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Advanced atherosclerosis in predialysis patients with chronic renal failure

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Background. Atherosclerosis is advanced in hemodialysis patients as shown by increased intima-media thickness of carotid arteries (CA-IMT), although it is not established whether the advanced atherosclerosis results from hemodialysis treatment or from chronic renal failure. The purpose of this study was to evaluate the effects of hemodialysis and renal failure on CA-IMT in patients with chronic renal failure.

Methods. CA-IMT was measured by high-resolution B-mode ultrasonography in 110 patients with chronic renal failure before starting dialysis (CRF group), and compared with CA-IMT of 345 hemodialysis patients (HD group) and 302 healthy control subjects. They were all nondiabetic and the three groups were comparable in age and gender.

Results. As compared with the healthy control subjects, the CRF and HD groups had greater CA-IMTs, whereas CA-IMTs of the CRF and HD groups were not statistically different. There was no significant correlation between duration of hemodialysis and CA-IMT in the HD group. Multiple regression analysis in the total subjects indicated that presence of renal failure, but not being treated with hemodialysis, was a significant factor associated with increased CA-IMT independent of age, gender, blood pressure, smoking, high-density lipoprotein (HDL) and non-HDL cholesterol levels.

Conclusions. These results demonstrate that thickening of arterial wall is present in patients with chronic renal failure before starting hemodialysis treatment, and support the concept that advanced atherosclerosis in hemodialysis patients is due not to hemodialysis treatment, but to renal failure and/or metabolic abnormalities secondary to renal failure.

The risk of cardiovascular death is substantially elevated in patients with end-stage renal disease who are treated with hemodialysis. As compared with the general population, dialysis patients have more than a 10 times higher relative risk for cardiovascular mortality [1]. Lindner et al pointed out this fact in their early work, and they thought that atherosclerosis was accelerated in long-term maintenance hemodialysis [2]. Our previous studies revealed that hemodialysis patients had advanced arterial wall changes as shown by increased intima-media thickness (IMT) of the carotid and femoral arteries as an index of thickening of arterial wall [3, 4]. Also, arterial wall stiffness is increased in hemodialysis patients as demonstrated by increased aortic pulse wave velocity [5, 6]. These arterial wall changes are significant predictors of cardiovascular mortality in nonuremic populations [7, 8] and in hemodialysis patients [9, 10]. However, it is not established whether atherosclerosis is accelerated by hemodialysis. Although some authors reported that carotid artery IMT (CA-IMT) correlated positively with duration of hemodialysis treatment [11–13], others failed to confirm such a significant relationship of duration of hemodialysis with CA-IMT [3, 14–16], with aortic pulse wave velocity [5, 6], or with histological grading of arteries [17]. According to Joki et al, significant stenosis of coronary arteries is frequently found in patients at the time of starting hemodialysis [18].

To examine the possibility that atherosclerosis is advanced before the patient begins hemodialysis treatment, we measured CA-IMT in 110 predialysis patients with chronic renal failure, 345 patients on maintenance hemodialysis and 302 healthy control subjects. The results demonstrated that CA-IMT of the predialysis patients was as great as that of the maintenance hemodialysis patients, suggesting that it is not hemodialysis itself, but chronic renal failure and/or metabolic alterations secondary to renal failure that have an adverse effect on carotid atherosclerosis.

Key words: carotid artery, intima-media thickness, renal failure, hemodialysis, end-stage renal disease, cardiovascular disease.

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Table 1. Subjects

	Healthy	CRF	Hemodialysis	*P* value
Number	302	110	345	—
Male:female	147:155	65:45	189:156	0.114
Age *years*	57.8 ± 0.5	59.4 ± 1.0	58.3 ± 0.5	0.352
Serum creatinine *μmol/L*	65 ± 2	564 ± 43[a]	1003 ± 14[a,b]	<0.0001
Smoking index *cigarette-year*	294 ± 29	392 ± 51	294 ± 24	0.180
Systolic BP *mm Hg*	126 ± 1	144 ± 3[a]	142 ± 1[a]	<0.0001
Diastolic BP *mm Hg*	76 ± 1	79 ± 1	68 ± 1[a,b]	<0.0001
BMI kg/m^2	22.6 ± 0.2	22.3 ± 0.4	21.6 ± 0.2[b]	0.0002
Glucose *mmol/L*	5.32 ± 0.03	5.28 ± 0.10	4.98 ± 0.05[a,b]	<0.0001
Total cholesterol *mmol/L*	5.13 ± 0.05	4.51 ± 0.13[a]	4.57 ± 0.06[a]	<0.0001
HDL-C *mmol/L*	1.48 ± 0.03	1.18 ± 0.04[a]	1.24 ± 0.02[a]	<0.0001
NonHDL-C *mmol/L*	3.66 ± 0.05	3.33 ± 0.14[a]	3.34 ± 0.06[a]	0.0001
Triglycerides *mmol/L*	1.33 ± 0.05	1.42 ± 0.07	1.50 ± 0.04[a]	0.023
Duration of HD *months*	—	—	88 ± 4	—

Data are mean ± standard error (SE). *P* values are by analysis of variance (ANOVA) and by the chi-square test. Abbreviations are: CRF, chronic renal failure; BP, blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NonHDL-C, non-high-density lipoprotein cholesterol; HD, hemodialysis.
[a] $P < 0.05$ vs. healthy control subjects, and [b] $P < 0.05$ vs. HD group by Scheffe-type multiple comparison

METHODS

Subjects

This study consisted of 757 nondiabetic subjects including 110 predialysis patients with chronic renal failure (CRF group), 345 patients with end-stage renal disease treated with maintenance hemodialysis (HD group), and 302 healthy control subjects who gave informed consent. These subjects were randomly selected from our database after categorization by age range and gender, so that the three groups were comparable in terms of age and gender. Clinical characteristics of the subjects were given in Table 1. This study was approved by the institutional ethical committee (Inoue Hospital Approval No. 103).

Patients in the CRF group had an increased serum creatinine level greater than 133 μmol/L (=1.5 mg/dL). The primary renal diseases of the CRF group were chronic glomerulonephritis (70%), hypertensive nephrosclerosis (9%), polycystic disease (4%), toxemia of pregnancy (1%), and unknown (16%). Medication for hypertension included calcium channel blockers (CCB; 57%), angiotensin-converting enzyme inhibitors (ACEI; 14%), α-, β- or αβ-receptor antagonists (29%), and loop diuretics (36%). Overall, 68% of the CRF patients received antihypertensive medication. Also, statins were used for 18% of the CRF patients for dyslipidemia. No patient was receiving steroids. The patients were studied without washing out these medications.

The HD group consisted of those who were on maintenance hemodialysis for more than three months. The HD patients received three to five hours of hemodialysis, three times a week, using bicarbonate dialysate. Dialyzer membranes were cuprophane (59%), polymethylmethacrylate (20%), cellulose triacetate (16%), and ethylene vinyl alcohol (5%). The average (±SD) dose of dialysis (Kt/V) was 1.41 ± 0.31. The underlying renal diseases of the HD patients were chronic glomerulonephritis (78%), polycystic disease (6%), lupus nephritis (4%), hypertensive nephrosclerosis (4%), toxemia of pregnancy (3%), chronic pyelonephritis (2%), and unknown (3%). Medication for hypertension included CCB (47%), ACEI (20%), α-, β- or αβ-blockers (3%), and loop diuretics (28%). Overall, 62% of the HD patients were treated with antihypertensive medication. Also, 4% of the HD patients were receiving statins for dyslipidemia. No patient was receiving steroids. The patients were studied without washing out these medications.

The healthy controls were participants of a health check program in Osaka City. The exclusion criteria for the healthy control subjects were fasting hyperglycemia as defined by fasting plasma glucose >7.0 mmol/L (126 mg/dL), overt proteinuria, and liver dysfunction as defined by increased serum ALT >50 IU. Also, we excluded those who were on medication for diabetes mellitus, hypertension, and/or hyperlipidemia. Therefore, the healthy control subjects included those who were hypertensive and/or hyperlipidemic without medication.

Measurement of CA-IMT

Carotid artery intima-media thickness (CA-IMT) was measured by high-resolution B-mode ultrasonography using a real-time ultrasonograph with a 10-MHz in-line Sectascanner (SSD 650 CL; Aloka Co. Ltd., Tokyo, Japan) as described previously [3, 4, 19–21]. The carotid artery was scanned bilaterally in the longitudinal and transverse projections. The examination included approximately 4 cm of the common carotid artery, the carotid bulb, and 1 cm each of the internal and external arteries. The image was focused on the far wall of the arteries. The site of the most advanced atherosclerotic lesion that showed the greatest distance between the lumen-intima interface and the media-adventitia inter-

face was located in both the right and left carotid arteries. The greatest thickness of intima-media complex was used for analysis in this study. The intra-observer coefficient of variation for CA-IMT was 3.6% as previously described [3].

Blood pressure

Blood pressure was measured with a standard mercury sphygmomanometer and cuffs, after the subject had rested in the supine position for at least five minutes. The systolic and diastolic blood pressure levels were taken as the points of appearance and disappearance of Korotkoff sounds, respectively. The average of three measurements was used for analysis.

Blood sampling and biochemical assays

Venous blood was taken in the morning after an overnight fast for at least 12 hours. In hemodialysis patients, blood was taken at least 44 hours after the previous dialysis session. Plasma glucose was measured by a glucose oxidase method. Total cholesterol was measured by an enzymatic method. High-density lipoprotein (HDL) cholesterol was determined in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with dextran sulfate and $MgCl_2$. Then, non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Other measurements were done by routine laboratory methods.

Information on smoking

Data on smoking was obtained by a questionnaire, and a smoking index was calculated as the product of cigarette number per day and years of smoking history to express life-long exposure.

Statistical analysis

The results were summarized as mean ± standard error (SE). Difference between groups was assessed by analysis of variance (ANOVA), and then post-hoc test was performed by Scheffe-type multiple comparison. Correlation between two variables was examined by linear regression analysis. Independent association between variables was evaluated by multiple regression analysis. Dummy variables were used for gender (0 for female, 1 for male), chronic renal failure (0 for the absence, 1 for the presence of renal failure), and hemodialysis (0 for non-hemodialysis, 1 for hemodialysis). Difference in prevalence was evaluated by chi-square test. P values less than 0.05 were taken as statistically significant. All these analyses were performed using a commercially available software for Windows (StatView 5; SAS Institute Inc., Cary, NC, USA) on personal computers.

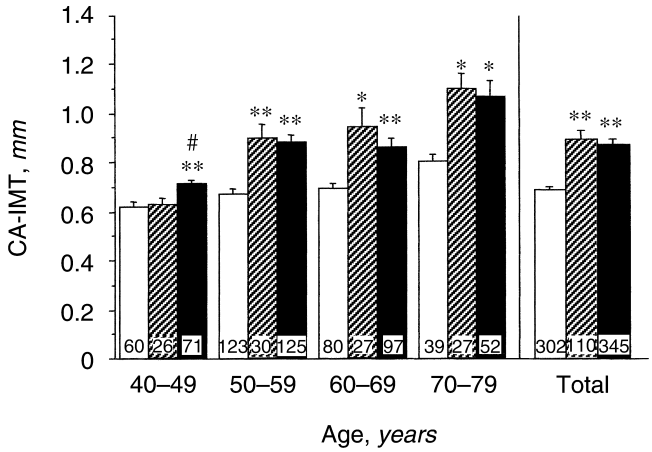

Fig. 1. Carotid artery-intima media thickness (CA-IMT) of the (□) healthy, (▨) predialysis and (■) hemodialysis (HD) groups. Data are mean ± SE. Numbers in each column indicate the number of subjects. *$P < 0.01$ vs. healthy control group, **$P < 0.001$ vs. healthy control group by Scheffe-type multiple comparison. There was no significant difference between the CRF and HD groups except in the 40- to 49-year-old range (#$P < 0.05$ vs. CRF group by Scheffe-type multiple comparison).

RESULTS

Comparison of CA-IMT among the three groups

Figure 1 shows CA-IMTs of the three groups. The HD group had a significantly greater CA-IMT (0.868 ± 0.019 mm, mean ± SE, $P < 0.0001$) than the healthy control subjects (0.685 ± 0.010 mm). CA-IMT of the CRF group (0.889 ± 0.035 mm, $P < 0.0001$) also was significantly greater than that of the healthy subjects, whereas it was not significantly different from CA-IMT of the HD group ($P = 0.821$).

In age-categorized comparison, the increased CA-IMT of the HD group was significant in all age ranges. Similarly, the CRF group showed greater CA-IMT than the healthy control group, although the difference was not significant in patients in their forties. When compared between the HD and CRF groups, CA-IMT did not differ significantly in the 50 to 59, 60 to 69, and 70 to 79-year-old age ranges; it differed between the two groups only in the 40 to 49-year-old range.

Correlation between CA-IMT and other variables

Factors affecting CA-IMT were examined by simple regression analysis (Table 2). In the total subjects, CA-IMT correlated positively with age, smoking, and systolic blood pressure, and negatively with HDL cholesterol. In addition to these factors, CA-IMT correlated with plasma triglycerides and non-HDL cholesterol levels in the healthy control group.

CA-IMT in the CRF group correlated significantly with age and smoking, and with systolic blood pressure at a borderline significance. Serum creatinine did not correlate with CA-IMT in this group.

Table 2. Simple regression analysis of factors correlating with CA-IMT

Variables	Total subjects	Healthy	CRF	Hemodialysis
Age	0.294[d]	0.304[d]	0.436[d]	0.262[d]
Serum creatinine	−0.072	−0.022	−0.065	−0.253[d]
Smoking index	0.134[d]	0.166[c]	0.242[b]	0.095[a]
Systolic BP	0.211[d]	0.270[d]	0.204[a]	0.018
Diastolic BP	−0.044	0.089	−0.106	0.031
BMI	−0.036	0.036	−0.078	0.021
Glucose	−0.001	−0.032	0.074	0.064
Total cholesterol	−0.030	0.013	0.123	0.040
Triglycerides	0.061	0.119[b]	0.142	−0.037
NonHDL-C	0.042	0.143[b]	0.144	0.056
HDL-C	−0.166[d]	−0.228[d]	−0.069	−0.036
Duration of HD	—	—	—	−0.017

Abbreviations are: CRF, chronic renal failure; BP, blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NonHDL-C, non-high-density lipoprotein cholesterol; HD, hemodialysis.

[a] $P = 0.07$–0.08, [b] $P < 0.05$, [c] $P < 0.01$, [d] $P < 0.001$ by simple regression analysis

Table 3. Multiple regression analysis of factors affecting CA-IMT

	Model 1	Model 2	Model 3
Age	0.275[c]	0.270[c]	0.270[c]
Male gender	0.016	0.016	0.016
Smoking index	0.077	0.095[b]	0.096[b]
Systolic BP	0.174[c]	0.081[b]	0.081[b]
NonHDL-C	0.036	0.079[b]	0.079[b]
HDL-C	−0.129[c]	−0.067[a]	−0.067[a]
Presence of renal failure	—	0.251[c]	0.245[c]
Hemodialysis	—	—	0.008
R^2	0.151[c]	0.199[c]	0.199[c]

Abbreviations are: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; NonHDL-C, non-high-density lipoprotein cholesterol.

[a] $P = 0.068$, [b] $P < 0.05$, [c] $P < 0.001$

In the HD patients, CA-IMT correlated significantly with age, and with smoking at a borderline significance. Duration of hemodialysis treatment did not correlate with CA-IMT. CA-IMT showed not a positive but a negative correlation with serum creatinine concentration in this group.

Independent factors associated with CA-IMT

Factors independently associated with CA-IMT were examined by using multiple regression models in the total subjects (Table 3). In the first model including classical risk factors, CA-IMT showed significant and independent association with age, systolic blood pressure and HDL cholesterol. In model 2 containing the presence of renal failure as an additional variable, renal failure was shown as a significant factor associated with CA-IMT independent of the above factors. In the final model (model 3) including hemodialysis as an additional variable, the effect of renal failure on CA-IMT remained significant, whereas the association between hemodialysis treatment and CA-IMT was not significant. In models 2 and 3, CA-IMT had significant and independent associations with age, smoking, systolic blood pressure and non-HDL cholesterol, whereas the association between CA-IMT and HDL cholesterol was at a borderline significance.

DISCUSSION

Atherosclerosis is advanced in patients with chronic renal failure treated with hemodialysis. Although earlier studies proposed the possibility that atherosclerosis is accelerated in long-term maintenance hemodialysis [2], it is not established whether hemodialysis is responsible for the advanced atherosclerosis in these patients. The present study demonstrates that predialysis patients with chronic renal failure had a significantly increased CA-IMT that was comparable with that of maintenance hemodialysis patients. In addition, the presence of renal failure, not hemodialysis treatment, showed a significant impact on the increased CA-IMT independent of age, gender, blood pressure, smoking and lipid levels. These results suggest that it is not hemodialysis per se, but chronic renal failure and/or metabolic alterations secondary to renal failure that promote the vascular change in these patients.

The degree of atherosclerosis can be evaluated from various aspects such as incidence of death from atherosclerotic disease, narrowing of arterial lumen, histological grading, and stiffening and thickening of arterial wall. The report by Lindner et al was the first that pointed out the extremely elevated risk of death from cardiovascular disease in long-term hemodialysis patients [2], and this has been confirmed by a number of subsequent studies [1]. Also, the incidence of myocardial infarction [22] and stroke [23] in hemodialysis patients is much higher than that in the general population. However, these facts do not directly mean that atherosclerosis was accelerated by hemodialysis, because subclinical but advanced atherosclerosis might have been present before hemodialysis treatment was initiated. According to Joki et al, 53.8% of asymptomatic patients starting hemodialysis had significant coronary artery stenosis as evidenced by coronary angiography [18]. Results of the present study are in good agreement with the above report [18], and provide further evidence that advanced atherosclerotic vascular change is present in patients with chronic renal failure before starting hemodialysis.

No previous studies found that duration of hemodialysis treatment correlated significantly with histological grading [17] or stiffness of arterial wall [5, 6, 11]. Regarding thickness of arterial wall, some studies found a significant positive correlation between CA-IMT and duration of hemodialysis [11–13], whereas others did not [3, 14–16]. The present study enrolling 345 hemodialysis patients was again unable to demonstrate any significant association between CA-IMT and duration of hemodialysis treatment by univariate or multivariate analysis. Fur-

thermore, we found that predialysis patients with chronic renal failure had a significantly increased CA-IMT that was comparable with that of maintenance hemodialysis patients. These results do not support the previous hypothesis that hemodialysis accelerates atherosclerosis [2], but strongly suggest that it is renal failure and/or metabolic alterations secondary to renal failure that promote atherosclerosis. This concept was further supported by the results by multiple regression analysis that the presence of renal failure, not hemodialysis, was associated with CA-IMT independent of other confounding variables.

What is responsible for the increased risk of atherosclerosis in chronic renal failure? Distinct changes can be detected in some of classical and non-classical risk factors of atherosclerosis as early as renal function begins to decline. Previous studies showed lipid and lipoprotein alterations [24] and increased serum lipoprotein(a) [Lp(a)] [25] in predialysis patients with chronic renal failure. Also, patients with renal failure have potentially atherogenic endocrinological abnormalities such as insulin resistance [26] and secondary hyperparathyroidism [27]. Secondary hyperparathyroidism was shown to be associated with increased CA-IMT in hemodialysis patients [3, 28, 29]. Furthermore, a high plasma concentration of homocysteine [30] has recently been regarded as a strong risk factor of atherosclerosis, and it is even higher in renal failure [31]. Finally, inflammation or increased serum C-reactive protein concentration may be involved in atherogenesis in predialysis patients as well as in those treated with hemodialysis [32, 33]. These factors may explain the increased risk of atherosclerosis in predialysis phase of chronic renal failure.

CA-IMT was comparable between the predialysis and hemodialysis groups in this study. If chronic renal failure but not hemodialysis promotes atherosclerosis, the lack of difference in CA-IMT suggests the presence of beneficial effects of hemodialysis. In fact, hemodialysis reduces some of the risk factors of atherosclerosis. Body fluid removal by hemodialysis improves control of blood pressure. Plasma concentration of Lp(a) decreases following the initiation of hemodialysis [34]. Predialysis patients with renal failure show the atherogenic small-dense low-density lipoprotein (LDL) phenotype [35], whereas LDL particle size returns to normal in hemodialysis patients [36]. These data suggest the existence of potentially beneficial effects of hemodialysis on atherosclerosis.

Within the subjects in the fourth decade of age, a significant increase in CA-IMT was found in the hemodialysis group but not in the predialysis patients. We have no clear explanation for this result. It may be a chance observation because the number of the predialysis patients in this age category was the smallest, although we cannot rule out a possibility that hemodialysis promotes atherosclerosis in young patients.

There are a few limitations in the present study. First, the patients were studied while under medications for hypertension, dyslipidemia, and other metabolic abnormalities associated with renal failure. Therefore, our data might have underestimated the effects of these factors on CA-IMT. Second, although we showed that chronic renal failure was a significant factor associated with increased CA-IMT independent of the classical risk factors, we could not evaluate effects of the non-classical risk factors, such as parathyroid hormone [3], homocysteine [37], and C-reactive protein [32, 33], which might have added to the power of analysis. And finally, we measured CA-IMT as a morphological index of atherosclerosis. Measurement of arterial wall stiffness will provide additional information regarding the effects of renal failure and hemodialysis on functional changes of arterial wall in patients with chronic renal failure.

In conclusion, we demonstrate that CA-IMT of predialysis patients with chronic renal failure is as great as that of patients with maintenance hemodialysis. The presence of renal failure, rather than hemodialysis, was a significant factor associated with increased CA-IMT. These results support the concept that advanced atherosclerosis in patients with end-stage renal disease is due not to hemodialysis treatment, but to renal failure and/or metabolic abnormalities secondary to renal failure. Further studies are needed to elucidate the precise mechanism by which renal failure promotes atherosclerosis in the predialysis stage of renal failure. Also, it would be better to initiate the management of atherogenic risk factors at an earlier stage of renal disease.

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REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32 (Suppl):S112–S119, 1998
2. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697–701, 1974
3. Kawagishi T, Nishizawa Y, Konishi T, *et al*: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48:820–826, 1995
4. Shoji T, Kawagishi T, Emoto M, *et al*: Additive impacts of diabetes and renal failure on carotid atherosclerosis. *Atherosclerosis* 153: 257–258, 2000
5. London GM, Marchais SJ, Safar ME, *et al*: Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 37:137–142, 1990
6. Shoji T, Nishizawa Y, Kawagishi T, *et al*: Intermediate-density lipoprotein as an independent risk factor for aortic atherosclerosis in hemodialysis patients. *J Am Soc Nephrol* 9:1277–1284, 1998
7. O'Leary DH, Polak JF, Kronmal RA, *et al*: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and

stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 340:14–22, 1999
8. Blacher J, Asmar R, Djane S, *et al*: Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertens* 33:1111–1117, 1999
9. Blacher J, Guerin AP, Pannier B, *et al*: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99:2434–2439, 1999
10. Shoji T, Emoto M, Shinohara K, *et al*: Diabetes mellitus, aortic stiffness and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 12:2117–2124, 2001
11. Burdick L, Periti M, Salvaggio A, *et al*: Relation between carotid artery atherosclerosis and time on dialysis. A non-invasive study in vivo. *Clin Nephrol* 42:121–126, 1994
12. Sakurabayashi T, Fujimoto M, Takaesu Y, *et al*: Association between plasma homocysteine concentration and carotid atherosclerosis in hemodialysis patients. *Jpn Circ J* 63:692–696, 1999
13. Guz G, Nurhan Ozdemir F, Sezer S, *et al*: Effect of apolipoprotein E polymorphism on serum lipid, lipoproteins, and atherosclerosis in hemodialysis patients. *Am J Kidney Dis* 36:826–836, 2000
14. Hojs R: Carotid intima-media thickness and plaques in hemodialysis patients. *Artif Organs* 24:691–695, 2000
15. Malatino LS, Mallamaci F, Benedetto FA, *et al*: Hepatocyte growth factor predicts survival and relates to inflammation and intima media thickness in end-stage renal disease. *Am J Kidney Dis* 36:945–952, 2000
16. Fujisawa M, Haramaki R, Miyazaki H, *et al*: Role of lipoprotein (a) and TGF-beta 1 in atherosclerosis of hemodialysis patients. *J Am Soc Nephrol* 11:1889–1895, 2000
17. Vincenti F, Amend WJ, Abele J, *et al*: The role of hypertension in hemodialysis-associated atherosclerosis. *Am J Med* 68:363–369, 1980
18. Joki N, Hase H, Nakamura R, Yamaguchi T: Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 12:718–723, 1997
19. Hosoi M, Nishizawa Y, Kogawa K, *et al*: Angiotensin-converting enzyme gene polymorphism is associated with carotid arterial wall thickness in non-insulin-dependent diabetic patients. *Circulation* 94:704–707, 1996
20. Kogawa K, Nishizawa Y, Hosoi M, *et al*: Effect of polymorphism of apolipoprotein E and angiotensin-converting enzyme genes on arterial wall thickness. *Diabetes* 46:682–687, 1997
21. Taniwaki H, Kawagishi T, Emoto M, *et al*: Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. *Diabetes Care* 22:1851–1857, 1999
22. Iseki K, Fukiyama K: Long-term prognosis and incidence of acute myocardial infarction in patients on chronic hemodialysis. The Okinawa Dialysis Study Group. *Am J Kidney Dis* 36:820–825, 2000
23. Iseki K, Fukiyama K: Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. The Okinawa Dialysis Study (OKIDS) Group. *Nephrol Dial Transplant* 15:1808–1813, 2000
24. Attman PO, Samuelsson O, Alaupovic P: Lipoprotein metabolism and renal failure. *Am J Kidney Dis* 21:573–592, 1993
25. Kandoussi A, Cachera C, Pagniez D, *et al*: Plasma level of lipoprotein Lp(a) is high in predialysis or hemodialysis, but not in CAPD. *Kidney Int* 42:424–425, 1992
26. DeFronzo RA, Alvestrand A, Smith D, *et al*: Insulin resistance in uremia. *J Clin Invest* 67:563–568, 1981
27. Llach F, Massry SG: On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. *J Clin Endocrinol Metab* 61:601–606, 1985
28. Nishizawa Y, Shoji T, Kawagishi T, Morii H: Atherosclerosis in uremia: Possible roles of hyperparathyroidism and intermediate density lipoprotein accumulation. *Kidney Int* 52(Suppl 62):S90–S92, 1997
29. Shoji T, Nishizawa Y, Kawagishi T, *et al*: Secondary hyperparathyroidism, decreased hepatic triglyceride lipase, elevated intermediate density lipoprotein and atherosclerosis in hemodialysis patients. *Nephron* 78:121–122, 1998
30. Clarke R, Daly L, Robinson K, *et al*: Hyperhomocysteinemia: An independent risk factor for vascular disease. *N Engl J Med* 324:1149–1155, 1991
31. Chauveau P, Chadefaux B, Coude M, *et al*: Increased plasma homocysteine concentration in patients with chronic renal failure. *Miner Electrolyte Metab* 18:196–198, 1992
32. Stenvinkel P, Heimburger O, Paultre F, *et al*: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899–1911, 1999
33. Zimmermann J, Herrlinger S, Pruy A, *et al*: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55:648–658, 1999
34. Kawasaki K: Plasma Lp(a) in patients with chronic renal failure. *Osaka Shi Igakukai Zasshi* 47:285–295, 1998
35. Hirano T, Oi K, Sakai S, *et al*: High prevalence of small dense LDL in diabetic nephropathy is not directly associated with kidney damage: A possible role of postprandial lipemia. *Atherosclerosis* 141:77–85, 1998
36. Oi K, Hirano T, Sakai S, *et al*: Role of hepatic lipase in intermediate-density lipoprotein and small, dense low-density lipoprotein formation in hemodialysis patients. *Kidney Int* 56(Suppl 71):S227–S228, 1999
37. Bostom AG, Shemin D, Verhoef P, *et al*: Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients. A prospective study. *Arterioscler Thromb Vasc Biol* 17:2554–2558, 1997