Circulating vascular endothelial growth factor (VEGF) and its soluble receptor 1 (sVEGFR-1) are associated with inflammation and mortality in incident dialysis patients

Jiangzi Yuan1,2,*
Qunying Guo1,3
Abdul Rashid Qureshi1
Björn Anderstam1
Monica Eriksson1
Olof Heimbürger1
Peter Bárány1
Peter Stenvinkel1
and Bengt Lindholm1

1Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden,
2Renal Division, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China and
3Renal Division, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Correspondence and offprint requests to: Bengt Lindholm; E-mail: bengt.lindholm@ki.se
*J.Y. and Q.G. share first authorship.

ABSTRACT

Background. Vascular endothelial growth factor (VEGF) and its soluble receptor 1 (sVEGFR-1) predict mortality in nondia-
lyzed chronic kidney disease (CKD) stage 3–5 patients and prevalent hemodialysis (HD) patients. We investigated deter-
minants of VEGF and sVEGFR-1 as well as their relationship with all-cause mortality in incident dialysis patients.

Methods. In this longitudinal cohort study of 211 CKD 5 patients [64% males, mean age of 54 ± 12 years and median glomerular filtration rate (GFR) 5.9 [interquartile range (IQR), 4.6–7.2 mL/min/1.73 m²] who were enrolled at initiation of renal replacement therapy, demographics, clinical character-
istics, including comorbidities and laboratory data were ob-
tained at the beginning of the study. After 12 months, blood was again drawn from 95 dialysis patients [42 HD patients and 53 peritoneal dialysis (PD) patients]. The 211 patients were followed up for a median of 29 (IQR, 15–37) months for survi-
val analysis. Plasma was also obtained from 47 healthy controls.

Results. VEGF and sVEGFR-1 levels did not change signifi-
cantly after 12 months on HD or PD. The sVEGFR-1, but not

VEGF levels, differed between the patients and the healthy controls. VEGF and sVEGFR-1 correlated with high-sensi-
tivity C-reactive protein (hsCRP; rho = 0.19, P = 0.01 and
rho = 0.16, P = 0.03; respectively), leukocyte count (rho = 0.22;
P < 0.01 and rho = 0.23; P < 0.01; respectively) and sVEGFR-1 correlated also with interleukin-6 (IL-6) (rho = 0.21, P < 0.01). In Kaplan–Meier analysis, a high VEGF level was associated with increased all-cause mortality (Chi-square = 5.8, P = 0.02) which remained after adjustments for age, gender, body mass index (BMI), IL-6, GFR and comorbidities [hazard ratio, HR: 3.08, 95% confidence intervals (CI) 1.48–6.42]. Whereas
sVEGFR-1 per se did not predict mortality, a high sVEGFR-1 level in patients with concomitant high IL-6 was associated
with increased all-cause mortality (HR 2.83, 95% CI 1.32–6.06) which remained significant after adjustments for age, gender, BMI and comorbidities (HR 2.33, 95% CI 1.06–5.14) but not after adjusting also for GFR.

Conclusions. The circulating levels of VEGF and sVEGFR-1 are associated with biomarkers of inflammation. VEGF pre-
dicts all-cause mortality, independent of inflammation, while an elevated sVEGFR-1 level increased the mortality risk in in-
flamed patients.
INTRODUCTION

Traditional risk factors are highly prevalent among chronic kidney disease (CKD) patients and contribute to their high mortality; however, interventions targeting these risk factors have in general failed to improve survival among CKD patients, suggesting that nontraditional risk factors may also be of importance [1, 2]. Assessment of novel biomarkers reflecting these nontraditional risk factors could help identify underlying pathways and causes of the high mortality and this in turn could potentially lead to the design of novel therapeutic approaches to reduce the high mortality among CKD patients.

Vascular endothelial growth factor (VEGF) and its receptor vascular endothelial growth factor receptor 1 (VEGFR-1) are important regulators of blood vessel growth and play an important role in promoting endothelial survival and maintaining the microvasculature [3]. Soluble vascular endothelial growth factor receptor 1 (sVEGFR-1; also known as soluble fms-like tyrosine kinase-1, sFlt-1) is a splice variant of VEGFR-1, lacking the transmembrane and cytoplasmic domains. sVEGFR-1 is likely to be a negative regulator of VEGF availability, or may prolong the different VEGF activities [4]. Recent studies in nondialyzed CKD stage 3–5 patients and prevalent hemodialysis (HD) patients showed that VEGF or sVEGFR-1 are associated with endothelial dysfunction, left ventricular hypertrophy and systolic dysfunction and may predict mortality in CKD patients [5–7]. However, the role of VEGF or sVEGFR-1 and their relationship with mortality in incident dialysis patients are less known.

Therefore, in this longitudinal cohort study of 211 incident dialysis patients who were investigated prior to or in conjunction with start of dialysis, we determined VEGF and sVEGFR-1 at baseline and, in a subgroup of the patients, also after 1 year of dialysis, and analyzed the relationship of VEGF and sVEGFR-1 with clinical and laboratory parameters and all-cause mortality.

MATERIALS AND METHODS

Patients

Two hundred and eleven CKD 5 patients (64% males, mean age of 54 ± 12 years) were enrolled at the initiation of renal replacement therapy at the Karolinska University Hospital Huddinge, Sweden between 1994 and 2007. The patients were investigated as a part of an ongoing prospective cohort study (see [8] for detailed information about design) and post hoc analyses were performed. Patients with age above 70 years or with clinical signs of acute infection, acute vasculitis or hepatitis B at the time of evaluation, or unwillingness to participate in the study were excluded. All patients were interviewed to obtain data on demographics, comorbidities [i.e. diabetes mellitus (DM), cardiovascular disease (CVD) and protein-energy wasting (PEW)] and blood samples at the beginning of the study. A large proportion of the patients were receiving drugs common for CKD stage 5 patients such as erythropoiesis-stimulating agents, phosphate and potassium binders, vitamin B, C and D supplementation, lipid-lowering medication with statins and almost all of the patients (97%) used antihypertensive drugs: angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists (63% of the patients), beta-blockers (67%), calcium-channel blockers (48%) and diuretics (87%). After 12 months, blood samples were obtained again from 95 patients [42 HD patients and 53 peritoneal dialysis (PD) patients] out of the 211 patients. Plasma was also obtained from 47 healthy controls (70% males, mean age: 62 ± 12 years, glomerular filtration rate; GFR: 86 ± 16 mL/min/1.73²). In a subgroup analysis of the 95 patients, we compared VEGF and sVEGFR-1 levels at baseline, and, in the same patients, at 12 months following treatment with either HD or PD, and these levels were also compared with those of the healthy controls. The 211 patients were followed up until death or the end of the observation time. Survival, censored at transplantation, was determined from the day of examination, with a median follow-up period of 29 (interquartile range, IQR, 15–37) months. The Ethics Committee of the Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden approved the study protocol and informed consent was obtained from all patients.

Laboratory analyses

After an overnight fast, blood samples were collected. Plasma was kept frozen at −70°C if not analyzed immediately. Plasma levels of VEGF (VEGF-A) (PDVE00; R & D Systems, Minneapolis, MN) and sVEGFR-1 (DVR100B; R & D Systems) were determined in duplicate using commercially available enzyme-linked immunosorbent assay kits. Intra- and interassay coefficients of variation for VEGF, sVEGFR-1 kits were 6.7% and 8.8%, 3.8% and 9.8%, respectively. Results are expressed as the average of two measurements. ELISA commercial kits were also used for analyses of interleukin-6 (IL-6) (Roche Diagnostics GmbH, Penzberg, Germany), soluble vascular adhesion molecule 1 (VCAM-1) and soluble intracellular adhesion molecule 1 (ICAM-1) (both from R&D System Inc., Minneapolis, MN). High-sensitivity C-reactive protein (hsCRP) was measured by nephelometry. Serum cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were analyzed by standard enzymatic procedures (Boehringer Mannheim, Germany). Low-density lipoprotein cholesterol was calculated according to the Friedewald formula [9]. Additional biochemical analyses were performed using routine methods at the Department of Clinical Chemistry at Karolinska University Hospital Huddinge. GFR, expressed in mL/min/1.73², was calculated as the mean of urea and creatinine clearances [10].

Nutritional state

Body mass index (BMI) was defined as the body weight in kilograms divided by the square of patient height in meters. Subjective global assessment (SGA) was used to evaluate the overall PEW [11]. SGA included six subjective assessments; three were based on the patient’s history of weight loss, incidence of anorexia and incidence of vomiting, and three were based on subjective grading of muscle wasting, presence of
edema and loss of subcutaneous fat. On the basis of these assessments, each patient was given a score that reflects the nutritional status as follows: 1 = normal nutritional status, 2 = mild PEW, 3 = moderate PEW and 4 = severe PEW. Thus, PEW was defined as a SGA assessment score of >1. Lean body mass, fat body mass and truncal fat mass were estimated by means of dual-energy X-ray absorptiometry using the DPX-L device (Lunar Corp, Madison, WI).

### Statistical analyses

All values are expressed as mean ± SD or median (interquartile range, IQR) or percentage, as appropriate. Comparison among three groups was performed by the Kruskal–Wallis test or between two groups with the Mann–Whitney test. Spearman’s rank correlation was used for univariate analysis. Survival analyses were done with the Kaplan–Meier survival curve and the Cox proportional hazard model, presenting data as hazard ratio [HR; 95% confidence intervals (CI)]. For the survival analyses, we compared patients with baseline VEGF level >75th percentile (>392.7 pg/mL), defined as high VEGF group, and patients with baseline VEGF level ≤75th percentile (≤392.7 pg/mL), defined as low VEGF group (used as the reference category); and patients with an sVEGFR-1 level >75th percentile (>137.6 pg/mL), defined as high sVEGFR-1 group, to those with an sVEGFR-1 level ≤75th percentile (≤137.6 pg/mL), defined as low sVEGFR-1 group, (used as the reference category). Finally, we also examined the presence of biological interaction between inflammation (defined as an IL-6 level >7.0 pg/mL according to [12]) and elevated sVEGFR-1 levels on mortality. This was done by a comparative analysis of mortality in four categories of patients characterized by inflammation and high and low sVEGFR-1, inflammation and low sVEGFR-1, no inflammation and high sVEGFR-1 and no inflammation and low sVEGFR-1, respectively. Crude and adjusted HR with 95% CI was estimated for each category using noninflamed patients with low sVEGFR-1 values as the reference category. We used the synergy index to evaluate the degree of biological interaction between inflammation (IL-6) and sVEGFR-1 levels on mortality. The statistical analysis was performed using statistical software SAS version 9.3 (SAS Campus Drive, Cary, NC).

### RESULTS

#### General characteristics

General demographics, clinical characteristics and laboratory variables of the 211 starting dialysis patients at baseline are summarized in Table 1. The median serum VEGF and sVEGFR-1 at baseline were 226.5 (IQR, 89.6–392.7) pg/mL and 113.7 (IQR, 94.9, 137.6) pg/mL, respectively.

| Table 1. Characteristics and laboratory variables in 211 incident dialysis patients |
|---------------------------------|---------------------|
| Age (year)                      | 54 ± 12             |
| Gender (male, %)                | 64                  |
| Systolic BP (mmHg)              | 151 ± 22            |
| Diastolic BP (mmHg)             | 87 ± 12             |
| DM (%)                          | 34%                 |
| CVD (%)                         | 40%                 |
| BMI (kg/m²)                     | 23.9 (21.7–28.0)    |
| Total fat mass (kg)             | 19.9 (14.2–28.1)    |
| Truncal fat mass (kg)           | 10.5 (7.4–15.2)     |
| Lean body mass (kg)             | 50.0 (41.9–57.0)    |
| SGA>1 (%)                       | 25%                 |
| Creatinine (µmol/L)             | 723.5 (551.5–938.3) |
| GFR (ml/min/1.73²)              | 5.9 (4.6–7.2)       |
| Albuminuria (g/24 h)            | 1.8 (0.5–3.1)       |
| Albumin (g/L)                   | 33.0 (29.0–36.0)    |
| Hemoglobin (g/L)                | 106 (95–116)        |
| Glucose (mmol/L)                | 5.4 (4.7–6.7)       |
| HDL (mmol/L)                    | 1.3 (1.0–1.6)       |
| Triglyceride (mmol/L)           | 1.8 (1.3–2.3)       |
| Cholesterol (mmol/L)            | 4.7 (3.9–5.6)       |
| LDL (mmol/L)                    | 2.5 (1.8–3.4)       |
| hsCRP (mg/L)                    | 5.4 (1.8–14.0)      |
| Leukocyte count (×10⁹/L)        | 7.6 (7.7–9.5)       |
| IL-6 (pg/mL)                    | 6.3 (3.7–10.8)      |
| VCAM-1 (ng/mL)                  | 1416 (1105–1649)    |
| ICAM-1 (ng/mL)                  | 234 (201–294)       |
| VEGF (pg/mL)                    | 226.5 (89.6–392.7)  |
| sVEGFR-1 (pg/mL)                | 113.7 (94.9–137.6)  |

Data are expressed as mean ± SD or median (interquartile range, IQR) or percentage.

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; ICAM-1, soluble intra cellular adhesion molecule 1; IL-6, interleukin-6; SGA, subjective global assessment; sVEGFR-1, soluble vascular endothelial growth factor receptor 1; VCAM-1, soluble vascular adhesion molecule 1; VEGF, vascular endothelial growth factor.

Also, there were no significant differences (P > 0.05) between sVEGFR-1 levels at baseline and after 12 months, neither among HD patients [111.5 (IQR, 95.8–136.0) versus 113.5 (IQR, 90.8–137.5) pg/mL] nor among PD patients [111.0 (IQR, 95.0–137.6) versus 125.0 (IQR, 105.0–147.5) pg/mL]; however,
the patients had higher sVEGFR-1 levels than the healthy controls [75.6 (IQR, 66.8–87.0) pg/mL], both at baseline and after 12 months on dialysis with HD or PD. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; Base, baseline; 12 M, 12 months after start of dialysis. Statistically significant differences are marked as *P < 0.05.

**VEGF correlated with hsCRP (rho = 0.19, P = 0.01), leucocyte count (rho = 0.22; P < 0.01), BMI (rho = 0.15; P = 0.04) and serum albumin (rho = −0.21; P < 0.01), while there were no significant relationships with IL-6 (rho = 0.17, P = 0.09), age, GFR, VCAM-1 or ICAM-1. On the other hand, sVEGFR-1 correlated with hsCRP (rho = 0.16, P = 0.03), leucocyte count (rho = 0.23; P < 0.01), IL-6 (rho = 0.21, P < 0.01), age (rho = 0.15, P = 0.04), GFR (rho = −0.21, P = 0.01; see Figure 2), VCAM-1 (rho = 0.29, P < 0.001) and ICAM-1 (rho = 0.33, P < 0.001). Neither VEGF nor sVEGFR-1 correlated with gender, DM, CVD, SGA, glucose, lipids or with body fat mass, truncal fat mass or lean body mass. In the healthy controls, sVEGFR-1 (but not VEGF) correlated with age (rho = 0.48, P < 0.01) and GFR (rho = −0.30, P = 0.04).

**Inflamed patients** (defined as IL-6 >7.0 pg/mL, N = 79) had significantly elevated VEGF levels, when compared with non-inflamed (IL-6 ≤7.0 pg/mL, N = 109) patients, 266.6 (IQR, 115.3–479.2) and 202.0 (IQR, 80.9–332.5) pg/mL, respectively; P = 0.02 (Figure 3A). Inflamed patients (N = 73) had also significantly elevated sVEGFR-1 levels, when compared with noninflamed (N = 118) patients, 124.6 (IQR, 102.4–161.2) and 110.9 (IQR, 92.9–128.5) pg/mL, respectively; P = 0.001 (Figure 3B). VEGF and sVEGFR-1, respectively, were also associated with inflammation as defined as hsCRP >10 mg/L.

**Survival analysis**

During a median follow-up period of 29 (IQR, 15–37) months, 45 patients died. The Kaplan–Meier curve (Figure 4) showed that patients in the high VEGF group (>392.7 pg/mL) had a higher all-cause mortality (Chi-square = 5.8, P = 0.02) than those in the low VEGF group (≤392.7 pg/mL). The two groups had similar mean age (53 ± 12 versus 56 ± 13 years; P = 0.13) and gender distribution (males 65 versus 66%). In a Cox proportional hazards model of all-cause mortality, adjusting for age, gender and BMI, patients in the high VEGF group had increased all-cause mortality risk (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2). We also performed the analysis using continuous data of VEGF in Cox proportional hazards model for mortality risk. VEGF was significantly related to mortality in the crude model (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2). We also performed the analysis using continuous data of VEGF in Cox proportional hazards model for mortality risk. VEGF was significantly related to mortality in the crude model (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2). We also performed the analysis using continuous data of VEGF in Cox proportional hazards model for mortality risk. VEGF was significantly related to mortality in the crude model (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2). We also performed the analysis using continuous data of VEGF in Cox proportional hazards model for mortality risk. VEGF was significantly related to mortality in the crude model (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2). We also performed the analysis using continuous data of VEGF in Cox proportional hazards model for mortality risk. VEGF was significantly related to mortality in the crude model (HR: 2.04, 95% CI 1.10–3.78), also when including other independent variables (age, gender, DM, SGA, CVD, IL-6) (HR: 1.99, 95% CI 1.05–3.77) and also when adjusting for age, gender, DM, SGA, CVD, IL-6 and GFR (HR: 3.08, 95% CI 1.48–6.42) (Table 2).
difference was not statistically significant. No survival difference was found between patients in the high and low sVEGFR-1 groups in the Kaplan–Meier analysis (Chi-square = 0.27, P = 0.61) or when assessed by Cox proportional hazards model using continuous data of sVEGFR-1; thus, sVEGFR-1 was found not to be related to mortality, not even in a crude model (HR: 1.04, 95% CI 0.96–1.14). However, there was an apparent impact of concomitant inflammation; patients with inflammation (IL-6 >7.0 pg/mL) and high sVEGFR-1 level (>137.6 pg/mL) had higher mortality after adjusting for age, gender and BMI (HR: 2.42, 95% CI 1.12–5.23), and even after adjusting for age, gender, BMI, DM, SGA and CVD (HR: 2.33, 95% CI 1.06–5.14); however, the statistical significance was lost after further adjusting also for GFR (HR 1.40, 95% CI 0.52–3.81) (Table 3). The degree of biological interaction between inflammation (IL-6) and sVEGFR-1 level on mortality according to the synergy index was 4.32 (95% CI, 1.86–10.04). Inclusion in the models of hsCRP (>10 mg/L) instead of IL-6 as the inflammatory marker did not change the results of the Cox proportional hazards models.

DISCUSSION

In this longitudinal study of CKD stage 5 patients starting on dialysis, VEGF levels did not change significantly following initiation of dialysis and did not differ from those of healthy controls. The sVEGFR-1 levels also did not change following dialysis; however, sVEGFR-1 levels were higher than in the healthy controls both at baseline and after 1 year. VEGF and sVEGFR-1 levels were positively associated with markers of inflammation and sVEGFR-1 also correlated with age, GFR and two markers of endothelial dysfunction (VCAM-1 and ICAM-1). Higher levels of VEGF predicted all-cause mortality, independent of inflammation, and an elevated sVEGFR-1 level combined with inflammation (but not sVEGFR-1 per se) also increased the risk of all-cause mortality.

VEGF has multiple properties and is involved in the pathogenesis of cancer, arteriosclerosis, obesity and DM [13–15]. Hypoxia together with a wide variety of hormones, growth factors and cytokines are involved in regulating VEGF release [16]. Existing data regarding determinants and implications of

Table 2. Multivariate Cox regression models examining the relationship of high (>392.7 pg/mL) versus low (≤392.7 pg/mL) VEGF and mortality

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>2.07 (1.13–3.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 1: Adjusted for age, gender and BMI</td>
<td>2.04 (1.10–3.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2: Adjusted for age, gender, BMI, DM, SGA, CVD and IL-6</td>
<td>1.99 (1.05–3.77)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 3 Adjusted for age, gender, BMI, DM, SGA, CVD, IL-6 and GFR</td>
<td>3.08 (1.48–6.42)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
Table 3. Cox regression models examining all-cause mortality risk of high or low sVEGFR-1 in the presence or not of concomitant inflammation as assessed by IL-6

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td><strong>Interaction sVEGFR-1-inflammation</strong></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Low IL-6, low sVEGFR-1 (n = 89)</td>
<td>1</td>
</tr>
<tr>
<td>Low IL-6, high sVEGFR-1 (n = 29)</td>
<td>1.27 (0.42–3.83)</td>
</tr>
<tr>
<td>High IL-6, low sVEGFR-1 (n = 54)</td>
<td>2.15 (1.08–4.27)</td>
</tr>
<tr>
<td>High IL-6, high sVEGFR-1 (n = 19)</td>
<td>2.83 (1.32–6.06)</td>
</tr>
</tbody>
</table>

Synergy index: 4.32 (95% CI, 1.86–10.04).

HR, hazard ratio; CI, confidence interval.

Significant difference (P < 0.05) is marked as bold.

High sVEGFR-1 defined as sVEGFR-1 > 137.6 pg/mL; low sVEGFR-1 defined as sVEGFR-1 ≤ 137.6 pg/mL.

Inflammation: defined as high IL-6 (>7.0 pg/mL); low IL-6 defined as IL-6 ≤ 7.0 pg/mL.

Model 1: Adjusted for age, gender and BMI.

Model 2: Adjusted for age, gender, BMI, DM, SGA and CVD.

Model 3: Adjusted for age, gender, BMI, DM, SGA, CVD and GFR.
of these drugs (data not shown) or the presence or not of clinical signs of CVD did not associate with the concentrations of VEGF and sVEGFR-1.

CKD is a condition characterized by chronic subclinical inflammation and inflammatory markers are strong predictors of mortality in CKD patients; interventions targeting inflammation have therefore been proposed [28, 29]. VEGF and sVEGFR-1 participate in the inflammatory process, e.g. by promoting inflammatory cell chemotaxis [30]. In the current study, both VEGF and sVEGFR-1 were correlated with CRP and leukocyte count, and sVEGFR-1 was also associated with IL-6. In our study, VEGF was an independent predictor of mortality after adjustments for confounders including also inflammatory biomarkers. On the other hand, whereas a high sVEGFR-1 per se was not associated with mortality, patients with a high sVEGFR-1 and concomitant elevation of IL-6 had an increased mortality risk even adjustments for confounders including demographics and comorbidities. This finding suggesting a possible synergistic effect of sVEGFR-1 and inflammation goes beyond observations in cell culture assays assessing the potential pathophysiological role of sVEGFR-1 on endothelial cell activation and showing that sVEGFR-1 sensitizes endothelial cells to proinflammatory factors [31]. However, the statistical significance of the association between a high sVEGFR-1 and mortality was lost after adjusting for GFR possibly reflecting that VEGF-1 levels correlated with GFR, which in the current study correlated with inflammation, a well-established predictor of mortality, and which, in general, is found to be an independent predictor of mortality in CKD patients [1, 32]. VEGF and sVEGFR-1 have also been shown as predictors of mortality in ischemic acute kidney injury, cancer and critical illness [33–35]. One may speculate that elevated levels of VEGF and sVEGFR-1 could increase the risk of mortality of CKD patients, as observed in the current study, by promoting increased capillary permeability, increased signaling resulting in release of cytokines and chemokines from endothelial cells, and induction of the expression of pro-coagulant factors, and by these mechanisms could lead to organ dysfunction [36, 37].

Several weaknesses of the present study should be acknowledged. First, the number of investigated incident patients starting on dialysis was rather low and patients were younger and leaner compared with the majority of CKD patients in our center. Second, as data on VEGF and sVEGFR-1 were available in less than half of the patients after 1 year, this constitutes a selective bias which limits the generalizability of the results. Finally, this is an observational hypothesis generating study, and thus neither claims to, nor is designed to prove causality. While the results of this study raise several intriguing questions regarding the impact of VEGF and sVEGFR-1 in CKD patients, further studies are clearly needed to assess the putative roles of pathways involving VEGF and sVEGFR-1 as mediators of uremic complications. In summary, this longitudinal study shows that levels of VEGF did not differ between healthy controls and CKD stage 5 patients neither prior to initiation of dialysis nor after 1 year of dialysis treatment with PD or HD. In contrast, sVEGFR-1 levels were increased in patients starting on dialysis when compared with healthy controls and this significant difference remained also after 1 year of dialysis therapy. In addition, the circulating levels of VEGF and sVEGFR-1 are associated with biomarkers of inflammation. Moreover, an increased plasma concentration of VEGF was a predictor of increased all-cause mortality, independent of biomarkers of inflammation, whereas an elevated sVEGFR-1 level not per se, but only together with concomitant inflammation, also increased the mortality risk among these incident dialysis patients.

ACKNOWLEDGEMENTS

Baxter Novum is the result of a grant from Baxter Healthcare Corporation to the Karolinska Institutet. B.L. is an employee of Baxter Healthcare Corporation. P.S. is a member of the scientific advisory board of Gambro AB. J.Y. was supported by Shanghai Education Commission. We also benefited from Karolinska Institute research funds, Swedish Heart and Lung Foundation, the Swedish Society for Medical Research, and the Swedish Medical Research Council.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

Section I. Measurement of renal function, when to refer and when to start dialysis. Nephrol Dial Transplant 2002; 17(Suppl. 7): 7–15


19. Utsal L, Tillmann V, Zilmer M et al. Elevated serum IL-6, IL-8, MCP-1, CRP, and IFN-gamma levels in 10- to 11-year-old boys with increased BMI. Horm Res Paediatr 2012; 78: 31–39


37. Wada T, Jesmin S, Gando S et al. Elevated serum IL-6, IL-8, and MCP-1, CRP, and IFN-gamma levels in 10- to 11-year-old boys with increased BMI. Horm Res Paediatr 2012; 78: 31–39


53. Utsal L, Tillmann V, Zilmer M et al. Elevated serum IL-6, IL-8, MCP-1, CRP, and IFN-gamma levels in 10- to 11-year-old boys with increased BMI. Horm Res Paediatr 2012; 78: 31–39


Received for publication: 25.1.2013; Accepted in revised form: 19.4.2013