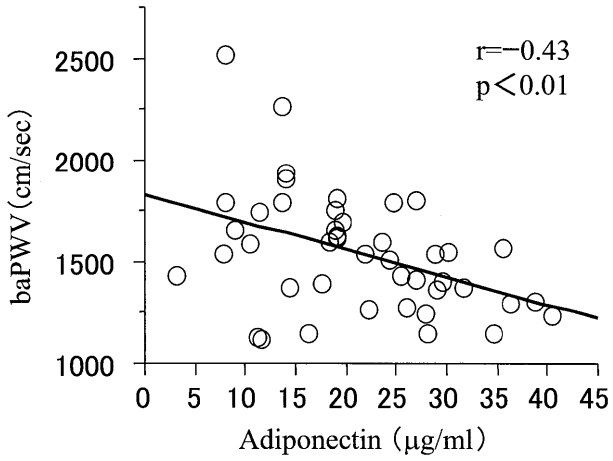

Fig. 1 Relationship between serum adiponectin and baPWV
Serum adiponectin correlated negatively with baPWV.

negative correlation between the serum adiponectin and the visceral fat area (r=−0.49, p=0.001) (Fig. 2).

Step-wise multiple regression analysis was then carried out, using the serum adiponectin as the dependent variable and age, duration of dialysis, sex, visceral fat area, subcutaneous fat area, LDL-C and hsCRP as independent variables. Sex (F value=8.4, p=0.007) and visceral fat (F value=7.0, p=0.01) were identified as significant independent variables for the serum adiponectin (Table 3).

Table 2 Results of multiple step-wise regression analysis for determinants of baPWV

	F value	p value
Adiponectin	14.77	0.0005
Age	4.88	0.03
Total cholesterol	2.80	0.10
Ca × P product	0.27	0.61
hsCRP	0.22	0.64
Triglycerides	0.18	0.68
Hemodialysis duration	0.16	0.69
Visceral fat area	0.02	0.88

Ca: calcium, P: phosphorous.

To analyze the relationship between the serum levels of adiponectin and various parameters of atherosclerosis, the serum adiponectin levels were divided into tertiles, as follows low group (serum adiponectin less than 15 μg/ml; n=16), medium group (serum adiponectin less than 25 μg/ml, but more than 15 μg/ml; n=16), and high group (serum adiponectin more than 25 μg/ml; n=17). Basal char-

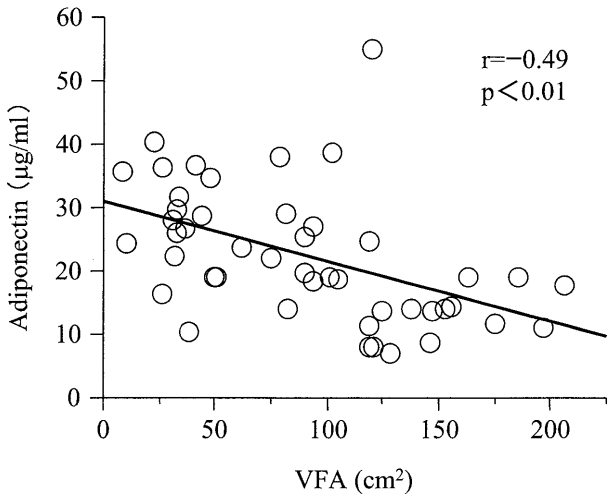

Fig. 2 Relationship between visceral fat area (VFA) and serum adiponectin
VFA correlated negatively with serum adiponectin.

Table 3 Results of multiple step-wise regression analysis for determinants of Adiponectin

	F value	p value
Sex	8.35	0.007
Visceral fat area	6.96	0.01
Age	3.52	0.07
LDL cholesterol	1.61	0.21
Hemodialysis duration	1.10	0.30
hsCRP	0.31	0.58
Subcutaneous fat area	0.22	0.64

LDL: low-density lipoprotein.

Table 4 Basal characteristics of the patients according to the Adiponectin levels

	Low	Medium	High	p
Number	16	16	17	
Age (years)	58.6 ± 14.1	49.9 ± 12.4	55.4 ± 14.2	0.22
Hemodialysis duration (years)	9.7 ± 9.7	12.2 ± 9.5	17.7 ± 9.1	0.05
Visceral fat area (cm^2)	132.6 ± 40.0	91.9 ± 58.1	59.6 ± 53.8	< 0.01
Body mass index (kg/m^2)	22.8 ± 3.1	21.1 ± 4.7	19.3 ± 1.9	0.02
Systolic blood pressure (mmHg)	143.6 ± 12.7	135.1 ± 12.6	136.5 ± 17.9	0.24
Diastolic blood pressure (mmHg)	70.0 ± 11.8	71.2 ± 12.1	70.3 ± 10.0	0.95
Serum albumin (g/dl)	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	0.82
Hemoglobin (g/dl)	10.6 ± 1.2	10.2 ± 0.9	10.3 ± 0.9	0.56
Serum urea nitrogen (mg/dl)	68.1 ± 17.3	73.8 ± 11.3	78.4 ± 19.2	0.21
Serum creatinine (mg/dl)	12.0 ± 2.4	11.9 ± 2.4	10.8 ± 1.9	0.22
Total cholesterol (mg/dl)	151.5 ± 32.2	161.3 ± 27.1	165.6 ± 33.4	0.43
Triglycerides (mg/dl)	129.1 ± 72.2	83.4 ± 37.2	77.8 ± 32.4	0.01
HDL cholesterol (mg/dl)	41.4 ± 13.7	55.8 ± 16.4	62.8 ± 21.3	< 0.01
FBS (mg/dl)	94.9 ± 26.2	88.9 ± 7.1	95.6 ± 34.2	0.73
HOMA-R	2.1 ± 1.6	1.3 ± 0.6	2.3 ± 3.6	0.52
Ca (mg/dl)	9.1 ± 0.6	9.3 ± 0.8	9.2 ± 0.9	0.77
P (mg/dl)	5.4 ± 1.5	5.7 ± 1.6	5.3 ± 1.6	0.71
hsCRP (mg/dl)	2,682 ± 4,096	3,194 ± 6,876	1,889 ± 3,299	0.39

The comparison between 3 groups were performed by ANOVA.
FBS: fasting blood sugar, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, Ca: calcium, P: phosphorous.

acteristics of the patients according to the adiponectin levels are shown in Table 4. Observation of the changes of the baPWV over one year revealed that the value increased significantly in those with serum adiponectin levels in the low group as compared with that in the patients with the values in the high group and medium group (Fig. 3).

None of the cases with serum adiponectin levels in the medium group and high group developed cardiovascular disease, while one patient each with the serum adiponectin level in the low group died of acute myocardial infarction, developed angina pectoris, and developed cerebral infarction.

Discussion

Adiponectin is a protein expressed and secreted specifically by fat cells, that is found at high concentrations (5-20 μg/ml) in vivo. The median adi-

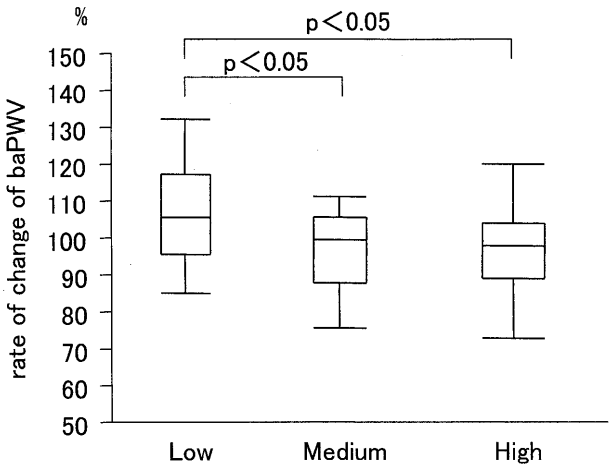

Fig. 3 Adiponectin tertiles and the rate of change of baPWV
The patients were divided into tertiles as described in Table 4. The ANOVA for differences in tertiles revealed no significant differences, and comparisons between low group and other groups were analyzed using the Student's t-test.

ponectin level is significantly higher in females (8.7 μg/ml) than in males (5.5 μg/ml)[15]. Patients with chronic kidney disease reportedly show elevation of the serum adiponectin levels as the GFR decreases, and the serum adiponectin levels in dialysis patients have been reported to be about 3 times higher than those in healthy individuals[14]. This previous report was supported by the present study results indicating significantly higher serum adiponectin levels (about 3 times higher) in the female (28.3 ± 16.2 μg/ml) than in the male (19.3 ± 11.1 μg/ml) patients. Although the pathways of metabolism or elimination of adiponectin have not yet been fully clarified, it would seem that compromised elimination capacity is one of the factors responsible for the high serum adiponectin levels in dialysis patients. One factor responsible for the higher serum adiponectin levels in the females is could be the smaller visceral fat area in females than in the males, but a possible influence of adiponectin-resistant hormones (e.g., testosterone) has also been suggested[16]. In the hemodialysis patients, although the serum adiponectin levels were high, the death rate from atherosclerotic diseases was also high. Whether or not elevated serum adiponectin levels contribute to prevention of atherosclerosis is, therefore, under debate. Stepwise multiple regression analysis carried out in this study revealed that adiponectin is an important factor determining the baPWV. In the univariate analysis, a significant negative correlation was noted between the baPWV and the serum adiponectin, indicating that reduced serum adiponectin levels were associated with atherosclerosis. Observation of the changes of the baPWV over one year revealed that the value increased significantly in those with serum adiponectin levels in the low group as compared with that in the patients with the values in the high group and medium group. None of the cases with serum adiponectin levels in the medium group and high group developed cardiovascular disease, while three patients in the low adioponectin group developed cerebral infarction and severe and fatal myocardial infarction. From these results of the one-year prospective study, we propose that low serum adiponectin levels contribute to the development of arteriosclerois and cardiovascular disease. It was also shown in this study that adiponectin exerts anti-atherosclerotic activity in hemodialysis patients in the multiple arteriosclerotic disease. In the stepwise multiple regression analysis, sex and visceral fat area were identified as important factors determining the serum levels of this anti-atherosclerotic protein. Univariate analysis revealed a significant negative correlation between the serum adiponectin and the visceral fat area, indicating that accumulation of visceral fat is also an important factor associated with the reduction in the serum adiponectin levels in hemodialysis patients.

The limitations of our study were the limited number of patients and the relatively short follow-up period of one year, and we used baPWV as the surrogate marker of arteriosclerosis. it would be desirable for a prospective study to be carried out to analyze the relationship between the serum adiponectin levels and the risk of atherosclerosis in hemodialysis patients. In the future, therefore, we propose to conduct a prospective study on a larger number of patients to determine the relation between the serum levels of adiponectin and the onset of arteriosclerotic diseases, and death.

Conclusion

The results of this study indicate that visceral fat accumulation and serum adiponectin are important factors determining the rate of progression of atherosclerosis in chronic hemodialysis patients.

References

1) **No authors**: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA **285**: 2486–2497, 2001
2) **Alberti KG, Zimmet PZ**: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1:diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med **15**: 539–553, 1998
3) **Matsuzawa Y, Funahashi T, Nakamura T**: Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive substances. Ann N Y Acad Sci **892**: 146–154, 1999
4) **Iannucci CV, Capoccia D, Calabria M et al**: Metabolic syndrome and adipose tissue: new clinical aspects and therapeutic targets. Curr Pharm Des. **13**: 2148–2168, 2007
5) **Lara-Castro C, Fu Y, Chung BH et al**: Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol **18**: 263–270, 2007
6) **Arita Y, Kihara S, Ouchi N et al**: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun **257**: 79–83, 1999
7) **Hotta K, Funahashi T, Bodkin NL et al**: Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes **50**: 1126–1133, 2001
8) **Iwashima Y, Katsuya T, Ishikawa K et al**: Hypoadiponectinemia is an independent risk factor for hypertension. Hypertension **43**: 1318–1323, 2004
9) **Ouchi N, Kihara S, Funahashi T et al**: Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation **107**: 671–674, 2003
10) **Pischon T, Girman CJ, Hotamisligil GS et al**: Plasma adiponectin levels and risk of myocardial infarction in men. JAMA **291**: 1730–1737, 2004
11) **Kumada M, Kihara S, Sumitsuji S et al**: Coronary artery disease. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol **23**: 85–89, 2003
12) **Foley RN, Parfrey PS, Sarnak MJ**: Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol **9**: 16–23, 1998
13) **Stack AG, Bloembergen WE**: Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: a cross-sectional study. J Am Soc Nephrol **12**: 1516–1523, 2001
14) **Odamaki M, Furuya R, Kinumura Y et al**: Association between plasma adiponectin concentration and visceral fat accumulation in hemodialysis patients. Nephron Clin Pract **102**: 8–13, 2006
15) **Miwa R, Nakamura T, Kihara S et al**: Adiponectin as a biomarker of the metabolic syndrome. Circ J **68**: 975–981, 2004
16) **Kollerits B, Fliser D, Heid IM et al**: Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. Kidney Int **71**: 1279–1286, 2007

慢性血液透析患者におけるアディポネクチンと動脈硬化

[1]東京女子医科大学第四内科学教室（主任：新田孝作教授）
[2]東京女子医科大学血液浄化療法科（指導：菊地　勘助教）
青木明日香[1]・菊地　勘[2]・塚田三佐緒[1]・秋葉　隆[2]・新田　孝作[1]

〔目的〕内臓脂肪より分泌されるアディポネクチンは抗動脈硬化作用を有する．透析患者では健常者と比較しアディポネクチンは高値であるが，動脈硬化は進行しており心血管疾患が死因の上位を占める．そこで，透析患者の動脈硬化とアディポネクチンとの関連について検討した．

〔方法〕当院で慢性透析中の男性25名，女性24名，年齢54.3±13.8歳，透析歴12.4±9.6年の患者を対象とした．対象者に空腹時採血を施行し，動脈硬化検査として上腕-足首間の脈波速度（baPWV）を測定した

〔結果〕単回帰分析でbaPWVとアディポネクチンは，r=−0.43，p=0.003と有意な負の相関を認めた．ステップワイズ重回帰分析で，baPWVに対する重要な因子はアディポネクチンと年齢であった．アディポネクチン値で3分位し，1年後のbaPWV変化を比較した場合，低値群で有意なbaPWVの上昇を認めた．

〔考察〕透析患者のアディポネクチンは高値であるが動脈硬化性疾患による死亡は高く，アディポネクチンが動脈硬化に関与するか不明であった．動脈硬化のマーカーであるbaPWVとアディポネクチンは有意な負の相関があり，アディポネクチン低値の患者では1年後のbaPWVが有意に上昇した．健常者と同様に透析患者でも，アディポネクチンが動脈硬化に関与する重要な因子であることが示された．

〔結論〕透析患者においても，アディポネクチンが動脈硬化の進展に影響を与える重要な因子である．