Circulating Soluble Vascular Cell Adhesion Molecule 1: Relationships With Residual Renal Function, Cardiac Hypertrophy, and Outcome of Peritoneal Dialysis Patients

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• ***Background:*** **Vascular cell adhesion molecule 1 (VCAM-1) is involved in leukocyte-endothelial cell interaction and has a pivotal role in inflammation. Whether it contributes to excessive mortality in dialysis patients remains uncertain. In this study, we examined circulating soluble VCAM-1 (sVCAM-1) in relation to different clinical and biochemical parameters, as well as mortality and cardiovascular events, in peritoneal dialysis (PD) patients.** ***Methods:*** **Values for serum sVCAM-1, together with C-reactive protein (CRP), homocysteine, albumin, lipid profile, blood hemoglobin, and indices of dialysis adequacy, were determined at study baseline, and echocardiography was performed in 160 long-term PD patients. Patients were followed up for a mean of 35 ± 16 (SD) months.** ***Results:*** **Serum sVCAM-1 levels were elevated in our continuous ambulatory PD (CAPD) patients and showed a negative correlation with residual glomerular filtration rate (GFR; $P < 0.001$) and low-density lipoprotein (LDL) cholesterol level ($P = 0.004$), but a positive correlation with left ventricular mass index ($P = 0.025$). Using Kaplan-Meier analysis, overall survival rates at 2 years were 96.2%, 75.2%, and 50.6% for patients in the lower, middle, and upper tertiles of sVCAM-1 levels, respectively ($P < 0.0001$). Fatal and nonfatal cardiovascular event-free survival rates were 58.2%, 56.9%, and 19.4% for patients in the lower, middle, and upper tertiles, respectively ($P < 0.0001$). Using Cox regression analysis with adjustment for confounding covariates, every 100-ng/mL increase in sVCAM-1 level was associated with 8% (95% confidence interval, 1.03 to 1.13) and 5% (95% confidence interval, 1.00 to 1.10) increases in risk for death and fatal and nonfatal cardiovascular events, respectively. Its significance for all-cause mortality remained with additional adjusting for LDL cholesterol level, but was lost when adjusting for residual GFR. Its association with cardiovascular events became insignificant when adjusting for LDL cholesterol level or residual GFR. Furthermore, patients with both sVCAM-1 and CRP levels elevated at the 50th percentile or greater were associated with the greatest death and fatal and nonfatal cardiovascular event rates compared with those with either CRP or sVCAM-1 level elevated at the 50th percentile or greater.** ***Conclusion:*** **Circulating sVCAM-1 levels show an important link with residual renal function, LDL cholesterol level, and cardiac hypertrophy in CAPD patients. Furthermore, residual renal function, which correlates inversely with circulating sVCAM-1 level, shows an important association with all-cause mortality and cardiovascular events and displaces sVCAM-1 level from the models for all-cause mortality and future cardiovascular events in CAPD patients. Additional study is needed to explore possible mechanistic links between inflammation, soluble adhesion molecules, residual renal function, and cardiac hypertrophy in CAPD patients.** ***Am J Kidney Dis*** **45:715-729.**

INDEX WORDS: Adhesion molecule; residual renal function; cardiac hypertrophy; dialysis; cardiovascular events; mortality.

LEUKOCYTE ADHESION and transmigration into the arterial intima are important early cellular events in atherosclerosis[1,2] and are mediated through a diverse family of cellular adhesion molecules expressed on the surface of vascular endothelial cells, including intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1).[3] In experimental atherosclerosis, endothelial cells express VCAM-1 even before monocytes/macrophages appear in the subendothelium.[4] Other than its involvement in atherogenesis, VCAM-1 has a pivotal role in other inflammatory processes.[3] Monocytes cocultured with endothelial cells induce endothelial VCAM-1 expression, leading to the recruitment and activation of flowing leukocytes, which further perpetuates the inflammatory response.[5]

A soluble form of VCAM-1 (sVCAM-1) that can now be measured in serum,[6] has been reported to be indicative of the expression of membrane-bound VCAM-1[7] and VCAM-1 mes-

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senger RNA expression, and is considered a marker of endothelial activation.[8] Increased circulating sVCAM-1 levels are correlated with the extent of atherosclerosis, reflected by carotid artery intima-media thickness, and severity of peripheral vascular disease on angiography.[9-11] Elevated levels of soluble cellular adhesion molecules have been reported in patients with chronic renal failure and dialysis patients.[12,13] In predialysis patients, C-reactive protein (CRP) level correlated significantly with soluble ICAM-1 and sVCAM-1 levels, and a greater sVCAM-1 level was observed in patients with malnutrition.[14] In hemodialysis patients, carotid atherosclerosis is associated with inflammation, as well as circulating soluble ICAM-1 and sVCAM-1 levels,[15] suggesting that cellular adhesion molecules may be important mediators of inflammation in dialysis patients. Whether this contributes to the excessive cardiovascular mortality in the end-stage renal disease population remains unknown.

Prospective studies have evaluated the prognostic significance of cellular adhesion molecules, but results are conflicting to date. Although some studies of patients without renal failure showed that a high sVCAM-1 level is predictive of future cardiovascular events,[16-18] others showed no association between sVCAM-1 level and cardiovascular events.[19,20] These studies,[19,20] as well as studies of predialysis and hemodialysis patients,[13-15] showed that an elevated soluble ICAM-1, but not sVCAM-1, concentration is predictive of mortality.

In the present prospective study, we evaluated mortality, as well as fatal and nonfatal cardiovascular events, in relation to serum circulating sVCAM-1 levels in a peritoneal dialysis (PD) population. Furthermore, we investigated associations between circulating sVCAM-1 levels and different clinical and biochemical parameters.

METHODS

This is a prospective follow-up study performed in the dialysis unit of the Prince of Wales Hospital, Hong Kong. The research protocol was approved by the Clinical Research and Ethics Committee of the Chinese University of Hong Kong. All patients provided informed consent before study entry. We prospectively enrolled 160 patients with end-stage renal disease who received continuous ambulatory PD (CAPD) treatment for at least 3 months into our study. Exclusion criteria for the study were patients with underlying malignancy, chronic liver disease, systemic lupus erythematosus, chronic rheumatic heart disease, and congenital heart disease. All patients were dialyzed using conventional glucose-based lactate-buffered PD solutions.

At study baseline, all patients underwent blood tests, echocardiographic examination, measurement of indices of dialysis adequacy, and assessment of cardiovascular parameters.

Blood Sampling and Laboratory Analysis

Twenty milliliters of fasting venous blood was collected at the time of echocardiography for measurement of serum sVCAM-1; high-sensitivity CRP; albumin; homocysteine; total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol; triglyceride; and blood hemoglobin. sVCAM-1 was measured by means of solid-phase enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN); high-sensitivity CRP, by using the Tinaquant CRP (Latex) ultra-sensitive assay (Roche Diagnostics GmBH, Mannheim, Germany); homocysteine, by means of fluorescence polarization immunoassay (IMx analyzer; Abbott Laboratories, Abbott Park, IL); and albumin, by using the bromcresol purple method (Roche Diagnostics GmBH). Total cholesterol and triglyceride were measured using the Hitachi 911 analyzer (Roche Diagnostics GmbH). HDL cholesterol was measured by means of the precipitation of apolipoprotein B–containing lipoproteins with phosphotungstate, whereas LDL cholesterol was calculated using the Friedwald formula. Hemoglobin was measured in the standard hematology laboratory.

Echocardiographic Examination

Two-dimensional echocardiography was performed using a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB, Horten, Norway) with a 3.3-mHz multiphase array probe in subjects lying in the left decubitus position by a single experienced cardiologist blinded to all clinical details of patients. All echocardiographic data were recorded according to guidelines of the American Society of Echocardiography.[21,22] Left ventricular mass was indexed by body surface area. Left ventricular hypertrophy (LVH) is defined as a left ventricular mass index (LVMi) of 131 g/m^2 or greater in men and 100 g/m^2 or greater in women, in accordance with Framingham criteria.[23] Relative wall thickness, measured at end-diastole as the ratio of 2 times the posterior wall thickness at end-diastole to left ventricular end-diastolic diameter,[23] is a marker of left ventricular remodeling. Relative wall thickness of 0.45 or greater is considered abnormally elevated and indicates abnormal left ventricular remodeling. Systolic and diastolic blood pressures were measured at the time of echocardiography after 15 minutes' rest.

Indices of Dialysis Adequacy

Patients were asked to bring 24-hour urine and dialysate samples on the day of blood sampling for measurement of urine and dialysate volume, as well as serum urea and creatinine concentrations. Adequacy of dialysis was determined by measuring total weekly urea clearance (Kt/V) and creatinine clearance using standard methods.[24] Weekly creatinine clearance was normalized to 1.73 m^2 of body surface