Vascular endothelial growth factor and soluble vascular endothelial growth factor receptor-1 in patients with end-stage renal disease

Associations with laboratory findings, comorbidities, and medications

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ABSTRACT

الأهداف: إظهار مستويات sVEGFR-1، VEGF في المرضى الذين يعانون من الداء الكلوي بمراحله الأخيرة (ESRD) و إظهار العلاقات مع النتائج السريرية مثل السمات الديموغرافية، والنتائج المخبرية، والأمراض المصاحبة، والأدوية.

الطريقة: اشتملت الدراسة على مجموعه 73 شخصاً، تتكون من المرضى الذين يعانون من الداء الكلوي بمراحله الأخيرة (n=38) والأصحاء (n=35) في مستشفى غولهان للتعليم والبحوث، أنقرة، تركيا ، في هذه الدراسة المستعرضة خلال السنوات 2011م و 2013م تم الحصول على عينات الدم وتم إجراء تحليل البلازما ، VEGF sVEGFR-1.

النتائج: لم يكن مستوى VEGF لمجموعة ESRD أعلى (0.280±0.264) بشكل إحصائي من مجموعة التحكم (0.321±0.210)؛ p=0.475. كان مستوى sVEGFR-1 من المجموعة ESRD أعلى (0.217±0.135) بكثير من مجموعة التحكم (0.068±0.047)؛ (p<0.001). كان الارتباط بين VEGF و sVEGFR-1 معنوياً وسلبياً (p=0.036، r=-0.246). كان متوسط مستوى VEGF لمرضى الداء الكلوي بمراحله الأخيرة باستخدام الإريثروبويتين البشري المؤتلف (rhEPO) أعلى (0.567±0.28) بكثير من مرضى الداء الكلوي بمراحله الأخيرة الذين لا يستخدمون rhEPO 0.246±0.24)؛ (p=0.025).

الخاتمة: دراستنا هي الأولى التي تبين أهمية sVEGFR-1 في مرضى الداء الكلوي بمراحله الأخيرة ، والعلاقة مع الأمراض المصاحبة، والأدوية. خاصة أن اكتشافنا لـ rhEPO و VEGF قد ينير تأثيراً إيجابياً معقولاً لـrhEPO على تولد الأوعية. قد تكون sVEGFR-1 و VEGF علامات مهمة في الفيزيولوجيا المرضية للـ ESRD.

Objectives: To show the levels of vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) in patients with end-stage renal disease (ESRD) and to show the associations with clinical findings such as demographic features, laboratory findings, comorbidities, and medications.

Methods: A total of 73 people, consisting of patients with ESRD (n=38) and healthy subjects (n=35) in Gulhane Education and Research Hospital, Ankara, Turkey, were included in this cross-sectional study between the years 2011 and 2013. Blood samples were obtained and plasma VEGF, sVEGFR-1 analyzes were performed.

Results: The VEGF level of ESRD group was not significantly higher (0.280±0.264) than the control group (0.321±0.210) (p=0.475). The sVEGFR-1 level of ESRD group was significantly higher (0.217±0.135) than the control group (0.068±0.047) (p<0.001). The correlation between VEGF and sVEGFR-1 was significant and negative (r=-0.246, p=0.036). Average VEGF level of ESRD patients using recombinant human erythropoietin (rhEPO) was significantly higher (0.567±0.28) than the ESRD patients not using rhEPO (0.246±0.24) (p=0.025).

Conclusion: Our study is the first showing the significance of sVEGFR-1 in ESRD patients, and associations with comorbidities, medications. Especially our finding of rhEPO and VEGF may illuminate a reasonable positive effect of rhEPO on angiogenesis. Soluble vascular endothelial growth factor receptor-1 and VEGF may be important markers in the pathophysiology of ESRD.

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The term "end-stage renal disease" (ESRD) usually refers to chronic kidney disease (CKD) treated with either dialysis or transplantation. For the exact definition of ESRD, the estimated glomerular filtration rate (eGFR) is <15 mL/minute/1.73 m^2.[1-3] Vascular endothelial growth factor (VEGF) is a prominent growth factor that is responsible for the angiogenic process in the kidneys.[4-6] The VEGF was formerly thought to be an angiogenic molecule that both supported blood vessel dilation and provided new blood vessel formation. The majority of VEGF receptors are VEGF receptor-1 (VEGFR-1) and VEGFR-2, which are transmembrane proteins. Soluble vascular endothelial growth factor receptor-1 is mainly found on endothelial cells and monocytes. Soluble vascular endothelial growth factor receptor-1-mediated signaling is an important action, as it increases vascular permeability.[7,8] In pathological conditions like ESRD, extreme VEGF production may cause new vessel formation; this condition may destroy the tissue and organ structure. Soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) is produced by alternative splicing of VEGFR-1 mRNA. It acts as a decoy peptide, and it is likely that it negatively regulates VEGF. Its levels correlate with prognosis; it is a severe sign of disease intensity in the intensive care unit (ICU) patients.[9,10] Sufficient release of VEGFR-1 can be crucial in preventing exaggerated angiogenesis, and it contributes to the remodeling process of ESRD.

However, studies reporting the association among circulating VEVGF, sVEGFR-1 levels and clinical information of patients with ESRD are very limited. In this study, we hypothesized that circulating sVEGFR-1 and VEGF would be clinically important in hemodialysis (HD) patients. We tested this hypothesis in 38 HD patients by evaluating their clinical features such as the medications they used and their comorbidities.

Methods. A total of 73 participants, including patients with ESRD (n=38) and healthy subjects (n=35), attending Gulhane Education and Research Hospital, Ankara, Turkey were included in this comparative cross-sectional study between 2011 and 2013.

All of the participants gave their informed consent. The local ethics committee of Gulhane Education and Research Hospital approved this study protocol. All of the procedures that we followed were in accordance with the ethical standards of the respective committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Every members of the ESRD group and control group were older than 18. All of the patients underwent HD 3 times per week (3-5 hours per session) using bicarbonate dialysate and high-flux (22%) or low-flux (72%) dialysis membranes. Any patients with infections, acute or chronic inflammatory disease, cerebrovascular occlusion, high sedimentation rate, or C-reactive protein with malignancy were excluded from the study. Serum VEGF and sVEGFR-1 levels were measured using Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA) and a Synergy HT plate reader (Bio-Tek Instruments Inc, Winooski, VT, USA). All of the patients' clinical features, medical history, medication regimens, and laboratory results were recorded and compared.

The Statistical Package for the Social Sciences for Windows, Version 16.0 (Chicago, SPSS Inc.) was used for the data analysis. For the descriptive statistics, discontinuous variables were demonstrated as numbers and percentages (%); continuous variables were demonstrated as mean±standard deviation. The Kolmogorov-Smirnov test was used to measure the normality of the data. A chi-square test was used to evaluate the relationships among the independent variables. Student's t-test was used to evaluate the difference between the averages of the 2 groups for continuous variables with normal distributions. The Mann-Whitney U test was used to evaluate the difference between the averages of the 2 groups for continuous variables without normal distribution. A p-value <0.05 was considered to be significant.

Results. The average ages and body mass indexes (BMIs) of the patient and control groups were similar and were not significantly different from each other (**Table 1**). In the ESRD group, 7 of the patients had coronary artery disease (CAD), 22 had hypertension (HT), and 12 had heart failure (HF). The healthy control group had no chronic disease or medication (**Table 2**). The laboratory results and demographic features of patients were assessed. The white blood cell (WBC) count, urea, creatinine, hemoglobin, eGFR, alanine aminotransferase (ALT), albumin, high-density lipoprotein-cholesterol (HDL-C), parathormone (PTH), uric acid, calcium, phosphor, magnesium, and ferritin levels of patients and the control group were significantly different (**Table 1**) (p<0.05). Mean VEGF level of all ESRD patients was not significantly different

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from the control group while the mean sVEGFR-1 level of all HF patients was significantly higher (p=0.475) than the control group (p<0.001) (**Table 1**). Mean VEGF levels of ESRD patients with CAD, HF, and HT were not significantly different from the ESRD patients without any accompanying disease and the control group. Mean sVEGFR-1 levels of the ESRD patients with CAD, HF, and HT were significantly different from the control group but were not significantly different from the ESRD patients without an accompanying disease (**Table 2**).

Average VEGF level of ESRD patients using recombinant human erythropoietin (rhEPO) was significantly higher than the ESRD patients not using rhEPO (**Table 2**). Average VEGF level of ESRD patients using insulin was significantly lower than the ESRD patients not using insulin (**Table 2**). Average sVEGFR-1 level of ESRD patients using calcium channel blocker (CCB) was significantly lower than the ESRD patients not using CCB. Average sVEGFR-1 level of ESRD patients using beta blockers, acetylsalicylic acid, enoxaparin, CCB, rhEPO, and insulin were significantly different from the healthy control group (**Table 2**).

Table 1 - Comparison of demographic and laboratory features, VEGF, and sVEGFR-1 levels of ESRD group and control group.

Demographic and laboratory features	ESRD (n=38)	Control (n=35)	*P*-value
Age (years)	70.08±11.91	70.69±9.54	0.812
Gender (F/M)	21/17	16/19	0.415**
BMI (kg/m²)	26.28±4.91	27.99±4.30	0.119
Glucose (fasting) (mg/dL)	109.79±35.70	98.51±17.79	0.161
Urea (mg/dL)	138.76±66.74	32.38±8.36	<0,001
Creatinine (mg/dL)	5.06±2.17	0.88±0.20	<0.001
eGFR (mL/min/1.73m²)	11.51±5.71	77.00±15.55	<0,001
Hemoglobin (g/dL)	10.6 (7.04-14.4)	13.25 (9.3-16.23)	<0.001*
Platelet (10^3/mm³)	228 (41-507)	274 (111-394)	0.108*
White blood cell (/mm³)	9118±4046	6014±1759	<0.001
Sedimentation (mm/h)	28.95±24.01	20.26±14.66	0.064
CRP (mg/L)	1.89±0.93	1.39±1.06	0.073
Albumin (g/dL)	3.11±0.67	4.38±0.33	<0.001
HDL-C (mg/dL)	39.21±11.27	49.60±10.22	<0.001
LDH (IU/L)	322 (165-734)	380 (262-495)	0.024*
Uric acid (mg/dL)	6.57±2.43	5.16±1.42	0.004
Parathormone (ng/L)	288.2±220.6	57.61±9.56	<0.001
Calcium (g/dL)	8.54±0.92	9.65±0.54	<0.001
Phosphorus (g/dL)	4.91±1.63	3.18±0.34	<0.001
Magnesium (g/dL)	2.19±0.28	2.07±0.15	0.028
sVEGFR-1 (ng/mL)	0.217±0.135	0.068±0.047	<0.001
VEGF (ng/mL)	0.280±0.264	0.321±0.210	0.475

BMI - body mass index, CRP - C-reactive protein, eGFR - estimated glomerular filtration rate, ESRD - end-stage renal disease, HDL - high-density lipoprotein-cholesterol, LDH - lactate dehydrogenize, sVEGFR-1 - soluble vascular endothelial growth factor receptor-1, VEGF - vascular endothelial growth factor. Values are given as mean±standard deviation; variables, which are not normally distributed, are given as medians (minimum, maximum). *The result of mann-whitney U test according to the median values, **Result of Chi-square test

Discussion. In the present study, we have investigated putative links of VEGF and its soluble receptor sVEGFR-1 in prevalent HD patients. We have aimed to evaluate the levels and clinical significance of VEGF and sVEGFR-1 (relationships between VEGF and sVEGFR-1 with demographics, laboratory findings, co-morbidities, and medications) in patients on HD treatment.

We have found the level of sVEGFR-1 higher than the control group due to inflammation likely to the previous studies.[11] Also, according to the literature, an increased level of sVEGFR-1 is an independent risk factor for CKD, which causes low prognosis and high cost.[11] Increased plasma VEGF levels have been reported in CKD or ESRD patients underwent HD.[12,13] In the literature, bilateral nephrectomy in mice has caused an extreme increase in plasma VEGF.[14] On the contrary, VEGF levels of HD patients were not higher than the control group in our study, unlikely to the literature. This may be due to the nonspecific increases in VEGF levels because of inflammation, coagulation or such other biological processes. Tomas Lenz et al[15] were not able to show a significant correlation between VEGF and sVEGFR-1 in diabetic patients with reduced renal function. We have found a significant correlation between VEGF and sVEGFR-1. From this point of view, VEGF reduction by an increase in sVEGFR-1 may be one of the causes of decreased angiogenesis in ESRD patients. Because we have also found sVEGFR-1 levels significantly higher in ESRD patients. We believe that it can be an important clinical sign in ESRD clinical course.

It was previously known that sVEGFR-1 was correlated with morbidity and mortality and was a potent indicator of disease severity in septic or seriously ill patients.[16,17] In this regard, we believe that sVEGFR-1 is an important molecule in an aspect of ESRD pathogenesis and clinical course. In our study, the correlation analysis between VEGF and sVEGFR-1 was significantly negative. We speculate that a decreased level of sVEGFR-1 by increased level of VEGF is a physiological response to inflammation, designed to increase angiogenesis in ESRD patients.

Table 2 - Comparison of VEGF and sVEGFR-1 levels in comorbidities and medications of ESRD patients.

Comorbidities and medications		VEGF			sVEGFR-1		
	n	Mean±SD	P1	P2	Mean±SD	P1	P2
CAD (-)	31	0.263±0.24	0.665		0.213±0.13	0.418	
CAD (+)	7	0.354±0.34		0.800	0.234±0.13		<0.001
HT (-)	16	0.304±0.30	0.701		0.215±0.10	0.605	
HT (+)	22	0.262±0.23		0.184	0.218±0.15		<0.001
HF (-)	26	0.282±0.25	0.753		0.220±0.14	0.838	
HF (+)	12	0.297±0.27		0.242	0.210±0.11		<0.001
ACE inh (-)	35	0.282±0.26	0.551		0.194±0.08	0.159	
ACE inh (+)	3	0.254±0.25		0.343	0.481±0.31		0.007
ARB (-)	35	0.289±0.26	0.465		0.222±0.13	0.417	
ARB (+)	3	0.173±0.17		0.223	0.156±0.06		0.016
ASA (-)	31	0.247±0.24	0.118		0.215±0.13	0.735	
ASA (+)	7	0.424±0.32		0.578	0.227±0.13		<0.001
Enoxaparin(-)	28	0.296±0.27	0.654		0.215±0.10	0.220	
Enoxaparin(+)	10	0.234±0.22		0.140	0.222±0.19		<0.001
B.Blocker (-)	29	0.246±0.24	0.154		0.212±0.14	0.192	
B.Blocker (+)	9	0.390±0.29		0.611	0.235±0.11		<0.001
CCB (-)	30	0.287±0.26	0.816		0.237±0.14	0.012	
CCB (+)	8	0.254±0.26		0.190	0.141±0.04		<0.001
rhEPO (-)	34	0.246±0.24	0.025		0.220±0.14	0.617	
rhEPO (+)	4	0.567±0.28		0.064	0.190±0.02		0.004
OAD (-)	28	0.292±0.25	0.436		0.206±0.14	0.037	
OAD (+)	10	0.246±0.24		0.096	0.248±0.11		<0.001
Insulin (-)	31	0.318±0.27	0.033		0.202±0.10	0.169	
Insulin (+)	7	0.111±0.10		0.004	0.284±0.21		<0.001

ACE inh - angiotensin-converting enzyme inhibitor, ARB - angiotensin II receptor blocker, B.Blocker - beta blocker, ASA - acetylsalicylic acid, CAD - coronary artery disease, CCB - calcium channel blockers, ESRD - end-stage renal disease, HF - heart failure, HT - hypertension, OAD - oral antidiabetic, rhEPO - recombinant human erythropoietin, sVEGFR-1 - soluble vascular endothelial growth factor receptor-1, VEGF - vascular endothelial growth factor, P1 - Comparison of the accompanying diseases or medications used in heart failure group, P2 - Comparison with the control group, values were given as mean±standard deviation

The age, gender, and the BMI of the 2 groups were similar. The average age was 70.08±11.91 in patients group. The increased incidence of ESRD in elderly is compatible with the literature.[18]

As sVEGFR-1 is expressed in both endothelial cells and macrophages, VEGFR-1 has been related to inflammation.[19] With this knowledge, we can see increasing of sVEGFR-1 by increasing levels of WBCs. We have reported a significant and positive correlation between WBC and sVEGFR-1.

The CKD is an independent risk factor for the development of CAD, and for the everity of CAD.[20] It is known that incidence of CAD increases in renal osteodystrophy in CKD patients, most probably by one of the mechanisms of a decrease in the angiogenic process. The correlation analysis between parathormone and sVEGFR-1 was significantly positive. We have also found a positive correlation between phosphorus and sVEGFR-1, and a negative correlation between calcium and sVEGFR-1. The levels of calcium and phosphorus are similar to the levels in renal osteodystrophy patients. Qunying Guo et al[21] found significant associations between sVEGFR-1 and cardiac disease. The sVEGFR-1 may be one of the mechanisms of decrease of angiogenesis in CKD patients with renal osteodystrophy. The positive correlation between phosphorus and sVEGFR-1 is a new finding among the studies in this area. Also, the correlation between sVEGFR-1 and albumin, HDL-C, calcium were found to be significantly negative for the first time.

Tomas Lenz et al[22] suggested that in vivo erythropoietin does not affect the functionality and/or production of components of the VEGF system in diabetics with CKD. According to this study, the effects of exogenous rhEPO upon VEGF and/or the sVEGFR-1 have not been evaluated before. In the present study, the average VEGF level of ESRD patients using rhEPO was significantly higher than the ESRD patients not using rhEPO. The average sVEGFR-1 level of ESRD patients using rhEPO was not significantly different from the ESRD patients not using rhEPO. Further investigations with more participants may reveal significant results

Table 3 - Correlation analyses of VEGF and sVEGFR-1 levels with other clinical features in ESRD group (n=38).

Clinical features	VEGF		sVEGFR-1	
	r	*P*-value	r	*P*-value
VEGF	1		-0.246	0.036
sVEGFR-1	-0.246	0.036	1	
White Blood Cell	-0.029	0.809	0.371	0.001
Hemoglobin	0.166	0.161	-0.479	<0.001
Urea	-0.038	0.751	0.340	0.003
Creatinine (Predialysis)	-0.022	0.850	0.401	<0.001
GFR	0.117	0.323	-0.548	<0.001
Albumin	0.053	0.654	-0.505	<0.001
HDL-C	0.030	0.801	-0.287	0.014
LDH	0.119	0.315	0.000	0.999
Uric acid	-0.125	0.291	0.215	0.068
Parathormone	0.112	0.346	0.322	0.005
Calcium	0.101	0.395	-0.259	0.027
Phosphorus	0.002	0.986	0.360	0.002
Magnesium	-0.046	0.702	0.150	0.205

eGFR - estimated glomerular filtration rate, HDL-C - high-density lipoprotein-cholesterol, LDH - lactate dehydrogenase, sVEGFR-1 - soluble vascular endothelial growth factor receptor-1, VEGF - vascular endothelial growth factor

about sVEGFR-1. The fact that rhEPO has been given with remarkable clinical benefit to patients with preterminal and terminal renal failure, now makes it likely that convenient effects on the angiogenesis may be a relevant effect of this agent. Further investigations may be needed in this area. Tartare et al[23] & Miele et al[24] have declarated that VEGF induction by insulin treatment occurs via different signaling pathways. In our study, we found that average VEGF level of ESRD patients using insulin was significantly lower than the ESRD patients not using insulin contrary to literature. This result may show that insulin treatment in diabetic patients with ESRD may decrease angiogenesis via the reduction of VEGF. The average sVEGFR-1 level of ESRD patients using CCB was significantly lower than the ESRD patients not using CCB. All of our patients were using dihydropyridine CCB. Allanore et al[25] reported that nifedipine concentration did not affect the VEGF and sVEGFR-1 levels. Our finding may reveal a positive effect of CCB on angiogenesis in patients under HD treatment. Further investigations are needed in this area.

Study limitations. This study is based on a limited number of patients and thus, cannot ascertain whether these findings can be applied to other patients with ESRD. Due to this limitation the associations with clinical findings such as demographic features, laboratory findings, comorbidities, and medications have been considered as secondary objectives. Further studies with more participants should be performed. But evaluating both of these agents (VEGF and sVEGFR-1) concurrently makes it easy to evaluate the balance of angiogenic/anti-angiogenic factors in patients with ESRD.

In conclusion, sVEGFR-1 levels of ESRD patients are significantly higher than the control group. We found novel associations among the sVEGFR-1 and VEGF levels and medications. Especially our finding of rhEPO and VEGF illuminates a reasonable positive effect of rhEPO on angiogenesis. We report novel associations between VEGF, sVEGFR-1, insulin and CCB medication. Accordingly, larger clinical studies will be necessary for confirmation of these findings.

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