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C-reactive protein and cardiovascular disease in peritoneal dialysis patients

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Background. Elevated plasma concentrations of C-reactive protein (CRP) is a risk factor for cardiovascular disease (CVD) in the general population and in hemodialysis patients. The prognostic value of CRP is less well known in peritoneal dialysis (PD) patients. We examined the association between CRP and cardiovascular event (CVE) in a large population of PD patients.

Methods. Two hundred and forty patients starting PD were enrolled in this prospective study. The role of CRP was analyzed with respect to other known cardiovascular risk factors.

Results. The patients were followed for a mean duration of 41 ± 21 months; the median value of CRP was 7 mg/L. Eighty-nine cardiovascular events (CVE; 37.1%) occurred in 84 patients and the CRP levels were higher in patients who experienced CVE (27 ± 14 vs. 6 ± 8 mg/L; $P < 0.0001$). In the Cox model, patients in the three lower quartiles of the CRP levels had a decreased risk of CVE compared with those in the highest quartile. Cox regression analysis also revealed that age, a previous history of cardiovascular disease, hyperhomocysteinemia and hypoalbuminemia were risk factors for CVE. CRP levels were higher in patients who died during the study period (25 ± 12 vs. 5 ± 8 mg/L; $P = 0.003$). In the Cox model, patients with CRP levels above the median had an increased risk of death compared with those in the lowest quartile.

Conclusions. Chronic inflammation, as reflected by elevated CRP levels, is frequent in patients starting PD and independently contributes to an increased incidence of CVE in this population.

Dialysis patients have disproportionately high rates of arteriosclerotic outcomes and cardiovascular (CVD) mortality [1, 2]. A higher prevalence of classic cardiovascular (CV) risk factors (such as smoking, hypertension, hypercholesterolemia, etc.) and non-modifiable risk factors (such as age, sex, and family history of CVD) cannot fully explain this increased incidence of CVD [3]. Recent studies support a role for non-traditional CV risk factors such as hyperhomocysteinemia [4], oxidative stress [5], and calcium-phosphate product [6] in the pathogenesis of cardiovascular disease in dialysis patients. Elevated plasma concentrations of C-reactive protein (CRP), a sensitive marker of underlying inflammation [7], have been shown to predict an increased risk of future cardiovascular outcomes in the general population [8] as well as in hemodialysis patients [9, 10].

The prognostic value of CRP is less well known in peritoneal dialysis (PD) patients. To date, only two small studies have focused on the predictive value of elevated CRP in this population [11, 12]. The authors concluded that CRP elevation occurred in a substantial proportion of patients and was found to be predictive of future myocardial infarction. Nevertheless, the small size of these studies population hampered the relevance of their results.

In our single center study, we prospectively examined the association between CRP elevation and cardiovascular event (CVE) in a large population of PD patients.

METHODS

Patient characteristics

The aim of the study was to evaluate the relevance of different parameters as cardiovascular risk factors in a large population of patients starting peritoneal dialysis. A total of 240 consecutive patients starting PD between November 1994 and August 2001 were included in this prospective, single center study. Oral information concerning the study was provided to each patient.

Cardiovascular risk factors

Age, gender, weight, size, blood pressure, diabetes mellitus, smoking status, past history of cardiovascular events (CVE), and different biological parameters were assessed at inclusion the day before the first dialysis session.

Key words: atherosclerosis, chronic inflammation, homocysteine, malnutrition, risk factors, dialysis, myocardial infarction risk.

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Past history of CVE

A past history of CVE was defined by: (*1*) coronary heart disease, including myocardial infarction, coronary revascularization including coronary artery bypass surgery or percutaneous transluminal coronary angioplasty, typical history of angina with abnormal coronarography or myocardial scintigraphy; (*2*) stroke/cerebrovascular disease, including both non-hemorrhagic and hemorrhagic strokes, and carotid endarterectomy; (*3*) abdominal aortic or lower extremity arterial disease, including abdominal aortic repair; lower extremity amputation; intermittent claudication confirmed by Doppler or arteriography findings.

Nutritional status

The albumin concentration was determined. Body mass index (BMI) was calculated as weight/height^2.

Smoking behavior

With respect to smoking behavior, subjects were categorized as current smokers or non-smokers.

Blood pressure

Blood pressure (BP) was measured by a nurse using a semi-automatic device, based on an oscillometric method with the patients in a sitting position after resting more than five minutes. Pulse pressure [systolic BP (SBP) − diastolic BP (DBP)] was calculated.

LVH

Left ventricular hypertrophy (LVH) was defined by a Sokolow index (wave R measured in derivation V1 + wave S measured in derivation V6) ≥35 mm.

Lipid profile

Triglycerides, and total and high-density lipoprotein (HDL) cholesterol concentrations were measured. Low-density lipoprotein (LDL) cholesterol was calculated using the method described by Friedwald, Levy and Fredrickson [13].

Homocysteine

Total plasma homocysteine (Hcy) was measured using a previously described method [14]. Briefly, venous blood samples were drawn after an overnight fast. The blood sample was centrifuged within 15 minutes, and plasma stored frozen at −20°C. Hcy concentration, the sum of the acid-soluble (that is reduced Hcy, homocysteine, disulphide, and homocysteine-cysteine mixed disulphide), and protein-bound moieties was measured by high-performance liquid chromatography. This assay involves the following steps: reduction of the sample with tri-n-butylphosphine, precipitations of proteins, alkalinization of the supernatant with sodium borate, derivitization with 7-fluoro-2-oxa-1,3 diazole-4 sulfuronate, followed by 8-aminonaphtalene-1,3,6-trisulphonic acid, and high-pressure liquid chromatography (HPLC) separation with fluorescence detection. The normal values of plasma Hcy concentration ranged from 7 to 15 μmol/L. The precision of the assay corresponds to a coefficient of variation <3%.

C-reactive protein

C-reactive protein was measured by the Nephelometry Kit (Beckman, Fullerton, CA, USA).

Renal function

Serum creatinine concentration and urinary protein excretion were measured. Creatinine clearance was calculated using the Gault-Cockcroft formula.

PTH, vitamin D, Ca, pH

Parathyroid hormone (PTH) was measured using an immunoradiometric assay, with a normal range between 15 and 80 pg/mL. Calcium and phosphorus were measured by standard autoanalyzer techniques.

Arteriosclerotic events

Coronary heart disease. Myocardial infarction documented by (*1*) serial 12-lead electrocardiogram evidence or Q-wave infarction and appropriate myocardial enzyme elevations; (*2*) coronary revascularization including coronary artery bypass surgery or percutaneous transluminal coronary angioplasty; (*3*) typical history of angina with abnormal coronarography.

Stroke/cerebrovascular disease. Both non-hemorrhagic and hemorrhagic strokes were confirmed by neurologic examination findings consistent with new onset focal neurologic deficits, with or without computed tomography or magnetic resonance imaging evidence of cerebral infarction. Symptomatic extracranial artery stenosis resulting in carotid endarteriectomy was also a confirmatory factor.

Abdominal aortic or lower extremity arterial disease. Abdominal aortic repair; lower extremity revascularization via bypass surgery or angioplasty; lower extremity amputation; new onset of intermittent claudication confirmed by Doppler or arteriography findings.

Two physicians independent of the study were responsible for ascertaining cardiovascular events (CVE). This analysis was performed without any knowledge of the patient's baseline characteristics.

Statistical analysis

Arithmetic mean was calculated and expressed as ± SD.

Using log rank tests on Kaplan-Meier nonparametric estimates of the survival without CVE distribution, we selected variables with a P value ≤0.20. The selected variables were included into a Cox proportional hazards model, and a backward stepwise selection process was

Table 1. Description of categorical variables

Variable	Frequency (%)
Gender	
Male	150 (62.5%)
Female	90 (37.5%)
History of cardiovascular event	
Yes	95 (39.6%)
No	145 (60.4%)
Tobacco consumption	
Yes	58 (24%)
No	182 (76%)
Diabetes	
Yes	53 (22%)
No	187 (78%)
Left ventricle diameter	
≥35 mm	31 (12.9%)
<35 mm	209 (87.1%)

Table 2. Description of continuous variables

Variable	Mean	Standard deviation	Median
Age *years*	66	17	70
S_{Cr} clearance *mL/min*	8.7	3.9	7.6
PTH *pg/mL*	286	199	196
Vitamin D *ng/mL*	11	7	12
Phosphorus *mmol/L*	1.75	0.53	1.68
Calcium *mmol/L*	2.17	0.19	2.23
Hemoglobin *g/100 mL*	10.9	1.8	12.9
Fibrinogen *g/L*	3.94	0.98	3.82
LDL cholesterol *g/L*	1.33	0.34	1.34
HDL cholesterol *g/L*	0.36	0.22	0.32
Total serum cholesterol *g/L*	2.35	0.44	2.34
Triglycerides *g/L*	1.97	1.14	1.72
Serum homocysteine *μmol/L*	22.1	7.33	22.4
BMI kg/m^2	25.2	4.6	25.4
SBP *mm Hg*	145	21	140
DBP *mm Hg*	81	12	81
PP *mm Hg*	66	17	67
Glycemia *mmol/L*	6.4	1.3	6.11
CRP *mg/L*	9.2	8.4	7
Serum albumin *g/L*	37	4.4	37

Abbreviations are: S_{Cr}, serum creatinine; PTH, parathyroid hormone; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CRP, C-reactive protein.

performed, this time at a classical $\alpha = 0.05$. As gender and age were potential confounding variables, they were entered into the Cox model also, no matter the significance of their relationships with CVE. Age was split into two classes separated by its median = 70 years, CRP was split into quartiles (CRP limits 3.2, 7 and 12.9 mg/L), and so was serum homocysteine (limits 18.4, 22.4 and 26.8 μmol/L) as well as albumin (limits 33, 37, 40 g/L). Tobacco consumption was accounted for as currently smoking versus non-smoking. Variables that were split into quartiles were replaced by dummy variables in the Cox model, which tested quartile 2 versus quartile 1, quartile 3 versus quartile 1 and quartile 4 versus quartile 1. Results are expressed as relative risk (RR) and 95% confidence interval, with a *P* value testing the null hypothesis: RR = 1. Therefore when the *P* value is less than 0.05, RR is significantly different from 1, either greater than 1 (that is, the risk of CVE is increased) or less than 1 (that is, the risk of CVE is decreased).

Table 3. Relative risk estimates for CVD of the upper quartile of CRP (>12.9 mg/L) calculated for each class of tHcy and albumin levels

Variable	Relative risk[a]	95% CI
Serum albumin *g/L*		
<33 (1st quartile)	5.27	(1.43; 11.98)
33–37 (vs. 1st quartile)	5.31	(1.79; 13.09)
37–40 (vs. 1st quartile)	5.63	(1.54; 13.51)
≥40 (vs. 1st quartile)	5.44	(1.81; 11.82)
Serum homocysteine *μmol/L*		
<18.4 (1st quartile)	5.34	(1.71; 12.64)
18.4–22.4 (vs. 1st quartile)	5.53	(1.49; 11.96)
22.4–26.8 (vs. 1st quartile)	5.51	(1.77; 13.46)
≥26.8 (vs. 1st quartile)	5.29	(1.64; 12.59)

[a] Cox model is adjusted for gender

RESULTS

Demographic characteristics of the population

The patients were followed for a mean duration of 41 ± 21 months. Fourteen patients (9.9%) underwent renal transplantation during follow-up. Twenty-one were switched to hemodialysis during the study period. For these patients, the end of the follow-up was the last day on PD.

The demographic, clinical, and biological characteristics of the study population are shown in Tables 1 and 2. The mean age was 66 ± 17 years. Primary causes of ESRD were chronic glomerulonephritis in 15%, chronic interstitial nephritis in 13%, polycystic kidney disease in 13%, nephroangiosclerosis in 16%, diabetes mellitus in 22%, and undetermined in 21%. Serum albumin, hemoglobin and PTH were approximately normally distributed.

Cardiovascular events

Eighty-nine CVE (37.1%) occurred in 84 patients (cerebrovascular disease, $N = 11$; coronary heart disease, 56; peripheral vascular disease, 22), which corresponds to 108 CVE for 1000 patient-years. Ninety-two patients (38.3%) died during follow-up, 41 (45%) of cardiovascular disease. CRP levels were higher in patients who experienced CVE (27 ± 14 mg/L vs. 6 ± 8 mg/L; $P < 0.0001$).

Quartiles were defined according to CRP levels (Table 3). There was a linear increase in the risk of CVE from the lower quartile to the higher quartile of CRP concentrations [10.5% vs. 21% in Q2 (<0.0001) and vs. 33% in Q3 (<0.0001), 57% in Q4 (<0.0001); Fig. 1].

In univariate analysis, age ($P < 0.0001$), male gender ($P = 0.01$), a past history of cardiovascular disease ($P < 0.0001$), smoking status ($P = 0.03$), diabetes mellitus

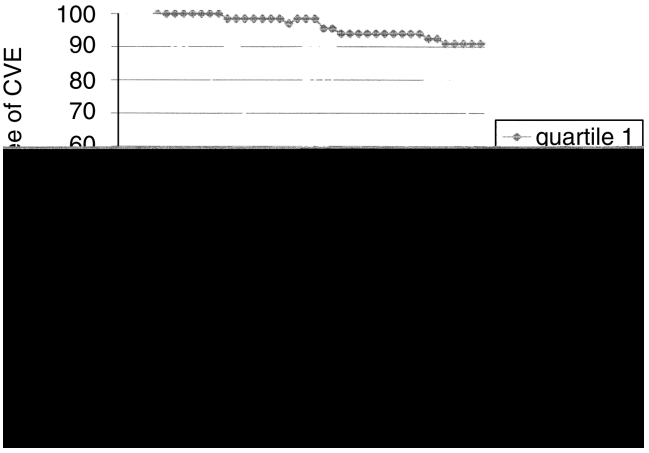

Fig. 1. Proportion of patients free of cardiovascular events (CVE) according to C-reactive protein (CRP) quartiles.

($P = 0.13$), high phosphorus concentration ($P = 0.08$), low calcium concentration ($P = 0.03$), high fibrinogen concentration ($P = 0.07$), low HDL cholesterol ($P = 0.02$), tHcy ($P = 0.0001$), systolic BP ($P = 0.07$), pulse BP ($P = 0.04$), glycemia ($P = 0.07$), CRP ($P = 0.0001$) and low albumin concentration ($P = 0.003$) were associated with CVE.

We tested for possible interactions between CRP and tHcy on the one hand, and CRP and albumin on the other. RR for CRP was calculated separately for each tHcy class, and for each albumin class. These interactions were minor because RR did not change much with both tHcy levels and albumin concentrations, and this did not modify the interpretation of the global RR (Table 3).

After backward stepwise selection, variables that remained in the Cox proportional hazards model that were linked to CVE with $P < 0.05$ were: CRP, age, albumin, history of CVE, serum homocysteine. Gender was kept in the model. Assumptions of Cox models (log-linearity, proportionality of risk in time) were met in this analysis. Relative risks (RR) and their 95% confidence intervals (95% CI) of CVE for each variable in the Cox model are displayed in Table 4, along with P values.

Table 4. Cox model: Relative risks (RR) of cardiovascular event (CVE) and 95% confidence intervals

Variable	Relative risk[a]	95% CI	P value
CRP *g/L*			
<3.2 (1st quartile)	1	—	—
3.2–7 (vs. 1st quartile)	2.34	(1.07; 4.38)	0.022
7–12.9 (vs. 1st quartile)	3.31	(2.01; 12.01)	0.001
≥12.9 (vs. 1st quartile)	5.41	(1.69; 12.85)	0.008
Age *years*			
<70	1	—	—
≥70	6.36	(1.78; 22.59)	0.001
Serum albumin *g/L*			
<33 (1st quartile)	1	—	—
33–37 (vs. 1st quartile)	0.95	(0.84; 1.44)	0.24[b]
37–40 (vs. 1st quartile)	0.85	(0.72; 0.97)	0.041
≥40 (vs. 1st quartile)	0.65	(0.31; 0.89)	0.01
History of CVE			
No	1	—	—
Yes	5.12	(1.88; 13.54)	0.001
Serum homocysteine *μmol/L*			
<18.4 (1st quartile)	1	—	—
18.4–22.4 (vs. 1st quartile)	1.40	(0.81; 9.57)	0.12[b]
22.4–26.8 (vs. 1st quartile)	1.81	(0.94; 9.52)	0.07[b]
≥26.8 (vs. 1st quartile)	4.58	(1.73; 17.64)	0.009

[a] Cox model is adjusted for gender
[b] Non-significant at $\alpha = 5\%$

Table 5. Cox model: Relative risks (RR) of death and 95% confidence intervals

Variable	Relative risk[a]	95% CI	P value
CRP *g/L*			
<3.2 (1st quartile)	1	—	—
3.2–7 (vs. 1st quartile)	1.41	(0.92; 1.41)	0.09[b]
7–12.9 (vs. 1st quartile)	1.82	(1.07; 3.17)	0.02
≥12.9 (vs. 1st quartile)	5.2	(1.37; 12.94)	0.009
Age *years*			
<70 years	1	—	—
≥70 years	6.11	(1.94; 17.247)	0.004
Serum albumin *g/L*			
<33 (1st quartile)	1	—	—
33–37 (vs. 1st quartile)	0.94	(0.89; 1.41)	0.24[b]
37–40 (vs. 1st quartile)	0.81	(0.59; 0.92)	0.035
≥40 (vs. 1st quartile)	0.49	(0.27; 0.79)	0.007
History of CVE			
No	1	—	—
Yes	4.06	(1.61; 7.32)	0.01

[a] Cox model is adjusted for gender
[b] Non-significant at $\alpha = 5\%$

Influence of CRP on survival

Ninety-two patients (38.3%) died during the follow-up period, 41 (45%) of cardiovascular disease. CRP levels were higher in patients who died during the study period (25 ± 12 vs. 5 ± 8 mg/L; $P = 0.003$).

In univariate analysis, age ($P < 0.0001$), a past history of cardiovascular disease ($P < 0.0001$), smoking status ($P = 0.05$), diabetes mellitus ($P = 0.04$), high fibrinogen concentration ($P = 0.09$), tHcy ($P = 0.01$), CRP ($P = 0.003$) and low albumin concentration ($P = 0.008$) were associated with death.

After backward stepwise selection, the variables remaining in the Cox proportional hazards model, that is, those linked to death with $P < 0.05$, were CRP, age, albumin, and a history of CVE. Gender was kept in the model. Assumptions of Cox models (log-linearity, proportionality of risk in time) were met in this analysis. Relative risks (RR) and their 95% confidence intervals (95% CI) of death for each variable in the Cox model are displayed in Table 5, along with P values.

DISCUSSION

There is a high incidence of cardiovascular complications in the PD population. In our study, the cumulative

risk for developing CVE was 10.8% within one year. Both traditional and non-traditional CV risk factors are very prevalent and take into account this increased incidence of atherosclerotic events. Nevertheless, our study outlined the importance of non-traditional risk factors such as acute phase response, malnutrition, and hyperhomocysteinemia over traditional CV risk factors in this population.

Few studies have focused on the relationships between inflammation and CV outcomes in the restricted population of end-stage renal disease patients on PD. Elevated CRP levels have been associated with carotid atherosclerosis [15] and cardiac valve calcification [16] in the PD population. Nevertheless, cross-sectional analysis such as these can only be regarded as hypothesis-generating. A number of weaknesses are inherent in this study design, including biases such as selection, survival, as well as confounding. Some prospective studies have been recently published; Haubitz and Brunkhorst studied 34 PD patients during 72 months for the occurrence of cardiovascular complications and found that the incidence of coronary artery disease was significantly increased in patients with higher CRP levels [11]. Herzig et al, in a prospective study including 50 PD patients, reported that an elevated CRP was associated with an increased risk of myocardial infarction and a trend toward an increased risk of both cardiovascular and all-cause mortality [12]. Nevertheless, the small size of these study samples hampered the relevance of their conclusions. Our study in a single-center large population confirms that elevated CRP levels are predictive of cardiovascular complications in PD patients. The RR for the occurrence of cardiovascular complications increased gradually with CRP levels, and patients in the highest quartile of CRP concentrations had a fivefold increase in risk of CVE compared to those in the lowest quartile.

The mechanisms supporting the association between atherosclerotic complications and elevated CRP remain unclear. CRP elevations may be a consequence of vascular injury with secondary release of proinflammatory cytokines by monocytes and macrophages recruited into atherosclerotic plaques. Alternatively, CRP may reflect chronic infection by infectious agents that have been linked with atherosclerosis progression, such as *Chlamydia pneumoniae* and cytomegalovirus [17]. This way, CRP may be a marker of rather than an actor in the progression of atherosclerosis. Nevertheless, recent evidence suggests that CRP by itself may promote cardiovascular injury via activation of complement [18] and induction of monocyte expression of tissue factor [19].

Contrary to hemodialysis, PD is not associated with an exacerbation of the acute phase response [20]. CRP levels are significantly higher in patients receiving hemodialysis as compared to healthy subjects and predialysis end-stage renal disease patients [21]. The use of bioincompatible materials seems to be the main cause of the burst in acute phase response markers observed after the initiation of hemodialysis [9, 20, 22, 23]. Our study analyzed the influence of pre-dialysis CRP concentrations as a predictor of subsequent cardiovascular outcomes. Because of the absence of effect of PD on CRP levels, these measures are likely to reflect post-dialysis values. Moreover, all patients started PD in a stable state, and although it is not possible to exclude occult infection in patients with elevated CRP, no patient had any evidence of infection. Finally, pre-dialysis evaluation eliminated the role of peritonitis and exit-site infections as confounding parameters in the elevation of CRP.

We found a strong association between elevated CRP levels and death. Such an association has been previously reported in hemodialysis patients [9, 24, 25]. Nevertheless, Owen and Lowrie did not find any relationship between CRP and survival in a large cohort of hemodialysis patients [26], and conflicting data have been reported in the PD population [12, 27]. Discrepancies between studies have been attributed to the variable extent of adjustment for covariates in the different studies. Nevertheless, in our study, CRP remains associated with death even after adjustment for major potential confounding covariates in the proportional hazards model, especially hemoglobin levels and markers of malnutrition. Our results highly suggest that elevated CRP carries an independent predictive risk of death in PD patients.

A strong relationship between CVE and both hypoalbuminemia and hyperhomocysteinemia was found in our PD patients, outlining the major role of non-traditional CV risk factors in this population. Several studies have demonstrated that CRP is inversely related to albumin levels [28–30]. Despite this relationship, we also identified low albumin concentration as an independent risk factor for CVE and death. Interestingly, there was no interaction between CRP and albumin in the increased risk of CVE conferred by high CRP levels. By contrast, there are conflicting data concerning the role of hyperhomocysteinemia as a cardiovascular risk factor in the PD population [31, 32]. Some studies have suggested that PD patients with the lowest tHcy, a condition frequently associated with malnutrition, were at an increased risk of cardiovascular complications and death [32]. In our study, tHcy concentrations in the higher quartile conferred a fourfold increase risk of CVE even after adjustment for nutrition markers. Otherwise, there was no U-curve for tHcy as a cardiovascular risk factor in PD patients.

There are some limitations to our study. We studied the influence of a baseline CRP determination on the occurrence of CVE in a population of patients starting PD. Peritoneal dialysis may itself modify both traditional and non-traditional cardiovascular risk factors [33, 34]. Serial measurements of CRP in a longitudinal cohort

design would certainly provide a more precise estimate of cardiovascular risk conferred by elevated CRP in this population.

Chronic inflammation, as reflected by elevated CRP levels, is frequent in patients starting PD and independently contributes to an increased incidence of CVE in this population. These data lend support to the hypothesis that inflammation plays a role in the pathogenesis of atherosclerosis in these patients.

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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 3):112–119, 1998
2. U.S. Renal Data System: *USRDS Annual Data Report*. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1997
3. Wilson PW, D'Agostino RB, Levy D, *et al*: Prediction of coronary heart disease using risk factors categories. *Circulation* 97:1837–1847, 1998
4. Bostom AG, Shemin D, Lapane KL, *et al*: Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein (a) excess in maintenance dialysis patients: A matched case-control study. *Atherosclerosis* 125: 91–101, 1996
5. Boaz M, Smetana S, Weinstein T, *et al*: Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): Randomized placebo-controlled trial. *Lancet* 356:1213–1218, 2000
6. Cozzolino M, Dusso AS, Slatopolsky E: Role of calcium-phosphate product and bone-associated proteins on vascular calcification in renal failure. *J Am Soc Nephrol* 12:2511–2516, 2001
7. Clyne B, Olshaker JS: The C-reactive protein. *J Emerg Med* 17: 1019–1025, 1999
8. Ridker PM, Cushman M, Stampfer MJ: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
9. Zimmermann J, Herrlinger S, Pruy A, *et al*: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55:648–658, 1999
10. Arici M, Walls J: End-stage renal disease, atherosclerosis, and cardiovascular mortality: Is C-reactive protein the missing link? *Kidney Int* 59:407–414, 2001
11. Haubitz M, Brunkhorst R: C-reactive protein and chronic chlamydia pneumoniae infection—Long-term predictors for cardiovascular disease and survival in patients on peritoneal dialysis. *Nephrol Dial Transplant* 16:809–815, 2001
12. Herzig KA, Purdie DM, Chang W, *et al*: Is C-reactive protein a useful predictor of outcome in peritoneal dialysis patients? *J Am Soc Nephrol* 12:814–821, 2001
13. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
14. Ducloux D, Motte G, Challier B, *et al*: Serum total homocysteine and cardiovascular disease in chronic, stable renal transplant recipients: A prospective study. *J Am Soc Nephrol* 11:134–137, 2000
15. Zoccali C, Benedetto FA, Mallamaci F, *et al*: Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis patients. *J Hypertens* 18:1207–1209, 2000
16. Wang AY, Woo J, Wang M, *et al*: Association of inflammation and malnutrition with cardiac valve calcification in continuous ambulatory peritoneal dialysis patients. *J Am Soc Nephrol* 12:1927–1936, 2001
17. Epstein SE, Zhou YF, Zhu J: Infection and atherosclerosis: Emerging mechanistic paradigms. *Circulation* 100:20–28, 1999
18. Lagrand WK, Niessen HW, Wolbink GJ, *et al*: C-reactive protein colocalizes with complement in human hearts during acute myocardial infarction. *Circulation* 95:97–103, 1997
19. Cermak J, Key NS, Bach RR, *et al*: C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 82:513–520, 1993
20. Haubitz M, Brunkhorst R, Wrenger E, *et al*: Chronic induction of C-reactive protein by hemodialysis, but not by peritoneal dialysis therapy. *Perit Dial Int* 16:158–162, 1996
21. Docci D, Bilancioni R, Buscaroli A, *et al*: Elevated serum levels of C-reactive protein in hemodialysis patients. *Nephron* 56:364–367, 1990
22. Chollet MS, Stamatakis G, Bailly S, *et al*: Induction of tumor necrosis factor-alpha during haemodialysis. Influence of the membrane type. *Clin Exp Immunol* 83:329–332, 1991
23. Bingel M, Lonneman G, Shaldon S, *et al*: Human interleukin-1 production during hemodialysis. *Nephron* 43:161–163, 1986
24. Iseki K, Tozawa M, Yoshi S, Fukiyama K: Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. *Nephrol Dial Transplant* 14:1956–1960, 1999
25. Yeun JY, Levine RA, Mantadilok V, Kaysen GA: C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 35:469–476, 2000
26. Owen WF, Lowrie EG: C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 54:627–636, 1998
27. No H, Lee SW, Kang SW, *et al*: Serum C-reactive protein: a predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 18:387–394, 1998
28. Kaysen GA, Chertow GM, Adhikaria R, *et al*: Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. *Kidney Int* 60:333–340, 2001
29. Level C, Chauveau P, Delmas Y, *et al*: Procalcitonin: A new marker of inflammation in haemodialysis patients? *Nephrol Dial Transplant* 16:980–986, 2001
30. Qureshi AR, Alvestrand A, Danielsson A, *et al*: Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int* 53:773–782, 1998
31. 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
32. Suliman ME, Qureshi AR, Barany P, *et al*: Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. *Kidney Int* 57:1727–1735, 2000
33. Ducloux D, Heuze-Lecornu L, Gibey R, *et al*: Dialysis adequacy and homocysteine concentrations in peritoneal dialysis patients. *Nephrol Dial Transplant* 14:728–731, 1999
34. O'Riordan E, O'Donoghue DJ, Kalra PA, *et al*: Changes in lipid profiles in non diabetic, non nephrotic patients commencing continuous ambulatory peritoneal dialysis. *Adv Perit Dial* 16:313–316, 2000