Original Article

Soluble adhesion molecules in end-stage renal disease: a predictor of outcome

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Abstract

Background. Inflammation is thought to contribute to initiation and aggravation of atherosclerosis through a process predominantly mediated by adhesion molecules. The aims of this study were to investigate the association between the concentrations of circulating soluble intercellular (sICAM-1) and vascular cellular (sVCAM-1) adhesion molecules and clinical outcome, and to evaluate the effect of antihypertensive drugs on sICAM-1 and sVCAM-1 concentrations in end-stage renal disease (ESRD) patients.

Methods. We prospectively investigated 310 (191 males) incident ESRD patients, 53±12 years old, shortly before the start of renal replacement therapy. Glomerular filtration rate (GFR) was 6.4 (range 0.8–16.5) ml/min/1.73 m². Plasma sICAM-1 and sVCAM-1 were measured by enzyme-linked immunosorbent assay (ELISA) kits. Survival was determined from the day of examination, with a mean follow-up period of 39 (range 1–123) months.

Results. In non-adjusted analysis, high sICAM-1 and sVCAM-1 levels were associated with all-cause and cardiovascular (P < 0.001) mortality. After adjusting for age, gender, diabetes mellitus, serum cholesterol, C-reactive protein (CRP), subjective global assessment and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), the association between high sICAM-1 and mortality remained significant for all-cause (HR 1.9; CI 1.2–2.9, P = 0.004) and cardiovascular (HR 1.8; CI 1.1–3.1, P = 0.02) mortality, and a high sVCAM-1 was associated with all-cause mortality (HR 1.7; CI 1.04–2.7, P = 0.03). Furthermore, the concentration of sICAM-1, but not sVCAM-1, was lower in patients receiving ACEI/ARB (254±83 vs 275±92 ng/ml; P < 0.05) or patients receiving calcium channel blockers (CCB, 251±75 vs 273±95 ng/ml; P < 0.05) than in non-users.

Conclusions. In ESRD patients, sICAM-1 and sVCAM-1 are independent predictors of all cause and cardiovascular death. The use of ACEI/ARB or CCB was associated with decreased concentrations of soluble adhesion molecules.

Keywords: angiotensin-converting enzyme inhibitors; cardiovascular disease; end-stage renal disease; inflammation; mortality; soluble adhesion molecules

Introduction

Premature atherosclerotic cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Low-grade inflammation and endothelial dysfunction play pivotal roles in the initiation, progression and propagation of the atherosclerotic process [1]. Adhesion of circulating leukocytes to the endothelial cells and subsequent trans-endothelial migration to sites of inflammation is suggested as an important step in the initiation and aggravation of atherosclerotic lesions [2]. This process is predominantly mediated by cellular adhesion molecules, which are expressed on the endothelial membrane in response to several inflammatory stimuli [3,4]. The expression process is induced by pro-inflammatory cytokines, which are present at increased levels in the uraemic circulation. The expression of vascular cellular (VCAM-1) and intercellular (ICAM-1) adhesion molecules has been demonstrated in human atherosclerotic plaques [5]. In addition, the expression of VCAM-1 was identified on activated endothelium and vascular smooth muscle cells in the course of atherogenesis [6,7]. The expression of VCAM-1 occurs particularly in the neovascular endothelium [8] and is strongly associated with the...
accumulation of leukocytes in the intima [9]. Recently, Bro et al. [10] have shown that acceleration of atherosclerosis is preceded by an up-regulation of ICAM-1 expression in uraemic apolipoprotein-E-deficient mice.

Although the role and functions of soluble adhesion molecules have not yet been completely elucidated, clinical evidence suggests their implication in disease progression and pathological processes associated with vascular wall inflammation. Elevated levels of soluble adhesion molecules have been detected in the plasma of patients with stable angina and acute coronary syndrome [4] and in renal patients [11].

Clinical data on soluble adhesion molecules are still limited in ESRD and their association with clinical outcome is controversial [12–15]. In this study, which included more patients and a longer observation period compared with our previous study [12], we investigated the concentrations of soluble adhesion molecules (sICAM-1 and sVCAM-1) in relation to all cause and cardiovascular mortality in ESRD patients. Furthermore, as long-term use of angiotensin-converting enzyme inhibitors (ACEI) may modify endothelial function [16], we analysed the effect of ACEI, angiotensin II receptor blockers (ARB) and other antihypertensive drugs on the circulating levels of soluble adhesion molecules.

**Patients and methods**

The study protocol was approved by the Ethics Committee of Karolinska University Hospital Huddinge, Stockholm, Sweden, and informed consent was obtained from each patient. The patients were investigated as part of an ongoing prospective study [17].

In the present study, post-hoc analyses were done in 310 ESRD patients (191 males; aged 53 ± 12 years; range 22–70 years). Fasting blood samples were taken on an average about 1 month before the start of renal replacement therapy (RRT). The median glomerular filtration rate (GFR), as estimated by the mean of creatinine and urea clearances from a 24 h collection of urine, was 6.4 (range 0.8–16.5, n = 274) ml/min/1.73 m². The study exclusion criteria were age below 20 years or above 70 years, clinical signs of acute infection, acute vasculitis or liver disease at the time of evaluation, or unwillingness to participate in the study.

The causes of ESRD were chronic glomerulonephritis in 82 patients (26%), diabetic nephropathy in 102 patients (33%), polycystic kidney disease in 35 patients (11%), interstitial nephritis in five patients (2%), nephrosclerosis in six patients (2%) and other, or unknown aetiologies in 80 patients (26%). Characteristics of the patients are shown in Table 1. Presence of clinical CVD was defined by medical history, clinical symptoms and/or findings of cardiac, cerebrovascular (stroke) and/or peripheral vascular disease. There were 109 (35%) patients with a clinical history or signs of cardiovascular, cerebrovascular and/or peripheral vascular disease at the start of the study. Of the 109 patients, 67 patients had one or more myocardial infarctions, clinical signs of ischaemic heart disease (angina pectoris), or had undergone coronary artery by-pass surgery; 24 patients had peripheral ischaemic vascular disease; 21 patients had a history of stroke or cerebral bleeding; and five patients had a history of an aortic aneurysm. A total of 267 patients were on antihypertensive medications. Most of them were on double or triple therapy including ACEI or ARB (for simplification both are grouped together as ACEI) (n = 181), calcium channel blockers (CCB, n = 122) and beta-blockers (n = 170), with various combinations of these drugs. Fifty-seven patients (18%) were on aspirin; 202 patients were being treated with erythropoetin. Most patients were treated with other commonly used drugs in terminal ESRD, such as phosphate and potassium binders, diuretics, and vitamin B, C and D supplementation.

**Biochemical methods**

The plasma levels of sICAM-1 and sVCAM-1 were determined by the commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D system Europe Ltd, Abingdon, UK). The limits of detection of sICAM-1 and

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<th>Table 1. Baseline characteristics of 310 incident ESRD patients close to start of dialysis treatment</th>
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<td><strong>Sex, male/female (n)</strong></td>
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<td><strong>Age (years)</strong></td>
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<td><strong>Inflammation (CRP ≥10 mg/l,%)</strong></td>
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<td><strong>β-blockers (%)</strong></td>
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Continuous variables are reported as mean ± SD or median (range). Categorical variables are reported as number or percentage. GFR, glomerular filtration rate; IGF, insulin-like growth factor; IGFBP, IGF binding protein; hsCRP, high sensitive C-reactive protein; IL, interleukin; TNF-α, tumour necrosis factor-α; WBC, white blood cell count; sICAM-1, soluble intercellular adhesion molecules; sVCAM-1, soluble vascular cellular adhesion molecules; ACEI, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; CCB, calcium channel blockers. 

\*n = 274, \*n = 301, \*n = 271, \*n = 239 and \*n = 213. 
sVCAM-1 were 0.60 ng/ml and 0.35 ng/ml, respectively. The intra-assay coefficient of variation (CV) for sICAM-1 and sVCAM-1 were 4.4 and 3.1% and the inter-assay CV were 7.4 and 7.0%, respectively. High sensitive C-reactive protein (hsCRP) was measured by ELISA kit (R&D System Inc., Minneapolis, MN, USA). Serum levels of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured by ELISA kits obtained from Boehringer Mannheim (Mannheim, Germany). Serum levels of IL-18 were measured by ELISA kits obtained from Medical & Biological Laboratories Japan (Nagoya, Japan). Plasma concentrations of insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3 were measured by a chemiluminescent immunometric assay (PILKGF-7 for Immulite® Automatic Analyzer, DPC, Los Angeles, CA, USA). Plasma IGFBP-1 was analysed by ELISA (IGFBP-1 IEMA Test, Medix Biochemica, Kauniainen, Finland). S-albumin (bromocresol purple method), creatinine, urea, calcium x phosphate, total cholesterol, triglyceride, high density lipid (HDL) cholesterol, haemoglobin and urinary creatinine, and urea were determined by routine procedures in the Department of Clinical Chemistry, Karolinska University Hospital, Huddinge.

Nutritional status

Subjective global assessment (SGA) was used to evaluate the overall protein–energy nutritional status. SGA included six subjective assessments, three based on the patient’s history of weight loss, incidence of anorexia and incidence of vomiting, and three based on the physician’s grading of muscle wasting, presence of oedema and loss of subcutaneous fat. Based on these assessments, each patient was given a score of 1–4, indicating normal, mild, moderate or severe malnutrition, respectively. Malnutrition was defined in terms of SGA score of 2–4, and patients meeting these criteria are grouped together as malnourished patients. The nutritional evaluation also included body mass index (BMI), calculated as weight in kg/(height in m²), and plasma IGF-1, IGFBP-3 and IGFBP-1.

Statistical analyses

Data are presented as mean±SD or median and range, as appropriate, with a P<0.05 indicating significance. The comparison between two groups was performed using the Wilcoxon-rank sum test for skewed distributed variables or using chi-square test for nominal variables. Correlations were performed by the Spearman rank test (ρ). To evaluate the sensitivity and specificity of sICAM-1 and sVCAM-1, as predictors of mortality, a receiver operating characteristic (ROC) analysis was performed. Optimum cut-off values, with the combination of the highest sensitivity and specificity, were calculated. Moreover, in a comparative analysis of predictors of all-cause and CV mortality, the area under the curve (AUC) derived from the ROC analysis was used to examine the predictive power of sICAM-1, sVCAM-1, hsCRP and IL-6. The general linear models (GLM) procedure with least square means was used to identify significant interactions between the age and the usage of ACEI and CCB, respectively. When significant interactions were found between factors, these were identified with the simple main effects tests. Survival analyses were made with the Cox proportional hazard model. The relative risks for mortality were determined by univariate and multivariate Cox regression analysis and presented as hazard ratio (HR; 95% CI). The Cox proportional hazard model (the PHREG procedure in the SAS System Release 8.2) was used to examine the effects of baseline and follow-up variables on the outcome variables. Survival was measured from the day of examination until death or censoring, which was made at the end of the follow-up. No patient was lost to follow-up. The statistical analysis was performed using statistical software SAS version 9.1 (SAS Campus Drive, Cary, NC, USA).

Results

Baseline characteristics of the investigated patients are summarized in Table 1. The mean plasma concentrations of sVCAM-1 (1360±469 vs 1363±602 ng/ml) and sICAM-1 (259±83 vs 270±97 ng/ml) did not differ significantly between males and females, respectively. Patients with diabetes mellitus had significantly higher concentrations of sVCAM-1 (1483±606 vs 1304±468 ng/ml; P<0.01) compared to non-diabetics, whereas sICAM-1 did not differ significantly between diabetic and non-diabetic patients (277±106 vs 257±78 ng/ml, respectively). Age was significantly correlated with sVCAM-1 and sICAM-1 (Table 2).

Nutritional markers and adhesion molecules

There were 104 (34%) patients classified as being malnourished based on SGA. The malnourished patients had significantly higher levels of sICAM-1 (295±126 vs 250±77 ng/ml; P<0.001) (Figure 1A) and sVCAM-1 (1526±590 vs 1280±467 ng/ml; P<0.0001) (Figure 1B), respectively, compared with the patients with normal nutritional status. Moreover, the concentration of sICAM-1 and sVCAM-1 were negatively correlated with s-albumin, s-creatinine, total cholesterol, IGF-1 and IGFBP-3, and positively correlated with IGFBP-1 (Table 2).

<table>
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<th>Table 2. Correlations of soluble adhesion molecules (sICAM and sVCAM) with nutritional and inflammation parameters in incident ESRD patients close to start of dialysis treatment</th>
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<td><strong>sICAM-1 (ρ)</strong></td>
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For abbreviations see Table 1. <sup>a</sup>P<0.05, <sup>b</sup>P<0.01, <sup>c</sup>P<0.001 and <sup>d</sup>P<0.0001.
Inflammation markers and adhesion molecules

Based on the level of CRP, the patients were divided into two groups [17], non-inflamed (CRP < 10 mg/l; n = 199) and inflamed (CRP ≥ 10 mg/l; n = 111, 36%). As expected, the plasma levels of sICAM-1 (294±91 vs 247±83 ng/ml; P < 0.0001) (Figure 1C) and sVCAM-1 (1566±640 vs 1248±403 ng/ml; P < 0.0001) (Figure 1D) were significantly higher in the inflamed patients than in non-inflamed patients. In 109 (35%) patients with CVD, the concentrations of sICAM-1 (282±89 vs 257±103 ng/ml; P < 0.001) (Figure 1E) and sVCAM-1 (1483±511 vs 1295±518 ng/ml; P < 0.0001) (Figure 1F) were significantly higher than in patients without CVD.

Table 2 shows that sICAM-1 and sVCAM-1 were positively correlated with hsCRP, IL-6 and TNF-α. Moreover, sICAM-1, but not sVCAM-1, correlated positively with fibrinogen, IL-18 and WBC.

Effect of antihypertensive drugs on adhesion molecule concentrations

The concentrations of sICAM-1 were significantly lower in patients receiving ACEI (254±83 vs 275±92 ng/ml; P < 0.05) (Figure 2A) or CCB (251±75 vs 273±95 ng/ml; P < 0.05) (Figure 2B) compared with non-users of these drugs. The ages of the patients receiving ACEI or CCB were significantly lower than in non-users (P < 0.01). Therefore, in a further analysis (using GLM) to adjust for the influence of age, we found that the sICAM-1 concentrations were still significantly lower in the users of ACEI than in non-users (P < 0.05). The interaction between ACEI and age was not statistically significant. When we adjusted for age, the sICAM-1 concentration was significantly lower in CCB users than in non-users (P < 0.05). However, there was a significant interaction between CCB and age (P < 0.05).

The circulating sVCAM-1 concentration did not differ significantly between the users and non-users of ACEI (1331±483 vs 1407±568 ng/ml) (Figure 2C) or CCB (1363±415 vs 1390±599 ng/ml) (Figure 2D), respectively. The sICAM-1 (260±84 vs 269±91 ng/ml) and sVCAM-1 (1398±570 vs 1326±468 ng/ml) concentrations did not differ significantly between the users and non-users of β-blockers, respectively.

Aspirin treatment and adhesion molecules

The 57 patients (18%) who were on aspirin treatment were older (60±9 vs 51±12 years, P < 0.0001) and had...
clinical CVD more often (75 vs 26%; \(P < 0.0001\)) than patients not taking aspirin. The concentrations of sICAM-1 (293 ± 93 vs 260 ± 100 ng/ml, \(P < 0.01\)) and sVCAM-1 (1446 ± 418 vs 1342 ± 542 ng/ml, \(P < 0.05\)) were significantly higher in aspirin users than in non-users.

**Adhesion molecules and survival rate**

Survival was determined from the day of examination, with a mean follow-up period of 39 (range 1–123) months, with no loss of follow-up of any patient. Within the follow-up period, 107 (35%) patients died, of whom 69 (64%) died of cardiovascular causes. Non-survivors had significantly higher concentrations of sICAM-1 (304 ± 112 vs 242 ± 64 ng/ml, \(P < 0.0001\)) and sVCAM-1 (1533 ± 618 vs 1271 ± 439 ng/ml, \(P < 0.0001\)) compared with survivors. In accordance, patients who died due to CVD had significantly higher concentrations of sICAM-1 (289 ± 98 vs 242 ± 64 ng/ml, \(P < 0.0001\)) and sVCAM-1 (1461 ± 466 vs 1271 ± 439 ng/ml, \(P < 0.01\)) compared with survivors. However, no significant differences were observed in either sICAM-1 (289 ± 98 vs 333 ± 130 ng/ml) or sVCAM-1 (1461 ± 466 vs 1664 ± 819 ng/ml) concentrations between patients who died from cardiovascular causes and those who died from non-cardiovascular causes, respectively.

The sensitivity and specificity were 66.7 and 53.3%, respectively, for sICAM-1 >242 ng/ml and 67 and 54%, respectively, for sVCAM-1 >1271 ng/ml, and these cut-off levels were used for dividing patients into two groups for comparison of survival rates. In a non-adjusted analysis, high sICAM-1 and sVCAM-1 were
significantly associated with all-cause (P < 0.0001) and CVD (P < 0.001) mortality (Figure 3). After adjusting for age, gender, diabetes mellitus, serum cholesterol, SGA, hsCRP and medication with ACEI, the association between high sICAM-1 and mortality remained significant for all-cause (HR 1.9; CI 1.2–2.9, P = 0.004) and cardiovascular (HR 1.8; CI 1.1–3.1, P = 0.02) mortality. Moreover, after adjustment for the same variables, a high sVCAM-1 was significantly associated with all-cause mortality (HR 1.7; CI 1.04–2.7, P = 0.03). After adjustment, the HR for cardiovascular mortality was higher in patients with high sVCAM-1 but this difference did not reach significance (HR 1.4; CI 0.8–2.6, P = 0.23).

By introducing aspirin use into the model, the associations between all-cause mortality and high sICAM-1 (HR 1.8; CI 1.2–2.9, P = 0.008), as well as high sVCAM-1 (HR 1.7; CI 1.1–2.7, P = 0.04), remained significant. However, the association between sICAM-1 and cardiovascular mortality lost its significance (HR 1.6; CI 0.89–2.74, P = 0.12), and the association between sICAM-1 and cardiovascular mortality remained insignificant (HR 1.3; CI 0.73–2.44, P = 0.56).

Comparison of mortality predictive power between adhesion molecules, CRP and IL-6

In a comparative analysis, AUC values from the ROC analysis were used to evaluate the predictive powers of sICAM-1 and sVCAM-1 for all-cause and cardiovascular mortality compared with the predictive powers of CRP and IL-6. For all-cause mortality, the AUC values were 0.69 for sICAM-1, 0.63 for sVCAM-1, 0.60 for hsCRP and 0.69 for IL-6 (Figure 4A). For cardiovascular mortality, the AUC values were 0.63 for sICAM-1, 0.61 for sVCAM-1, 0.60 for hsCRP and 0.65 for IL-6 (Figure 4B).

Discussion

The present study confirms that high levels of sICAM-1 and sVCAM-1 are associated with signs of malnutrition, inflammation and cardiovascular disease, and also that high sICAM levels predict all-cause and cardiovascular mortality in incident ESRD patients starting dialysis treatment. Furthermore, the use of ACEI and CCB was associated with decreased concentrations of sICAM-1.

Previous studies have shown that elevated levels of sICAM-1 are associated with fatal and non-fatal cardiovascular events in non-renal individuals [4,18]. However, this relation could not be demonstrated for sVCAM-1 in other cohorts [4,18]. A recent study [14] demonstrated that sVCAM-1 predicted all-cause and cardiovascular mortality in 160 long-term peritoneal dialysis patients. However, this association was lost after adjustment for residual renal function, which was correlated with sVCAM-1. On the other hand, Tripepi et al. [15] showed that sICAM-1, but not sVCAM-1,
concentration in 217 dialysis patients was associated with all-cause mortality only in univariate analysis. However, this association was lost after adjustment for conventional risk factors and confounders.

In the present study, both ICAM-1 and VCAM-1 concentrations were high in non-survivors and in the patients with signs of malnutrition, inflammation and cardiovascular disease. Moreover, in univariate analysis, both the adhesion molecules were associated with all-cause mortality and these associations persisted even after adjusting for confounding variables. On the other hand, sICAM-1 and sVCAM-1 were associated with cardiovascular mortality in univariate analysis and this relationship remained significant for sICAM-1 after adjusting for several risk factors and confounders. However, when aspirin use was added into the model, the association between sICAM-1 and cardiovascular mortality lost its significance. This effect is not unexpected, since patients on aspirin treatment were older and had a higher prevalence of CVD.

Several groups have reported that markers of inflammation, in particular CRP and IL-6, are associated with all-cause mortality and cardiovascular events in ESRD patients [19]. Recent studies have suggested that IL-6 may even be a better predictor of clinical outcome than CRP in ESRD patients [15,20,21]. In the current study, sICAM-1 and sVCAM-1 correlated with several inflammation markers. Moreover, according to the ROC analyses, both sICAM-1 and sVCAM-1, as well as IL-6, predicted all-cause and cardiovascular mortality better than CRP. Thus, our findings show that soluble adhesion molecules predict clinical outcome in ESRD patients as well as IL-6, but better than CRP.

A novel finding of the present study was that the use of ACEI and CCB was associated with significantly lower plasma ICAM-1 levels in ESRD patients, a finding not in accordance with results presented by Wang et al. [14]. The effect of ACEI and CCB on sVCAM-1 concentrations showed the same trend but did not reach statistical significance. Notably, the use of β-blockers did not show an effect on circulating soluble adhesion molecule levels. The use of ACEI, although not designed for lowering CRP, has been associated with lower CRP levels in non-renal patients with ischaemic heart disease, stroke or heart failure [22,23]. Furthermore, the administration of enalapril resulted in a reduced release of soluble endothelial-derived substances into the circulating blood in 40 surgical septic patients [24]. In accordance with these results in non-renal patients, we have previously demonstrated lower levels of the inflammatory biomarkers TNF-α in ESRD patients treated with ACEI [25].

Some shortcomings of the present study should be considered. First, as we relied on a single determination of soluble adhesion molecules, we cannot take into account any variation that may have occurred over time. Second, as repetitive analyses of soluble adhesion molecules were not performed, we could not consider in the analysis the potential effect of the RRT on the levels of adhesion molecules in relationship to the outcome. Third, the classification of CVD included only patients with clinically significant disease, which may limit and underestimate the true prevalence of CVD in this study [26]. Fourth, we did not take into account the duration of antihypertensive treatment prior to the investigation. Finally, it should be pointed out that this is a post-hoc analysis with increased risk for type-1 error and this may limit the value of the study.

In summary, the present study confirms that high levels of soluble adhesion molecules (sICAM-1 and sVCAM-1) in incident ESRD patients starting dialysis treatment are associated with malnutrition, inflammation and cardiovascular disease. Moreover, soluble adhesion molecules (especially sICAM-1) predict all-cause and cardiovascular death in ESRD patients, even after adjustment for conventional risk factors, suggesting that increased levels of soluble adhesion molecules may be involved in the process of atherosclerosis and increased mortality in ESRD patients. Finally, our data indicate that treatment with ACEI and CCB associated with lower concentrations of soluble adhesion molecules in this patient group.
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Conflict of interest statement: B.L. is an employee of Baxter Corp.

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