ORIGINAL ARTICLE

Endostatin and vascular endothelial growth factor: potential regulators of endothelial progenitor cell number in chronic kidney disease

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KEY WORDS

cardiovascular risk, chronic kidney disease, endostatin, endothelial progenitor cells, VEGF

ABSTRACT

INTRODUCTION Cardiovascular mortality is significantly increased in patients with chronic kidney disease (CKD). The number of circulating endothelial progenitor cells (EPCs) may affect vascular regenerative potential and thus influence cardiovascular mortality.

OBJECTIVES The aim of the study was to assess the number of circulating EPCs and the factors that potentially affect these cells, including vascular endothelial growth factor (VEGF) and endostatin, in patients with CKD.

PATIENTS AND METHODS The study involved 139 patients divided into groups depending on the severity of renal impairment: 67 predialysis patients with CKD, 46 patients on hemodialysis (HD), and 26 patients on peritoneal dialysis (PD). Plasma levels of VEGF and endostatin were measured by enzyme-linked immunosorbent assays. The number of circulating EPCs, defined as CD34+VEGFR2+, was assessed in the whole blood using flow cytometry.

RESULTS There was a positive correlation between VEGF and CD34+VEGFR2+ and the glomerular filtration rate. Endostatin levels increased with renal impairment. The highest endostatin levels were observed in HD and PD patients. The number of EPCs was significantly lower in predialysis patients with CKD and in HD patients, while in PD patients it was nonsignificantly lower compared with the control group.

CONCLUSIONS In patients with CKD, a decrease in circulating EPCs may impair vascular regenerative potential and thus contribute to a higher cardiovascular risk. The effect of significantly increased endostatin levels on the endothelial function and progenitors in patients with CKD requires further investigation.

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INTRODUCTION The discovery of circulating endothelial progenitor cells (EPCs) by Asahara[1,2] and further data suggesting their participation in postnatal vasculogenesis provide evidence for vascular regeneration. The phenomenon may play a role in a physiological response to vascular injury, which led to the development of revascularization therapies for ischemic limbs and myocardium.[3-5] Hill et al.[6] observed that a decreased number of circulating EPCs is an independent cardiovascular risk factor in patients without cardiovascular diseases.[6] In patients with chronic cardiovascular diseases, the number of EPCs is decreased and has a negative prognostic value.[7,8] Acute cardiovascular events are followed by a transient increase in EPCs, occurring after an increase in the plasma levels of the vascular endothelial growth factor (VEGF).[9,10] These findings confirm that EPCs take part in vascular endothelial regeneration and allow us to a+ssume that progression of chronic cardiovascular diseases may result from insufficient delivery or decreased production of EPCs.

Cardiovascular mortality is significantly higher in patients with chronic kidney disease (CKD) and increases with the progression of renal disease. Conventional factors and those associated with CKD mediate vascular injury.[11-15] Evidence is accumulating that vascular regeneration in patients with CKD is impaired not only as a result

TABLE 1 Characteristics of the study groups

Characteristics	CKD	HD	PD	C	*P*
n	67	46	26	46	–
men/women	27/40	21/25	9/17	19/27	NS
age, y	65.5 ±12.6	59 ±13.5	58 ±16	40.4 ±13	<0.01[a]
hypertension, n (%)	61 (91)	34 (74)	25 (96)	0	<0.05[b]
diabetes, n (%)	18 (27)	10 (22)	8 (31)	0	NS[c]
MDRD, ml/min	22	6.6	9.1	94.3	<0.01
CRP, mg/l	5.0	5.5	5.5	4.0	NS
total cholesterol, mmol/l	5.3	4.6	5.6	4.5	<0.05[d]
hemoglobin, g/dl	11.6	10.9	11.4	14.2	NS

a no difference between HD and PD
b no difference between CKD and PD
c no difference between CKD, HD, PD
d no difference between CKD and PD, HD, and control

Data are presented as mean ± SD

Abbreviations: C – control, CKD – chronic kidney disease, CRP – C-reactive protein, HD – hemodialysis, MDRD – Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate, NS – nonsignificant, PD – peritoneal dialysis, SD – standard deviation

of decreased number of circulating EPCs,[16-19] but also because of their function in the uremic milieu is impaired.[17,20] VEGF mobilizes endothelial precursors from the bone marrow and induces their differentiation into mature endothelial cells. VEGF, a 35kDa molecule, is a chemoattractant that enables the homing of regenerative endothelial cells into local vascular lesions.[21,22] Endostatin, a 20 kDa molecule, inhibits VEGF-dependent endothelial cell migration through decreased nitric oxide synthesis[23] and induces apoptosis of endothelial cells.[24] The key role of impaired vasculogenesis for the progression of CKD was demonstrated in animal models and human studies, in which a prominent reduction in peritubular capillary density has been observed.[25,26] In the aging kidneys, loss of VEGF expression in podocytes was associated with the reduced number of EPCs.[27] Therefore, the aim of the present study was to determine the effect of plasma endostatin and VEGF levels on the number of circulating EPCs in patients with chronic nephropathy with a varying degree of glomerular filtration rate (GFR) impairment.

PATIENTS AND METHODS

The study involved 139 patients (82 women, 57 men) aged 56.7 ±16.5 years, divided according to the stage of chronic nephropathy and dialysis modality into 3 groups: 67 predialysis patients (36%) with CKD, 46 patients (25%) on hemodialysis (HD; time on dialysis from 6 months to 18 years, mean 7.3 years), and 26 patients (14%) on peritoneal dialysis (PD). Characteristics of the study groups are presented in TABLE 1. Chronic nephropathy was caused by chronic glomerulonephritis in 39 patients (21.1%), ischemic nephropathy in 31 (16.8%), diabetic nephropathy in 25 (12.5%), polycystic kidney disease in 15 (8.1%), and interstitial nephropathy in 13 (7%). Other causes were observed in 5 patients (2.7%), and the cause was unknown in 11 patients (5.9%). Statins were administered in 34 patients from the study group. No statins were administered in the control group. Among patients with impaired kidney function (either from the CKD, HD, or PD group) 120 (65%) had arterial hypertension. They required from 1 to 6 antihypertensive drugs. No patient from the control group used antihypertensive drugs. The exclusion criteria, potentially affecting the number of EPCs, were as follows: acute coronary episode in the previous 12 months, blood transfusion in the previous 6 months, history of malignancy, hormone therapy, acute inflammation, and smoking. All patients were treated in the Dialysis Unit and Outpatient Nephrology Clinic of the Department of Nephrology and Transplantation Medicine at the Wroclaw Medical University, Wrocław, Poland. The control group consisted of 46 healthy volunteers recruited from the staff (19 men and 27 women, aged 40.4 ±13 years). Informed consent was obtained for the collection of clinical data and blood samples. The study was approved by the Bioethical Committee of the Wroclaw Medical University.

EPCs were assessed in peripheral blood by means of flow cytometry. Blood samples were drawn at routine control, or 4 hours before routine dialysis session in HD patients using polysulfone dialyzer. Samples of 0.5 ml of venous blood were suspended in RPMI 1660 medium with the addition of 20% DMSO and 10% FCS and stored in liquid nitrogen until the assay. Comparison of the assay results performed from fresh blood samples did not show a remarkable cell loss attributable to the sample storage. To estimate the number of EPCs, the samples were washed twice in phosphate buffered saline with 2 mM EDTA and centrifuged for 10 minutes at 400 × g in 20°C. Then the samples were incubated for 30 minutes at 4°C with fluorescent-labeled antibodies against surface cell antigens. EPCs were

TABLE 2 Mean values of circulating endothelial progenitor cells in the study groups

Group	Mean CD34+VEGFR2+ (cells/ml)	SD	*P*
C	430	425.15	
CKD	325	224.3	0.03
HD	269	278.5	0.02
PD	334	360.1	0.19

Abbreviations: see TABLE 1

identified by anti-CD34 antibody labeled with peridinin chlorophyll protein complex – PerCP (BD Biosciences, San Jose, California, United States) and anti-VEGFR2 antibody labeled with phycoerythrin – PE (R&D Systems, Minneapolis, United States). Fluorescent microbeads (1000/µl) Cyto Count (Dako Cytomation, Denmark) were added to calculate the number of EPCs. Cell populations were assessed from lymphocyte gate by means of FACSCalibur (BD Biosciences) with the acquisition of 1×10^5 cells from the sample.

Endostatin and VEGF levels were measured in plasma by means of colorimetric ELISA kits (Quantikine, R&D Systems, Minneapolis, United States). Absorption was read at the wavelength of 450 nm by BioTek (Vermont, United States).

The GFR was calculated from the shortened Modification of Diet in Renal Disease (MDRD) formula: GFR (ml/min/1.73 $m^{2)}$ = 186 × (plasma creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 for women).

Statistical analysis was performed using the statistical package R (version 2.6.2).[28] The Gaussian distribution of data was tested using the Lilliefors normality test. The analysis of variance was used to compare demographic variables of the groups. The Kruskal-Wallis test was used to compare other variables between the study groups. The Pearson's correlation and Spearman's rank correlation were used to examine the associations between variables. *P* value <0.05 was considered statistically significant.

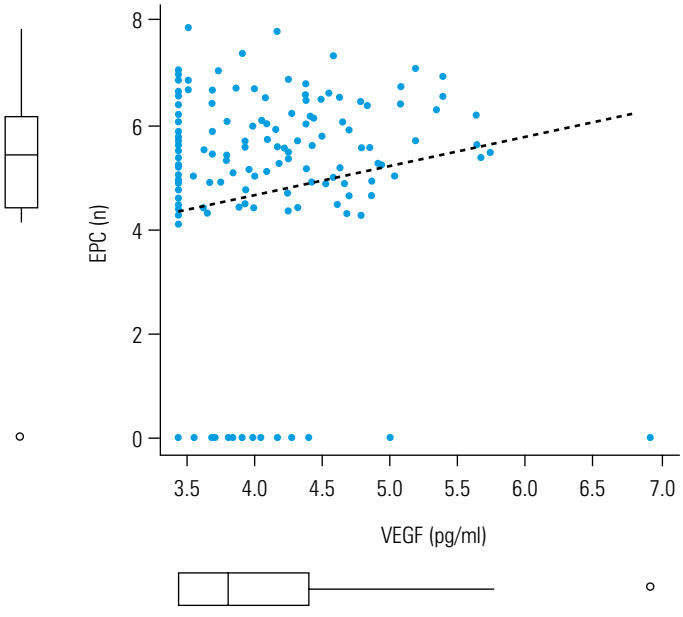

FIGURE 1 Number of circulating EPCs correlates with plasma VEGF levels (*P* = 0.035, r = 0.15)

Abbreviations: EPC – endothelial progenitor cell, VEGF – vascular endothelial growth factor

RESULTS The population of EPCs, CD34+ VEGFR2+ cells, was significantly decreased in CKD and HD patients (*P* = 0.03 and *P* = 0.02, respectively). In PD patients, the number of CD34+VEGFR2+ cells was insignificantly lower than in the control group (*P* = 0.19). The mean values of circulating EPCs in the study groups are presented in TABLE 2. The number of EPCs was not affected either by sex or age. Although the control group was younger than the study group, no effect of age on the number of EPCs was observed. There was no correlation between the number of EPCs and the hemoglobin level, C-reactive protein, albumins, high-density lipoprotein cholesterol, triglycerides, calcium-phosphate product, parathormone, statin administration, or the number of antihypertensive drugs administered to patients. Diabetes was present in 36 patients (19%). The prevalence of diabetes was the same in CKD, PD, and HD patients. Diabetes caused chronic nephropathy in 25 patients and only in these patients the number of EPCs was significantly decreased (*P* = 0.03). Other conditions that caused CKD did not affect the number of EPCs. Endostatin and VEGF levels were not different between diabetic and nondiabetic patients.

Plasma VEGF levels correlated with the number of CD34+VEGFR2+ cells, (r = 0.15, *P* = 0.035; FIGURE 1). Plasma VEGF levels were affected by renal function. A significant positive correlation was found between VEGF and GFR assessed by the MDRD formula r = 0.3 *P* <0.001 and negative correlation between VEGF and serum creatinine (r = – 0.3, *P* <0.001; FIGURE 2). VEGF levels were significantly lower in the HD group (42.87 pg/ml; *P* <0.001) and insignificantly higher in the PD group (87.87 pg/ml; *P* = 0.11). Moreover, VEGF levels were significantly higher in CKD patients compared with the control group (91.47 pg/ml vs. 57.1 pg/ml; *P* = 0.02). No correlation was found between plasma endostatin levels and EPC number. A strong positive correlation was observed between endostatin levels and serum creatinine (r = 0.59, *P* <0.01). GFR assessed by the MDRD formula showed a strong negative correlation with endostatin (r = –0.5, *P* <0.01; FIGURE 3). Endostatin levels were increasing with impaired renal function. Significant increments of endostatin levels were present between CKD and control (*P* <0.001) and between CKD and end-stage renal disease (HD and PD groups) (*P* <0.01; FIGURE 4). The modality of renal replacement therapy did not affect endostatin levels. The mean values of plasma endostatin levels were as follows: 110.9 ng/ml in the control group, 508.9 ng/ml in CKD, 624.3 ng/ml in HD, and 723 ng/ml in PD.

No correlation was found between weekly erythropoietin dose and the number of EPCs.

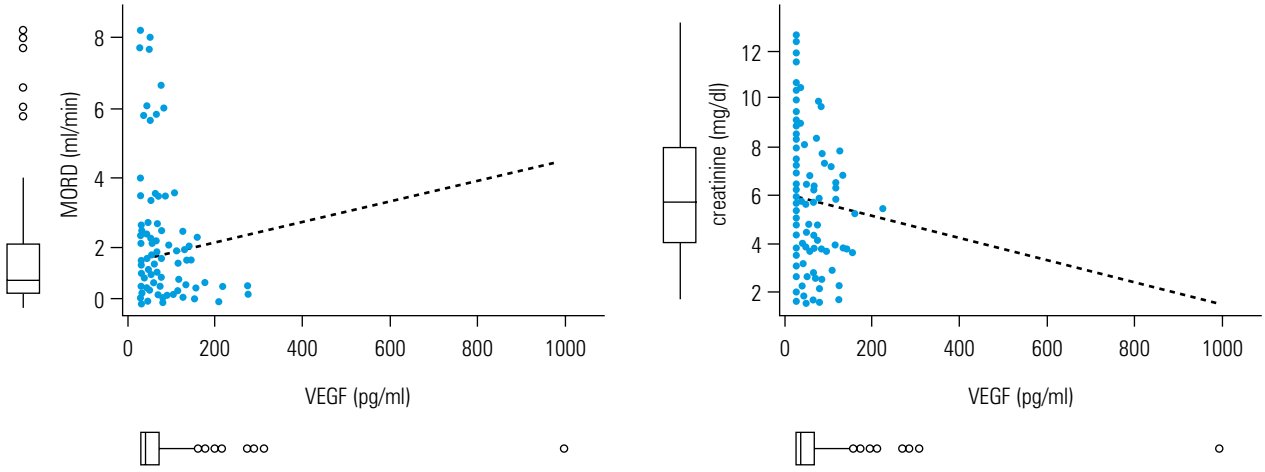

FIGURE 2 Plasma VEGF levels correlate with renal function (P <0.001)
Abbreviations: see TABLE 1 and FIGURE 1

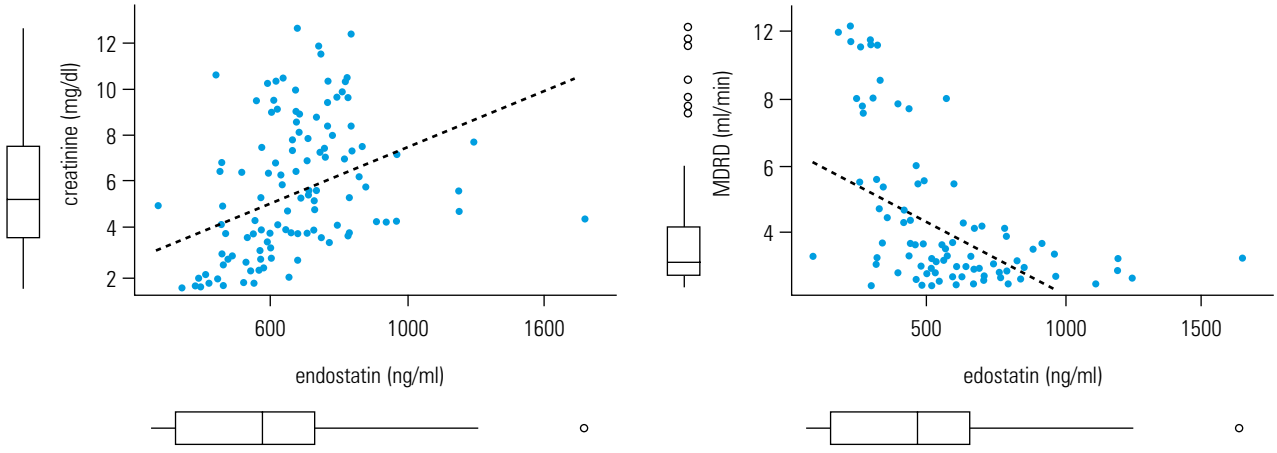

FIGURE 3 Plasma endostatin levels increase with renal impairment (P <0.01)
Abbreviations: see TABLE 1

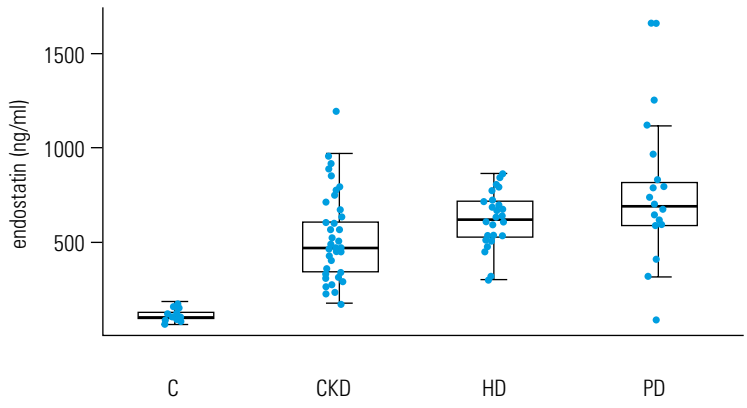

FIGURE 4 Plasma endostatin levels in the study groups
Abbreviations: see TABLE 1

In the CKD group, erythropoietin was administered in 3 patients (4%), in the PD group in 9 (35%), and in the HD group in 45 (98%). All study groups had the same serum hemoglobin levels, but the mean weekly erythropoietin doses to achieve these levels were the lowest in the CKD group, significantly higher in the PD group, and the highest in the HD group (2400 ±1100, 3100 ±1000, and 5300 ±2600 units per week, respectively). Patients with the lowest erythropoietin dose showed higher plasma VEGF levels (r = –0.3, P <0.001). VEGF levels were positively correlated with serum hemoglobin (r = 0.3, P <0.01). In contrast, plasma endostatin levels were positively correlated with erythropoietin dose (r = 0.5, P <0.01), and a significant negative correlation was observed between endostatin and hemoglobin levels (r = –0.4, P <0.01; FIGURE 5).

DISCUSSION Our results are in line with a number of other reports that demonstrated a decrease in EPC number in patients with chronic nephropathy.[16-18] In our study, the decrease was significant in predialysis patients with CKD and in patients on HD. It was not statistically significant in patients on PD, probably because the number of individuals was smaller. Another limitation of the study was that flow cytometry was the only method used to determine circulating EPCs. Flow cytometry is less elaborate than the cell culture, but it is closer to the "bedside". It is less accurate, which results from a low number of circulating EPCs, and there has been an ongoing debate on the best panel of surface

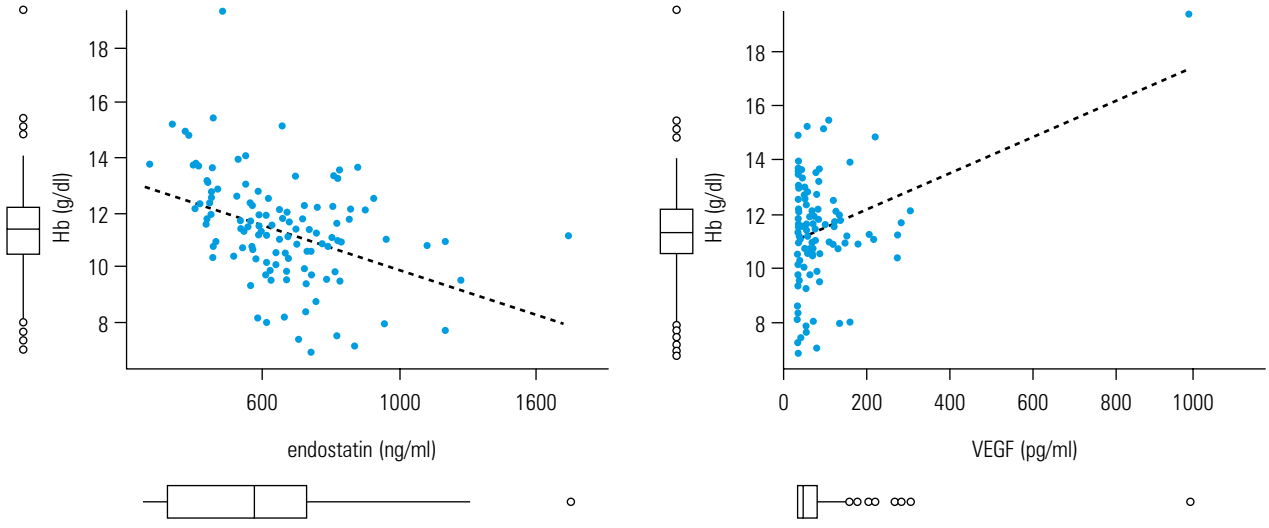

FIGURE 5 Plasma hemoglobin levels in patients with chronic nephropathies correlate positively with plasma VEGF and negatively with plasma endostatin levels ($P < 0.01$) Abbreviations: Hb – hemoglobin, others – see **FIGURE 1**

markers that most adequately define the above cell population.

Despite differences in the mean age between the control and the study group, no effect of age on the number of circulating EPCs was observed, which is in line with the results of Shaffer et al.[29] In their study, age was shown to exert qualitative rather than quantitative effect on EPCs.[30]

To our knowledge, our study is one of the few to report a significant elevation of plasma endostatin levels in patients with chronic nephropathy. Futrakul et al.[31] previously described elevated endostatin levels in the group of CKD patients with moderate GFR impairment. In turn, Rydzewska et al.[32] observed "extremely high" endostatin levels that were not affected by the scheme of anticoagulation used for HD.[32] We have shown for the first time that an increase in endostatin levels is linearly correlated with GFR decline. Dialysis modality did not affect plasma endostatin levels – they were the same in PD and HD patients.

In our study, VEGF was positively correlated with the GFR. Accordingly, VEGF levels were decreased in HD group, showed no difference in PD patients, and were significantly higher in CKD patients. There are scarce and confusing data on plasma VEGF levels in patients with chronic nephropathy. A number of authors observed no difference in VEGF levels between HD patients and controls.[18,20] In one report, a significant increase in plasma VEGF levels in predialysis patients was noted and was associated with tissue hypoxia and acidosis.[33] Futrakul et al.[31] observed decreased VEGF levels in CKD patients.[31]

Our study showed that in CKD the balance is shifted toward the inhibition of vasculogenesis, which is in line with other studies.[25,26] Under conditions of decreased nitric oxide availability, as in uremia, endothelial mRNA for endostatin is significantly upregulated, which inhibits vasculogenesis and promotes endothelial–mesenchymal transformation.[34] Reduced regenerative potential of renal microvasculature associated with scarring leads to sustained ischemia, which subsequently enhances CKD progression.

The analysis of associations between endostatin and VEGF levels and the number of circulating EPCs provided surprising results. We observed a positive correlation between VEGF levels and the number of CD34+VEGFR2+ cells, but there was no consistent relationship between a significant increase in inhibitory endostatin levels and a decrease in the number of circulating EPCs in patients with chronic nephropathy. This lack of direct correlations between the level of endostatin and the number and function of EPCs suggests that there is a more complex regulation of vascular regeneration in patients with chronic nephropathy.

Anemia is associated with increased cardiovascular mortality in CKD patients.[35] Erythropoietin has been shown to inhibit apoptosis of endothelial cells in an in vitro model,[36] to increase ischemia-induced neovascularization in an in vivo model,[37] and to increase the number of circulating EPCs both in animal models and in human studies.[37,38] Despite a positive effect of erythropoietin on EPCs demonstrated in previous studies, we did not observe any associations between the number of circulating EPCs and erythropoietin administration. Kohagura et al.[39] reported a negative correlation between the number of circulating CD34 cells and a dose of recombinant human erythropoietin in maintenance HD patients, which led to the conclusion that hyporesponsiveness to erythropoietin may result in a decrease in circulating EPCs and increased cardiovascular risk.[39] Because both hematopoietic and endothelial precursors originate from the bone marrow, the factors that influence vasculogenesis may also affect erythropoiesis. In the current study, the hemoglobin level was positively correlated with VEGF and negatively affected by endostatin. Increased demand for erythropoietin was associated with increased endostatin and decreased VEGF levels. Therefore, increased endostatin levels in patients with chronic nephropathies seem to affect various aspects of cardiovascular risk.

To summarize, we observed a linear increase in endostatin, which strictly correlated with GRF

decline. Moreover, we observed that plasma VEGF levels correlated with the number of circulating EPCs in patients with chronic nephropathy. Finally, we observed no significant correlation between endostatin levels and a decrease in the number of EPCs, suggesting that there are some other factors at work, which requires additional research.

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ARTYKUŁ ORYGINALNY

Endostatyna i czynnik wzrostu śródbłonka naczyniowego – potencjalne regulatory liczby krążących komórek progenitorowych śródbłonka w przewlekłej chorobie nerek

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SŁOWA KLUCZOWE

endostatyna, komórki progenitorowe śródbłonka, przewlekła choroba nerek, ryzyko sercowo-naczyniowe, VEGF

STRESZCZENIE

WPROWADZENIE Śmiertelność z powodu chorób sercowo-naczyniowych u chorych na przewlekłą chorobę nerek (PChN) jest istotnie zwiększona. Liczba krążących komórek progenitorowych śródbłonka może wpływać na możliwości regeneracyjne naczyń, a tym samym na ryzyko sercowo-naczyniowe.

CELE Celem pracy było oznaczenie liczby krążących komórek progenitorowych śródbłonka oraz czynników o potencjalnym wpływie na te komórki, takich jak czynnik wzrostu śródbłonka naczyniowego (*vascular endothelial growth factor* – VEGF) oraz endostatyna, w grupie chorych na PChN.

PACJENCI I METODY Badaniem objęto 139 chorych podzielonych w zależności od stopnia upośledzenia czynności nerek na grupę 67 chorych z PChN w okresie przeddializacyjnym, 46 hemodializowanych oraz 26 chorych dializowanych otrzewnowo. Osoczowe stężenie VEGF i endostatyny oznaczono metodą immunoenzymatyczną. Liczbę krążących komórek progenitorowych śródbłonka określonych jako CD34+VEGFR2+ oznaczono we krwi pełnej przy użyciu cytometrii przepływowej.

WYNIKI Stwierdzono dodatnią korelację między stężeniem VEGF a liczbą krążących komórek progenitorowych śródbłonka oraz filtracją kłębuszkową. Stężenie endostatyny zwiększało się istotnie wraz z upośledzeniem czynności nerek. Największe stężenia endostatyny odnotowano w grupie chorych hemodializowanych i dializowanych otrzewnowo. Liczba krążących komórek progenitorowych śródbłonka była mniejsza u chorych na PChN w okresie przeddializacyjnym oraz u chorych hemodializowanych, podczas gdy u chorych dializowanych otrzewnowo odnotowano nieznamiennie mniejszą liczbę krążących komórek progenitorowych śródbłonka w porównaniu z grupą kontrolną.

WNIOSKI U chorych na PChN zmniejszenie się liczby krążących komórek progenitorowych śródbłonka może się przyczynić do upośledzenia możliwości regeneracyjnych śródbłonka, zwiększając tym samym ryzyko sercowo-naczyniowe. Wpływ istotnie zwiększonego stężenia endostatyny na śródbłonek naczyniowy i na jego prekursory u chorych na PChN wymaga dalszych badań.

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