Progenitor cells and vascular function are impaired in patients with chronic kidney disease

Kim E. Jie¹, Masha A. Zaikova¹, Marloes W.T. Bergevoet¹, Peter E. Westerweel¹, Mehdi Rastmanesh¹, Peter J. Blankestijn¹, Walther H. Boer¹, Branko Braam² and Marianne C. Verhaar¹

¹Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands and ²Department of Medicine, Division of Nephrology and Hypertension, University of Alberta, Edmonton, Canada

Correspondence and offprint requests to: Marianne C. Verhaar; E-mail: m.c.verhaar@umcutrecht.nl

Abstract

Background. Endothelial dysfunction contributes to accelerated atherosclerosis in chronic kidney disease (CKD). Bone marrow-derived endothelial progenitor cells (EPC) constitute an endogenous vascular repair system protecting against atherosclerosis. Smooth muscle progenitor cells (SPC) may stimulate atherosclerosis development. We hypothesized that an imbalance in EPC and SPC occurs in CKD, which may contribute to the increased cardiovascular disease (CVD) risk.

Methods. EPC and SPC outgrowth from mononuclear cells (MNC), EPC migratory function and circulating CD34⁺KDR⁺-EPC were measured in 49 patients with varying degrees of CKD on regular therapy and 33 healthy volunteers. Renal function, CKD cause, CVD history and endothelial dysfunction parameters were determined as factors of influence on progenitor cells.

Results. Patients had reduced EPC outgrowth compared to controls [9 (2–22) vs 12 (1–38) cells/10⁶ MNC, \( P = 0.026\)], independent of CKD cause and degree, whereas SPC outgrowth levels were higher in patients with more impaired kidney function (\( r = -0.397, P = 0.008\)). Patients had lower CD34⁺KDR⁺-EPC compared to controls [9 (0–52) vs 19 (4–110) cells/10⁵ granulocytes, \( P = 0.004\)]. CVD history and increased endothelial dysfunction markers were related to lower EPC levels. Progenitor cell outgrowth was shifted towards SPC with progression of endothelial damage. Reduction in EPC could not be attributed to decreases in progenitor cell-mobilizing factors SDF-1α and VEGF as levels increased with progressive kidney and endothelial dysfunction, while EPC remained low.

Conclusions. Our data suggest that, already in mild CKD, EPC-mediated endogenous vascular regeneration is impaired, while SPC levels increase with declining kidney function.

Keywords: cardiovascular disease; endothelial progenitor cell; smooth muscle progenitor cell

Introduction

Cardiovascular disease (CVD) is a major threat to patients with chronic kidney disease (CKD) [10]. Endothelial dysfunction and impaired endothelial regenerative capacity play a key role in the pathogenesis of CVD [9]. Bone marrow (BM)-derived endothelial progenitor cells (EPC) constitute an endogenous vascular repair system that protects against atherosclerosis development [2]. A decline in EPC availability or function may contribute to the pathogenesis of CVD [29]. The presence of cardiovascular risk factors or CVD has been related to reduced EPC levels and function in many, but not all studies [17,28,29,31]. Besides differentiation towards endothelial cell phenotype, BM-derived vascular progenitors may differentiate towards smooth muscle cells and myofibroblasts in the vessel wall, participating in atherosclerosis development [22,26]. Increased levels of these smooth muscle progenitor cells (SPC) have been observed in diabetic and in coronary artery disease (CAD) patients, which may contribute to vascular complications [20,24].

In kidney disease, vascular progenitor cell availability and function may be adversely affected by accumulation of toxins, including oxidative products [14]. Several studies demonstrated reduced EPC levels in patients on dialysis [4,7]. We reported reduced EPC but unaffected SPC outgrowth in haemodialysis patients, suggesting impaired endothelial regenerative capacity, while the capacity of progenitor cells to contribute to adverse vascular remodeling is retained [30]. Interestingly, better correction of the uremic environment increases EPC levels in end-stage kidney disease [6,11]. In kidney transplant patients, a negative relation between EPC levels and graft dysfunction was observed [11]. Information on SPC and EPC in predialysis CKD is scarce.

We hypothesized that an imbalance between EPC and SPC is present in predialysis CKD. This imbalance may result in impaired regenerative and enhanced profibrotic
tendency and contribute to the increased cardiovascular risk. We determined circulating CD34⁺KDR⁻⁻EPC and mononuclear cell (MNC) outgrowth towards EPC and SPC in patients with varying degrees and different causes of CKD. Paracrine effects of cultured EPC were tested in a scratch wound assay. We investigated whether progenitor cell number and function in CKD are related to cause and degree of kidney insufficiency and to endothelial dysfunction markers or history of CVD. Finally, we investigated whether changed levels of progenitor cell-mobilizing factors underlie altered EPC levels.

Materials and methods

Subjects

Patients with different stages of CKD, defined as kidney damage or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for ≥3 months, and no diabetes, dialysis treatment or malignancy were consecutively recruited from the nephrology outpatient clinic, University Medical Center Utrecht (UMCU), The Netherlands. Recruited patients were not allowed to have current infection. Out of 50 recruited patients, 49 were eligible for enrolment due to exclusion of one patient with increased inflammatory markers. Patients maintained their regular medication. Thirty-five age-matched healthy subjects were recruited (colleagues, family, spouse of patient), of whom 33 were eligible to serve as controls (two controls were excluded due to multivitamin use and increased inflammatory markers). The study protocol was approved by the local ethics committee and all subjects gave informed consent. Procedures were in accordance with the Helsinki Declaration.

Biochemical parameters were measured in fasting blood samples using standard procedures. Albuminuria (immunoturbidimetric assay) and albumin-to-creatinine ratio were assessed in morning urinary specimen. The MDRD formula [18] was used to calculate the eGFR.

Patients were divided into groups with an atherosclerotic or non-atherosclerotic cause of CKD as diagnosed by the patient's nephrologist. Presence of a history of CVD was defined as myocardial infarction, angina pectoris, cerebrovascular accident, transient ischaemic attack, peripheral artery disease or revascularization diagnosed in medical history.

Endothelial dysfunction

As a surrogate marker of subclinical atherosclerosis, arterial stiffness was assessed by measuring augmentation index (Aix) and pulse wave velocity (PWV) using the SphygmoCor2000 system according to the manufacturer's instructions. Three good quality data runs for each measurement were averaged.

Markers reflecting endothelial activation and/or injury [E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), thrombomodulin] were measured using commercially available ELISA (R&D Systems, Minneapolis, USA; Diaclone, Stamford, USA).

Circulating EPC

EDTA blood was collected from fasting subjects. One hundred microlitres of blood was incubated with anti-CD34-FITC, anti-CD45-PE-Cy7 (BD Pharmingen, San Diego, USA) and anti-KDR-PE (R&D Systems) antibodies. Erythrocytes were lysed and cells were analyzed by flow cytometry (Beckman Coulter, Fullerton, USA). EPC were identified as CD34⁺KDR⁻⁻cells in the lymphocyte region of the forward/sideward scatter plot and quantified relative to 10⁶ granulocytes, identified as CD45⁺-cells with a typical granulocyte distribution. Measurements were performed in duplicate and results were averaged. Isotype-stained samples served as negative controls.

Outgrowth of EPC and SPC in culture

EPC and SPC outgrowth from MNC were assessed as previously described [30]. MNC were isolated from blood samples using Ficoll density gradient separation (Histopaque 1077, Sigma, St. Louis, USA). To evaluate EPC outgrowth, 10⁶ MNC per well were seeded on a human fibronectin (Sigma)-coated six-well plate in EGM-2 (Cambrex, Walkersville, USA), supplemented with accompanying aliquots, 20% foetal calf serum (Invitrogen, Carlsbad, California), 100 ng/mL recombinant VEGF-165 (R&D Systems) and antibiotics. Medium was changed after 4 days. After 7 days, cultured EPC in selected wells were placed on serum-free medium (EBM-2 with hEGF, hydrocortisone, GA-1000, R⃦-IGF-1, ascorbic acid, heparin and antibiotics) overnight. Conditioned medium was stored for functional experiments. Cultured EPC were detached by trypsin and cell scraping and automatically counted using a haemocytometer.

For assessment of SPC outgrowth, 5 × 10⁶ MNC per well were seeded on six-well plates coated with human fibronectin and cultured in low-glucose DMEM supplemented with 20% foetal calf serum, l-glutamine (Invitrogen), 0.5 μg/mL PDGF (R&D Systems) and antibiotics. Medium was changed after 4 days. At Day 8, cultured SPC were detached by trypsin and cell scraping and automatically counted using a haemocytometer.

In vitro scratch wound assay

The potential of EPC outgrowth to excrete paracrine factors that stimulate endothelial cell migration was assessed by in vitro scratch wound assay [19]. A mechanical scratch was created with a pipette tip in a confluent monolayer of human microvascular endothelial cells (HMECs; Centers for Disease Control and Prevention, Atlanta, USA). After washing with PBS, EPC outgrowth conditioned medium was placed on the cells. Serum-free EPC medium served as negative control. Reference lines were made on the bottom of the wells to obtain exactly the same field during image acquisition. The scratched area was photographed using a light microscope at the start and after 6 h of incubation (37°C). The extent of closure after 6 h was determined relative to the starting width of the scratch (Image-Pro plus software, Media Cybernetics 3.0). Each sample was measured in two wells and two picture fields per well were examined. Results were averaged for analysis.

VEGF/SDF-1α plasma measurements

Plasma vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1α (SDF-1α) levels were measured by ELISA (R&D Systems). All samples were measured in duplicate and averaged for analysis.

Statistical analysis

Data analysis was performed using SPSS 15.0 for Windows. The Kolmogorov–Smirnov statistical test was used to explore whether data were normally distributed. Data are expressed as mean ± standard deviation for parametric data and as median (minimum–maximum) for non-parametric data. Group differences were analyzed by Student’s t-test or Mann–Whitney test. Multiple group comparisons were performed using ANOVA with LSD post hoc testing for which non-parametric data were log-transformed. Fisher's exact test was used to analyze whether proportions of categories varied by group. Correlations were measured by Pearson's or Spearman's correlation coefficient where appropriate. P-value <0.05 was considered statistically significant.

Results

Patient characteristics

Patients with different stages of CKD were included (eGFR 60–69: n = 7; eGFR 45–59: n = 13; eGFR 30–44: n = 12; eGFR 15–29: n = 7; eGFR <15: n = 10). Patient characteristics are listed in Table 1.

Vascular progenitor cell levels in CKD

EPC outgrowth was lower in CKD vs controls (Figure 1A). No difference was observed in SPC outgrowth (Figure 1B). Levels of circulating CD34⁺-haematopoietic stem
cells were not significantly different between CKD and controls [56 (11–359) vs 72 (28–162) CD34⁻/cells/10⁵ granulocytes, *P* = 0.134]. CD34⁺/KDR⁺-EPC levels were lower in CKD (Figure 1C).

Conditioned medium from CKD patients did not induce lower migration of HMECs compared to healthy controls (Figure 1D, see online supplement for colour image).

**Factors that may influence progenitor cell levels in CKD**

**Underlying cause of CKD**

EPC and SPC outgrowth numbers were not different between patients with atherosclerotic and non-atherosclerotic causes of CKD [9 (4–18) vs 8 (3–22) EPC/10⁶ MNC, *P* = 0.460 and 12 (2–35) vs 10 (2–34) SPC/10⁶ MNC, *P* = 0.247]. Circulating EPC levels were also not different between these groups [9 (0–52) vs 9 (2–47) CD34⁺/KDR⁺ cells/10⁵ granulocytes, *P* = 0.424].

**Degree of kidney dysfunction.** Reduced EPC outgrowth was already observed in mild to moderate CKD [8 (2–22) in patients with eGFR >30 mL/min/1.73 m² vs 12 (1–38) cells/10⁵ MNC in controls, *P* = 0.021]. A further decline in kidney function was not related to cultured EPC numbers (*r* = 0.133, *P* = 0.272; Figure 2A). Among CKD patients, no correlations were found for eGFR with EPC migration capacity (*r* = 0.161, *P* = 0.304) or circulating CD34⁺/KDR⁺-EPC levels (*r* = −0.138, *P* = 0.351; Figure 2B). A significant negative association was found between SPC outgrowth and eGFR (*r* = −0.397, *P* = 0.008). Plasma urea, microalbuminuria and total albumin-to-creatinine ratio were also not associated with any of the progenitor cell measures (data not shown).

**Presence of a history of cardiovascular disease.** CKD patients with a history of CVD showed lower CD34⁺/KDR⁺-cells compared to patients without [6 (0–39) vs 12 (2–52) CD34⁺/KDR⁺-cells/10⁵ granulocytes, *P* = 0.053], whereas kidney function was not different between the groups (36 ± 5 vs 38 ± 3 mL/min/m², *P* = 0.721). The difference was more pronounced in patients with eGFR <30 mL/min/1.73 m² (Figure 3).

**Endothelial dysfunction.** Aix, thrombomodulin and VCAM-1 were higher in CKD compared to controls and increased with declining eGFR (Table 2). A significant association was observed between cultured EPC and Aix (r = −0.37, *P* = 0.013). The migratory capacity of HMECs was also lower in conditioned EPC medium from patients with increased VCAM-1 (r = −0.343, *P* = 0.023) and E-selectin levels (r = −0.262, *P* = 0.075). Higher SPC outgrowth was associated with higher ICAM-1 levels in CKD (r = 0.463, *P* = 0.006).

**Medication use.** Statin and renin–angiotensin system (RAS) blocker use were associated with lower circulating EPC levels [8 (0–47) vs 15 (2–52) for statins and 7 (0–40) vs 20 (4–52) CD34⁺/KDR⁺-cells/10⁵ granulocytes for RAS blockade; *P* = 0.048 and *P* = 0.009, respectively]. No associations with progenitor cell levels were seen for treatment with erythropoietin, diuretics, beta blockade or calcium receptor blockers.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 33)</th>
<th>CKD patients (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65 (31–81)</td>
<td>62 (30–84)</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (67)</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8 (19.6–30.7)</td>
<td>24.4 (19.6–37.6)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>80 ± 10</td>
<td>37 ± 19*</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>83 (69–101)</td>
<td>157 (76–845)*</td>
</tr>
<tr>
<td>Plasma urea, mg/dL</td>
<td>36.0 (9.9)</td>
<td>61.3 (58.9)*</td>
</tr>
<tr>
<td>Plasma total cholesterol, mg/dL</td>
<td>210 ± 43</td>
<td>205 ± 48</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>14.2 ± 1.0</td>
<td>13.1 ± 1.8*</td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>14.2 ± 1.0</td>
<td>18.1 ± 1.8*</td>
</tr>
<tr>
<td>Microalbuminuria, mg/dL</td>
<td>0.6 (0.2–1.9)</td>
<td>1.8 (0.2–6.3)*</td>
</tr>
<tr>
<td>Plasma urea, mg/dL</td>
<td>0.5 (0.2–3.0)</td>
<td>5.9 (0.2–190)*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120 (102–140)</td>
<td>136 (107–197)*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 (60–85)</td>
<td>82 (68–110)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (24)</td>
<td>16 (8 (2)</td>
</tr>
<tr>
<td>Smoker</td>
<td>8 (24)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>0</td>
<td>7 (14)*</td>
</tr>
<tr>
<td>Statin</td>
<td>0</td>
<td>32 (65)*</td>
</tr>
<tr>
<td>RAS blockade</td>
<td>0</td>
<td>37 (76)*</td>
</tr>
<tr>
<td>Beta blockade</td>
<td>0</td>
<td>15 (31)*</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>0</td>
<td>8 (16)*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0</td>
<td>24 (49)*</td>
</tr>
<tr>
<td>Cause of CKD</td>
<td>0</td>
<td>14 (29)*</td>
</tr>
<tr>
<td>Cause of CKD (atherosclerotic/one-atherosclerotic/unknown)</td>
<td>–</td>
<td>24 (39)/24 (49)/4 (8)</td>
</tr>
</tbody>
</table>

Values are n (number) (%), mean ± SD or median (minimum–maximum).

*P*-value <0.05 compared to healthy controls.

Hypertension: defined by the use of antihypertensive medication, systolic or diastolic blood pressure above 140 or 90 mmHg, respectively.

Mainly long-standing hypertension, kidney artery stenosis.

Mainly glomerulonephritis, polycystic kidney disease, nephrolithiasis, lithium-induced, membranous glomerulopathy.

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VEGF and SDF-1α in CKD patients

VEGF and SDF-1α levels were increased in CKD compared to controls (125 ± 29 vs 28 ± 24 pg/mL, \( P = 0.003 \) and 3.2 ± 0.7 vs 2.6 ± 0.6 ng/mL, \( P < 0.001 \), respectively).

VEGF and SDF-1α levels were related with degree of kidney dysfunction (\( r = -0.48, P < 0.001 \) and \( r = -0.72, P < 0.001 \), respectively) and presence of endothelial dysfunction (Table 3). EPC outgrowth and migratory capacity...
were most reduced in subjects with the highest VEGF levels ($r = -0.288$, $P = 0.028$ and $r = -0.418$, $P = 0.007$, respectively).

**Discussion**

Our study shows that pre-dialysis CKD patients on regular medical therapy have lower levels of circulating EPC and reduced EPC outgrowth compared to healthy controls. This reduction in EPC did not depend on cause or degree of kidney dysfunction. SPC outgrowth gradually increased with declining kidney function in CKD. These data suggest that, in a uraemic environment, EPC-mediated endogenous vascular regeneration may be impaired, whereas SPC-mediated development of atherosclerosis may be enhanced. Reduction in EPC levels could not be attributed to reduced VEGF or SDF-1α levels.

Few studies have yet reported on EPC and SPC levels in CKD. Previous studies demonstrated reduced EPC levels and function as well as an imbalance between EPC and SPC in haemodialysis patients [4,7,30]. These data suggested an adverse effect of uraemia on vascular progenitor cells. However, dialysis sessions, in themselves, were related to reduced EPC levels, and the overall worse condition and (cardiovascular) comorbidity of dialysis patients may have influenced these results. Several studies suggested that reduction of uraemia by kidney transplantation improved EPC numbers and function [11,13]. Furthermore, EPC levels, were related to graft function by some [11,13], but not others [23]. The effects of immunosuppressive therapy and former exposure to long-term dialysis treatment complicate interpretation of these findings. Surdacki et al. [25] studied a very specific population of patients with stable angina and severe angiographic CAD with strict criteria on medication use and comorbidity. They found lower CD34$^+$KDR$^+$-EPC counts in patients with impaired kidney function within their selected population. In this study, patients in the lower eGFR groups also had more severe CAD which may have influenced the re-
Correlation values ($r$) are shown as Pearson’s or Spearman’s correlation where appropriate. $P$-value <0.05.

<table>
<thead>
<tr>
<th></th>
<th>Plasma VEGF</th>
<th>Plasma SDF-1α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aix</td>
<td>$r = 0.368$, $P = 0.025^*$</td>
<td>$r = 0.247$, $P = 0.141$</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>$r = 0.300$, $P = 0.090$</td>
<td>$r = 0.209$, $P = 0.243$</td>
</tr>
<tr>
<td>Thrombomodulin, ng/mL</td>
<td>$r = 0.412$, $P = 0.002^*$</td>
<td>$r = 0.569$, $P &lt; 0.001^*$</td>
</tr>
<tr>
<td>VCAM-1, ng/mL</td>
<td>$r = 0.353$, $P = 0.010^*$</td>
<td>$r = 0.434$, $P = 0.001^*$</td>
</tr>
<tr>
<td>ICAM-1, ng/mL</td>
<td>$r = -0.082$, $P = 0.589$</td>
<td>$r = 0.184$, $P = 0.222$</td>
</tr>
<tr>
<td>E-selectin, ng/mL</td>
<td>$r = 0.192$, $P = 0.202$</td>
<td>$r = 0.289$, $P = 0.052$</td>
</tr>
</tbody>
</table>

We did not find a relation between the underlying cause of CKD and levels of progenitor cells. Previous studies in dialysis patients [7,30] also did not detect differences in EPC level when comparing patients with diabetic and non-diabetic causes. Since atherosclerosis may underlie, but also may result from CKD, absolute separation of atheroleserotic and non-atherosclerotic CKD remains difficult. Of note, most of the non-atherosclerotic CKD patients suffered from cystic kidney disease, recurrent nephrolithiasis or lithium-induced CKD. These data suggest that the effect of other factors than CKD degree or cause is dominant in the determination of EPC recruitment, mobilization and function.

Several studies have shown that the presence of cardiovascular risk factors or CVD is an important determinant of reduced EPC levels [28,29]. However, others did not observe such inverse relations or even reported a positive relation between EPC number and vascular risk factors [17,31], which could reflect a protective compensatory response to the vascular risk burden. We found that CKD patients with a history of CVD had reduced CD34$^+$KDR$^+$-EPC numbers compared to patients without such history. This is in line with previously reported associations between EPC levels and history of CVD in patients on peritoneal dialysis [23]. Furthermore, EPC outgrowth and function were negatively associated with endothelial dysfunction parameters in our subjects and increased levels of outgrowth SPC were found in patients with higher endothelial dysfunction markers. The combination of endothelial dysfunction with lack of a compensatory response but even reduced EPC levels, reflecting impaired endothelial repair, and enhanced numbers of SPC may accelerate atherosclerosis in CKD. Our population consisted of patients under current treatment regimen with minimal exclusion criteria, thus representing the CKD population, but heterogeneous in its composition, comorbidity, medication and other influencing factors. An important limitation of our study is that influences of reduced eGFR, (cardiovascular) comorbidity and medication on EPC and SPC cannot be fully separated from each other. However, cardiovascular risk factors can be the cause and result of renal insufficiency, which complicates such discerning analyses. In addition, cardiovascular risk indicators may manifest differently in CKD patients and may not correlate with CVD events as in subjects without CKD [15].

The cross-sectional nature of our study does not allow definitive conclusions on the mechanism underlying diminished EPC levels in CKD. We investigated whether a defect of EPC-mobilizing factors in response to endothelial injury could explain the reduced EPC levels in CKD. We found that, with progression of CKD and endothelial dysfunction, important stimuli SDF-1α and VEGF gradually suppress EPC numbers. This suggests that a decrease in EPC-driven angiogenesis might be at the basis of the observed reduction in EPC number in CKD. The fact that we did not observe a relation between EPC numbers and VEGF in CKD patients may be explained by the presence of concomitant inflammation. Inflammatory cytokines and stress-related hormones, which could be present in CKD, would interfere with the VEGF/EPC axis and might have counteracted the mobilization of EPC from bone marrow. Furthermore, we found a relation between the underlying cause of CKD and EPC levels. This might explain the observed variation in EPC levels between different types of CKD. Finally, we demonstrated that EPC levels are reduced in CKD patients compared to healthy controls. This suggests that EPC reduction is an early event in CKD progression. Therefore, our study supports the hypothesis that EPC reduction is an early event in CKD progression.
increased, while EPC levels remained low. Moreover, EPC outgrowth was most reduced in subjects with highest VEGF levels. Low circulating EPC pools could result from increased homing of EPC to injured tissue mediated by SDF-1α and VEGF [31]. SDF-1α and VEGF may be accumulated due to reduced renal clearance, which may result in continuous stimuli and eventually resistance of EPC. Alternatively, there could be a common underlying mechanism for endothelial dysfunction and impaired EPC mobilization. Impaired nitric oxide (NO) availability [5] in CKD may underlie endothelial dysfunction and impaired EPC mobilization despite the upregulation of SDF-1α and VEGF, as both processes are NO-dependent [1]. Increased SDF-1α levels together with endothelial NO synthase deficiency can also result in enhanced SPC levels [32], thereby contributing to neointimal lesion formation.

We used eGFR calculated by the MDRD equation to correlate the degree of uraemia to EPC levels. The eGFR represents the collection of a whole variety of accumulated uraemic toxins. Whereas a decrease in eGFR is associated with an increased risk for cardiovascular events [12], it is not known which uraemic toxin importantly influences EPC availability and function. Plasma urea concentration, microalbuminuria and total albumin-to-creatinine ratio as other markers for kidney function were also not associated with EPC levels in our study. More insight in toxic substances influencing EPC in CKD may provide a more specific uraemic marker set to correlate with EPC levels to monitor and predict CVD risk.

Conclusion

In conclusion, CKD patients on regular medication have lower circulating EPC levels and reduced EPC outgrowth already in mild CKD, whereas outgrowth towards SPC is increased with decline in kidney function. Moreover, lower EPC numbers were found in patients with a history of CVD and endothelial dysfunction. EPC reduction could not be attributed to impaired SDF-1α and VEGF levels.

Acknowledgements. We thank Judith Wierdsma and Dafna Groeneveld, Department of Nephrology, UMCU, The Netherlands, for the excellent technical assistance. This study was financially supported by the Dutch Kidney Foundation grant C04.2093. M.C.V. is supported by The Netherlands Organisation for Scientific Research (NWO) Vidi-grant 016.096.359. K.E.J. is supported by the Dutch Heart Foundation (NHS) grant 2005B192 and by UMCU (MD/PhD fellowship). M.R. is supported by the Dutch Kidney Foundation (NSN grant C03-2062).

Conflict of interest statement. None declared.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

References


The prevalence and prognostic implications of polyvascular atherosclerotic disease in patients with chronic kidney disease

Jan-Peter van Kuijk1, Willem-Jan Flu1, Michel Chonchol2, Gijs M.J.M. Welten1, Hence J.M. Verhagen1, Jeroen J. Bax3 and Don Poldermans1

1Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands, 2Division of Renal Diseases and Hypertension, University of Colorado Denver Health Sciences Center, Aurora, CO, USA and 3Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence and offprint requests to: Don Poldermans; E-mail: d.poldermans@erasmusmc.nl

Abstract

Background. Atherosclerotic disease is often extended to multiple affected vascular beds (AVB). Polyvascular disease (PVD) and chronic kidney disease (CKD) have both separately been associated with an adverse cardiovascular outcome. We assessed the prevalence of PVD in vascular surgery patients with preoperative CKD and studied the influence on long-term cardiovascular survival.

Methods. Consecutive patients (2933) were preoperatively screened for PVD, defined as 1-, 2- or 3-AVB. Preoperative glomerular filtration rate (GFR in ml/min/1.73 m² body-surface area) was estimated by the Modification of Diet in Renal Disease (MDRD) prediction equation, and patients were categorized according their estimated GFR. Primary end point was (cardiovascular) mortality during a median follow-up of 6.0 years (IQR 2–9).

Results. Preoperative MDRD-GFR was classified as normal kidney function (GFR ≥ 90) or mild (GFR 60–89), moderate (GFR 30–59) and severe (GFR < 30) kidney disease in 779 (27%), 1423 (48%), 605 (21%) and 124 (4%) patients, respectively. One-vessel disease was present in 54% of the patients with normal kidney function, while 62% of the patients with CKD (GFR < 60) had PVD. In patients with moderate or severe kidney disease, the presence of PVD was independently associated with even higher cardiovascular mortality rates (2-AVB: HR 1.65 95%CI 1.09–2.48; 3-AVB: 2.07 95%CI 1.08–3.99), compared to 1-AVB.

Conclusion. Patients with CKD had a high prevalence of PVD, which was independently associated with increased all-cause and cardiovascular mortality.

Keywords: chronic kidney disease; polyvascular disease; prevalence; prognosis

Introduction

With aging of the population, the prevalence of atherosclerotic disease and its associated adverse outcomes is increasing. It has to be noted that the process of established atherothrombosis is not limited to a single arterial location. The Reduction of Atherothrombosis for Continued Health (REACH) registry showed that one out of six patients with peripheral arterial disease (PAD), cerebro-