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The relationship between vascular endothelial growth factor (VEGF) in the serum and drained dialysate with the quality of peritoneal dialysis and peritoneal membrane transport rates

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Abstract: Vascular endothelial growth factor (VEGF), a powerful angiogenetic agent crucial for microvascular hyperpermeability and neoangiogenesis in the peritoneum, is associated with increased solute transport rates in chronic peritoneal dialysis (PD) patients. We investigated the correlation between serum and drained dialysate (dd) concentrations of VEGF and the transport characteristics of peritoneal membrane and dialysis quality in 20 patients with end-stage renal failure at the beginning and after six months of PD. The serum VEGF (sVEGF) concentration rose significantly (149.33±116.71 pg/mL vs 239.36±102.23 pg/mL; p=0.012) and ddVEGF concentration increased slightly (38.44±50.47 pg/mL vs 43.55±51.10 pg/mL) during the first 6 months of PD. At the beginning of chronic PD, ddVEGF concentrations correlated inversely with the peritoneal equilibrium test (PET) glucose (R=-0.565; p=0.009) and creatinine (R=-0.506; p=0.023) and residual renal function (RRF) (R=-0.691; p=0.001); sVEGF concentrations inversely correlated with PET creatinine (R=-0.457; p=0.043) and residual diuresis (RD) (R=-0.691; p=0.001). After 6 months of treatment, ddVEGF concentrations correlated directly with $PET_{creatinine}$ (R=0.450; p=0.047), and inversely with RRF (R=-0.552; p=0.012) and residual renal weekly Kt/V (R=-0.488; p=0.029). The sVEGF concentration inversely correlated with RD (R=-0.589; p=0.006). High ddVEGF at the beginning of PD is predictive of adverse alterations of the peritoneal membrane, i.e. increased transport rate of glucose and creatinine. ddVEGF values may help to identify patients who will preserve adequate transport characteristics of the peritoneal membrane and maintain successful long-term PD.

Keywords: dialysis quality; peritoneal dialysis; peritoneal equilibration test; residual renal function; vascular endothelial growth factor

Abbreviations: Vascular endothelial growth factor (VEGF); peritoneal dialysis (PD); total iron binding capacity (TIBC); drained dialysate (dd); residual renal function (RRF); residual diuresis (RD); creatinine clearance (ClCr); protein catabolic rate (PCR); normalized protein catabolic rate (nPCR); peritoneal equilibration test (PET); count of blood cells (CBC); diabetes mellitus (DM); body mass index (BMI); C-reactive protein (CRP)

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INTRODUCTION

Peritoneal dialysis is a well-established renal-replacement treatment for patients affected by end-stage renal disease. Long-term exposure to bioincompatible dialysis fluid, repeated episodes of bacterial peritonitis, chronic inflammation of the peritoneal membrane, mechanical problems with peritoneal catheter, hypoproteinemia and ultrafiltration failure all seriously affect patient survival in long-term PD [1].

Increased angiogenesis is believed to be a major pathohistological alteration during chronic PD, eventually leading to serious complications in long-term PD represented by increased peritoneal solute transport rates and ultrafiltration failure [2-5]. Angiogenesis is the formation of new blood vessels from pre-existing endothelium. Some angiogenetic factors, such as VEGF, are increased in uremic conditions and upon exposure to high glucose solution during PD [6].

The vasopermeability factor, also known as vascular endothelial growth factor (VEGF), is a glycoprotein with a huge affinity for endothelial cells and it is also a powerful factor of angiogenesis. Different cell types produce VEGF in ischemic, hypoglycemic and hyperglycemic conditions under the influence of cytokines such as IL-6, hormones, inactivated oncogenes, vHL and p53, and growth factors such as TGF-β1. The VEGF factor is detected on human endothelial cells of peritoneal blood vessels [7,8]. In patients on chronic PD, VEGF is upregulated in the peritoneal membrane and is present in drained dialysate. Cultured mesothelial and endothelial cells isolated from the peritoneum produce VEGF [9,10]. It has been proven that VEGF plays a key role in neoangiogenesis in diabetic proliferative retinopathy and, by analogy, in the development of microvascular hyperpermeability and neoangiogenesis of the peritoneum during chronic PD treatment [10]. Neoangiogenesis is responsible for the enlargement of the effective peritoneal vascular area and increased solute transport rate [11-13].

Serum VEGF (sVEGF) concentrations vary widely and different studies have reported ranges from 66 to 1180 ng/L, 20.1 to 1492 pg/mL and from 17.4 to 347.5 pg/mL [14, 15].

The aim of this study was to investigate the correlation between serum and drained dialysate VEGF concentrations, dialysis quality and transport properties of the peritoneal membrane in patients at the beginning and after six months of chronic PD.

MATERIALS AND METHODS

Patients

The study protocol was reviewed and approved by the Ethics Committee, Faculty of Medicine, University of Belgrade. After a thorough explanation of the study procedure, all patients signed informed consent to participate in the study. All blood samples were collected in accordance with the Declaration of Helsinki as revised in 2000.

We included 20 patients with end-stage kidney disease whose basic demographic data and presence of diabetes mellitus are presented in Supplementary Table S1. The patients were free of clinical and laboratory signs of infection 4 weeks prior to enrollment. Patients used at least 8 L of conventional lactate-buffered acidic (pH 5.5) PD fluid daily, with glucose concentrations ranging from 1.25 to 2.76%, and drained a higher amount than instilled.

Blood analyses

Fasting venous blood samples were taken in K_3EDTA vacutainer tubes to determine the complete blood count (CBC) and in biochemistry vacutainer vials to measure serum concentrations of glucose, urea, creatinine, albumin and iron, total iron-binding capacity (TIBC), ferritin, fibrinogen and C-reactive protein. The blood samples were centrifuged at 2000 x g for 10 min. The concentrations of glucose, urea, creatinine and albumin were assessed in 24-hour urine and drained dialysate.

The CBC was determined with the Beckman Coulter® HmX Hematology Analyzer. Hemoglobin (HGB) was determined by the cyanmethemoglobin method.

The biochemical analyzer ARCHITECT ci8200 (Abbott Diagnostics, Wiesbaden, Germany) was used to determine glucose, urea, creatinine and albumin concentrations in the serum, urine and drained dialysate.

Immunoassay by Quantikine® Human VEGF (R&D Systems, USA & Canada) was used to determine the

concentrations of VEGF in the serum and dd after an 8-h dialysis dwell. Sandwich enzyme-linked immunosorbent assay (ELISA) kits from Quantikine® Human VEGF were used to determine the concentrations of VEGF, sVEGF and ddVEGF. Blood and dialysate samples taken after an 8-h overnight dialysis dwell to determine concentrations of VEGF were immediately stored at -70°C before the estimation. A monoclonal antibody specific for VEGF was precoated onto microplates. Samples and VEGF standards were pipetted into the wells and any VEGF present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for VEGF was added to the wells. Following washing to remove any unbound reagent, a substrate solution was added to the wells and color proportionate to the concentration of bound VEGF bound in the initial step was developed, and its intensity was measured. Intra- and interassay coefficients of variation were 2.6 and 9.8%, respectively, and the lower limit of detectability was 3.5 pg/mL.

Peritoneal dialysis quality was assessed by calculating the total weekly Kt/V and the total weekly ClCr, which are the sum of the peritoneal and residual renal components. Peritoneal dialysis was performed continuously and dialysis quality was assessed at 7-day intervals [16].

Peritoneal and residual renal Kt/V and ClCr were calculated using Watson's formula [17]. ClCr was normalized according to the body surface area, calculated using Dubois-Dubois' formula [18].

RRF was calculated as the mean value of residual clearance of urea and residual ClCr.

PCR and nPCR were calculated according to Bergstrom's [19] or Randerson's formula [20].

Peritoneal membrane transport characteristics were examined by the standard PET according to Twardowski[19, 21].

Statistical analysis

Data were analyzed with SPSS ver. 20.0. Serum and ddVEGF concentrations were expressed as mean values±median, since they were not normally distributed. Other results were expressed as means±SD. Data were analyzed with Student's t-test, χ^2 and Mann-Whitney tests. Pearson's product-moment coefficient and Spearman's rank correlation coefficient were used to analyze the correlations. A p value of less than 0.05 was used as the criterion for a statistically significant difference.

RESULTS

Biochemical parameters

Biochemical parameters were in agreement with the underlying disease and treatment modality at the beginning and after 6 months of dialysis (urea plasma concentration 18.94±5.47 mmol/L and 18.99±6.11 mmol/L, serum creatinine 661.25±177.65 μmol/L and 698.85±243.30 μmol/L). Parameters of CBC (hemoglobin concentrations were 99.15±14.52 g/L and 102.95±10.90g/L respectively) and iron concentrations (10.77±5.00μmol/L and 10.30±3.68 μmol/L respectively) were adequate, while fibrinogen (5.50±1.41 g/L and 5.16±1.50 g/L respectively) and CRP concentrations (6.30±6.04 IU/L and 6.64±5.63 IU/L respectively) were above the reference range. No significant difference was found between the biochemical parameter values at baseline and at the end of the follow-up.

Residual diuresis and dialysis membrane parameters during follow-up

At the beginning of dialysis, the patients' residual diuresis was 867.5±426.82 mL/day and after 6 months it was 822.5±432.7 mL/day; the total weekly Kt/V was 2.198±0.403 and 2.154±0.450 respectively, and the ClCr was 70.490±13.580 L/week and 69.375±13.98 L/week, respectively, also in agreement with the suggested dialysis quality guidelines. The mean values of nPCR were lower than the suggested 1 g/kgTM/day at both measuring points (0.859±0.178 and 0.880±0.188 g/kgTM/day). No significant difference was observed between the values during the follow-up.

Peritoneal transport rates of glucose and creatinine increased slightly but not significantly during the follow-up. At the beginning and after 6 months of dialysis, the PET for glucose was 0.400±0.129 and 0.365±0.199, and $PET_{creatinine}$ was 0.614±0.170 and 0.647±0.130, respectively.

VEGF concentrations in the serum and drained dialysate

Serum VEGF concentrations were 149.33±116.71 pg/mL at the beginning and they rose significantly (p=0.012) to 239.36±102.23 pg/mL after 6 months of PD therapy. Drained dialysate VEGF concentrations were 38.44±50.47 pg/mL at the beginning and rose insignificantly to 43.55±51.15 after 6 months of PD (Table 1).

Table 1. Concentrations of serum vascular endothelial growth factor (sVEGF) and drained dialysate (ddVEGF) at the beginning (0) and after 6 months of PD.

	group	mean	med.	Z	t	p
sVEGF (pg/mL)	0	149.33±116.71	173.38	0.013	-2.793	0.012
	6	239.36±102.23	224.06			
ddVEGF (pg/mL)	0	38.44±50.47	15.60	0.560	-0.293	0.773
	6	43.55±51.15	16.7			

Z – Z test; med. – median; ddVEGF – drained dialysate vascular endothelial growth factor; sVEGF – serum vascular endothelial growth factor

Correlation between serum and drained dialysate VEGF and dialysis parameters

At the beginning of chronic PD no significant correlation was found between serum and ddVEGF concentrations and nPCR and Kt/V parameters (Table2). After 6 months of chronic PD, a significant inverse correlation was observed between ddVEGF concentrations and residual weekly Kt/V (R= -0.488, p=0.029) (Table 2), but no statistical correlation was found between the sVEGF concentration and total weekly, peritoneal weekly and residual weekly Kt/V, and between ddVEGF concentrations and total weekly and peritoneal weekly Kt/V.

Table 2. Correlation of Kt/V and concentrations of serum vascular endothelial growth factor (sVEGF) and drained dialysate (ddVEGF) at the beginning of PD and after 6 months of PD.

			nPCR (g/kg/day)	tot. weekly Kt/V	per. week. Kt/V	res. weekly Kt/V
beginning	sVEGF (pg/mL)	R	0.008	0.087	0.076	0.095
		sign.	0.972	0.714	0.750	0.690
	ddVEGF (pg/mL)	R	-0.032	0.435	0.355	0.273
		sign.	0.893	0.055	0.124	0.244
6 months	sVEGF (pg/mL)	R	-0.095	-0.206	0.022	-0.349
		sign.	0.691	0.384	0.925	0.132
	ddVEGF (pg/mL)	R	-0.042	-0.203	0.151	-0.488
		sign.	0.861	0.391	0.524	0.029

tot. – total; per. – peritoneal; res. – residual; nPCR – normalized protein catabolic rate; ddVEGF – drained dialysate vascular endothelial growth factor; sVEGF – serum vascular endothelial growth factor

At the beginning and after 6 months of chronic PD, no significant correlation was found between VEGF concentrations in the serum and drained dialysate and the ClCr parameters (Table 3).

Table 3. Correlation between creatinine clearance (ClCr) and concentrations of serum vascular endothelial growth factor (sVEGF) and drained dialysate (ddVEGF) at the beginning and after 6 months of PD.

			tot. week ClCr (L/week/m²)	per. week ClCr (L/week/m²)	res. week ClCr (L/week/m²)
beginning	sVEGF (pg/mL)	R	0.147	-0.083	0.066
		sign.	0.538	0.727	0.783
	ddVEGF (pg/mL)	R	0.214	0.181	0.199
		sign.	0.365	0.446	0.401
6 months	sVEGF (pg/mL)	R	-0.254	-0.374	0.075
		sign.	0.280	0.104	0.753
	ddVEGF (pg/mL)	R	-0.320	-0.198	0.367
		sign.	0.169	0.403	0.112

tot. week. – total weekly; per. week. – peritoneal weekly; res. week – residual weekly; ddVEGF – drained dialysate vascular endothelial growth factor; sVEGF – serum vascular endothelial growth factor; ClCr – creatinine clearance

At the beginning of chronic PD, a highly significant inverse correlation was found between ddVEGF concentrations and $PET_{glucose}$ (R= -0.565, p=0.009) (Fig. 1) and with RRF (R=-0.691, p=0.001) (Fig. 2), and was statistically significant with $PET_{creatinine}$ (R= -0.506, p=0.023) (Fig. 3). Furthermore, a significant inverse correlation was found between sVEGF concentrations and $PET_{creatinine}$ (R= -0.457, p=0.043) (Fig. 4), and a highly significant inverse correlation with RD (R=-0.691, p=0.001) (Fig. 4).

After 6 months of chronic PD treatment, we observed the following: a significant direct correlation between ddVEGF concentrations and $PET_{creatinine}$ (R=0.450, p=0.047), (Fig. 3); a significant inverse correlation between ddVEGF concentrations and RRF (R=-0.552, p=0.012) (Fig. 2), and a significant inverse correlation between sVEGF concentrations and RD (R=-0.589, p=0.006), (Fig. 4).

After 6 months of chronic PD, no significant correlation was found between sVEGF concentrations and $PET_{creatinine}$ and $PET_{glucose}$ (Table 4).

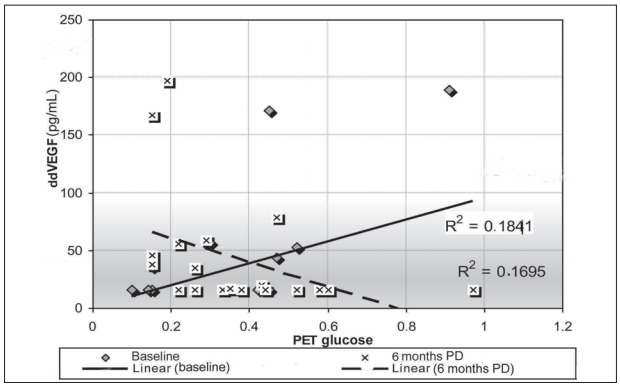

Fig. 1. Correlation between $PET_{glucose}$ and VEGF concentrations in the drained dialysate at the beginning and after 6 months of PD. ddVEGF – drained dialysate vascular endothelial growth factor; PET – peritoneal equilibration test; PD – peritoneal dialysis.

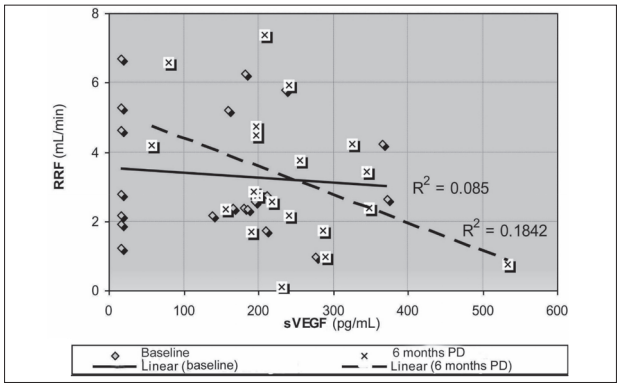

Fig. 2. Correlation between RRF and VEGF concentrations in the serum at the beginning and after 6 months of PD. sVEGF – serum vascular endothelial growth factor; RRF – residual renal function; PD – peritoneal dialysis.

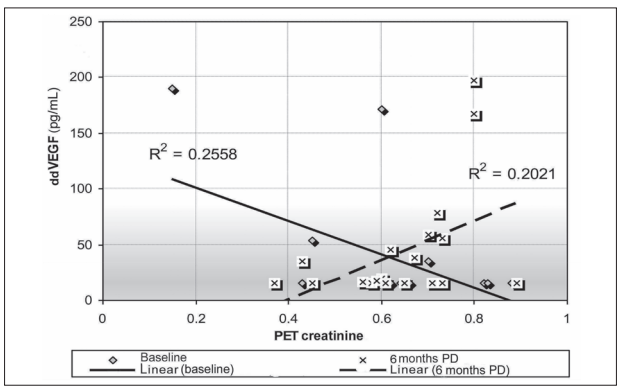

Fig. 3. Correlation between $PET_{creatinine}$ and VEGF concentrations in the drained dialysate at the beginning and after 6 months of PD. ddVEGF – drained dialysate vascular endothelial growth factor; PET – peritoneal equilibration test; PD – peritoneal dialysis.

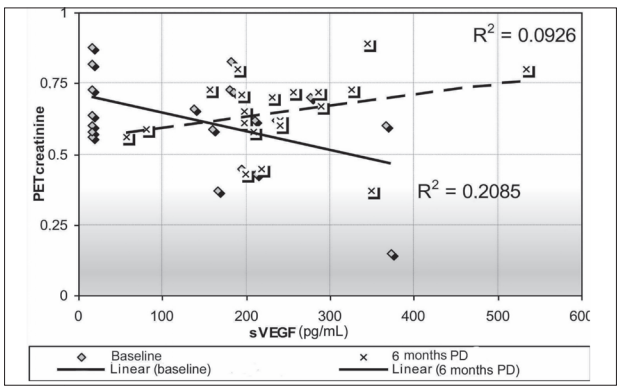

Fig. 4. Correlation between $PET_{creatinine}$ and VEGF concentrations in the serum at the beginning and after 6 months of PD. sVEGF – serum vascular endothelial growth factor; PET –peritoneal equilibration test; PD – peritoneal dialysis.

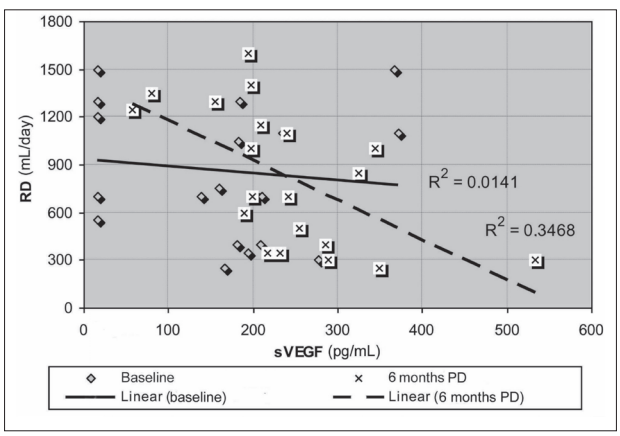

Fig. 5. Correlation between RD and VEGF concentrations in the serum at the beginning and after 6 months of PD. sVEGF – serum vascular endothelial growth factor; RD – residual diuresis; PD – peritoneal dialysis.

DISCUSSION

This investigation included 20 patients on PD. Analyses were performed at the beginning and after 6 months of dialysis.

The serum VEGF concentration rose significantly while the concentration of ddVEGF rose slightly during the follow-up. These findings correspond with literature data reporting a significant increase of locally-produced VEGF in the peritoneal membrane during long-term PD with conventional solutions [12].

The molecular weight of VEGF is 35 kDa, therefore serum VEGF is readily transferred to the dialysate. Both the serum and drained dialysate VEGF concentrations are modified not only by the uremic milieu but also

Table 4. Correlation between concentrations of serum vascular endothelial growth factor (sVEGF) and drained dialysate (ddVEGF) and the transport properties of the peritoneum and RRF at the beginning and after 6 months of PD.

		serum				drained dialysate			
		beginning		6 mounts		beginning		6 months	
		PET glucose	PET creatinine	PET glucose	PET creatinine	RD (mL/day)	RRF (mL/min)	RD (mL/day)	RRF (mL/min)
sVEGF (pg/mL)	R	0.016	-0.457	0.069	0.304	-0.692	-0.336	-0.589	-0.429
	sign.	0.946	**0.043**	0.772	0.192	**0.001**	0.147	**0.006**	**0.049**
ddVEGF (pg/mL)	R	-0.565	-0.506	-0.412	0.450	-0.327	-0.691	-0.409	-0.552
	sign.	**0.009**	**0.023**	0.071	**0.047**	0.160	**0.001**	0.073	**0.012**

PET – peritoneal equilibration test; RD – residual diuresis; RRF – residual renal function; ddVEGF – drained dialysate vascular endothelial growth factor; sVEGF – serum vascular endothelial growth factor;

by the dialysate glucose concentration and peritonitis episodes. Therefore we opted to enroll patients treated with glucose dialysate concentrations up to 2.76% and not higher, and that were also free of peritonitis.

In the examined group of patients, the concentrations of sVEGF did not correlate with peritoneal, residual renal and total weekly clearances of urea and creatinine, neither at the beginning nor after 6 months of PD. Still, sVEGF concentrations were significantly lower in patients with lower RRF and lower RD after 6 months of PD.

Previous studies documented significant difference in sVEGF concentrations that were related to RRF levels: the mean serum concentration of VEGF in patients with RRF<2 mL/min, 41.15 pg/mL (range 21.10-82.70 pg/mL), and in patients with RRF>2 mL/min, 27.15 pg/mL (range 18.90-36.60 pg/mL). Previous studies reported a direct correlation between sVEGF concentrations and chronic inflammatory state, represented by plasma concentrations of IL-1, CRP and fibrinogen [22]. Investigators found a negative correlation between RRF and the parameters of inflammation, such as hyalurone [20] and tumor necrosis factor (TNF)-α [14]. Serum CRP concentrations at the beginning of chronic PD were predictors of a deterioration of the RRF during a one-year follow-up [24]. It was concluded that preserved RRF contributes to better clearance of growth factors and inflammatory cytokines. However, high serum concentrations of growth factors and cytokines could influence RRF decline [25].

At the beginning of PD, we found a significant inverse correlation between sVEGF concentrations and the peritoneal transport rate of creatinine, suggesting that the baseline sVEGF concentration was not predictive of a high creatinine transport rate at the beginning of chronic PD. After six months of PD, we found no significant correlation between serum concentrations of VEGF and the peritoneal transport rate of creatinine. The sVEGF concentration was not correlated with the peritoneal transport rate of glucose, neither at the beginning nor after 6 months of PD. Previous studies reported somewhat different results. One study, which included 40 patients on chronic PD during 3 to 56 months, found significantly higher sVEGF concentrations in high and higher-than-average transporters when compared to low and lower-than-average transporters [14]. The short follow-up period in our study could explain the lack of correlation between sVEGF concentrations and solute peritoneal transport rates in our patients.

At the beginning of chronic PD, we found a significant inverse correlation between ddVEGF concentration and residual weekly Kt/V. The ddVEGF concentrations did not correlate with the clearance of other solutes during the entire follow-up.

Similar to previous reports, we found significant inverse correlations between ddVEGF concentrations and RD and RRF at the beginning and after 6 months of PD [22]. There is little data about the correlation between ddVEGF concentrations and RRF function and residual solute clearances, but we speculate that preserved RRF also contributed to a better clearance of growth factors and inflammatory cytokines in the drained dialysate, besides contributing to the clearance of systemic factors [25].

At the beginning of PD, the concentration of ddVEGF significantly inversely correlated with the transport rate of glucose. This suggests that higher ddVEGF concentrations at the beginning of PD are predictive of a higher transport rate of glucose, which represents an adverse characteristic of the peritoneal membrane, particularly at the beginning of the PD program. This correlation disappeared after 6 months of PD, probably because the concentrations of ddVEGF and transport rate depended on several different factors.

At the beginning of chronic PD, the concentration of ddVEGF significantly inversely correlated with creatinine peritoneal transport rate, but after 6 months of PD, the concentration of ddVEGF significantly correlated with creatinine peritoneal transport rate. Thus, higher ddVEGF concentrations are predictive of increased creatinine peritoneal transport rate in long-term PD.

The previously mentioned study of 40 patients with no signs of systemic inflammatory disease reported significantly higher ddVEGF concentrations in high and higher-than-average transporters when compared to the group of low and lower-than-average transporters [14]. In another study, a significant correlation was found between VEGF concentration and the concentration of proinflammatory cytokine IL-6 in drained dialysate, suggesting a pathogenetic link between inflammation, neoangiogenesis and a high peritoneal transport rate [23]. Further research proved the influence of genetic polymorphism on ddVEGF concentrations and changes in the peritoneal transport rate during a one-year follow-up of chronic PD [15].

A positive correlation was found between the concentration of locally-produced VEGF in the effluent dialysate and the peritoneal transport rate of creatinine and urate, as well as the glucose absorption rate [26]. The peritoneal transport rate of creatinine and urate and the glucose absorption rate characterize the effective vascular surface area of the peritoneal membrane [9]. The hyperglycemia-induced microvascular changes in the peritoneal membrane were mostly prevented by application of monoclonal anti-VEGF antibodies, while treatment with non-specific control antibodies was not effective. These experimental findings confirmed that VEGF plays an important role in glucose-induced neoangiogenesis and hyperpermeability of the peritoneal membrane in long-term PD [2,3,6].

VEGF was also found to be the mediator of neoangiogenesis in diabetic retinopathy [7,11]. High concentrations of VEGF in aqueous humor have been correlated with the level of retinopathy and, by analogy, it has been speculated that the correlation between solute transport rate and the concentration of VEGF in the effluent confirms that VEGF is an important mediator of neoangiogenesis in the peritoneal membrane during long-term PD [7,11,13].

CONCLUSION

This prospective study of the effects of VEGF on the peritoneal membrane exposed to PD is among the few conducted *in vivo* on human subjects. Increased VEGF concentrations in the serum and drained dialysate were observed during the first six months of PD. Significant inverse correlations between the concentrations of VEGF in the drained dialysate and RD and RRF at PD initiation suggest an important role of preserved RRF in the clearance of growth factors. Increased concentrations of VEGF in the drained dialysate at the beginning of PD are predictive of a higher transport rate of glucose, as well as of an increased creatinine peritoneal transport rate in long-term PD, with both representing adverse characteristics of the peritoneal membrane. We believe that the presented data may be of clinical importance as they suggest predictive value of drained dialysate VEGF in identifying patients who will preserve adequate transport characteristics of peritoneal membrane and maintain successful long-term PD.

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Author contributions: Nataša Jovanović and Biljana Stojimirović were responsible for conceiving the study and its design and for drafting the manuscript. JasnaTrbojević-Stanković and Dejan Nešić collected the literature. Nataša Jovanović and Biljana Stojimitović made critical revisions to the paper. Snežana Žunić and Žarko Laušević provided statistical expertise.

Conflicts of interest disclosure: The authors have no actual or potential conflicts of interest.

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Supplementary Data

Supplementary Table S1.
Available at: http://serbiosoc.org.rs/NewUploads/Uploads/Jovanovic%20et%20al_3651_Supplementary%20Fig.%20S1.pdf