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Levels of Vascular Endothelial Growth Factor during First Six Months of Peritoneal Dialysis

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SUMMARY

Introduction Chronic peritoneal dialysis (PD) up-regulates vascular endothelial growth factor (VEGF) synthesis and VEGF is found in drained dialysate (dd).

Objective Aims of this prospective study were to evaluate serum (s) and ddVEGF concentration during the first six months of PD, relationships between these concentrations and demographic and biochemical parameters, presence of diabetes, peritonitis, and the use of medications.

Methods The study included 20 patients, with the mean age of 62.9±12.69, 11 of whom were affected by diabetes mellitus. Fasting venous blood samples were taken at the beginning and after six months of PD, in tri-potassium ethylenediaminetetraacetic acid (K_3EDTA) vacutainer.

Results After six months of PD, sVEGF concentrations increased significantly, without significant change in ddVEGF. Concentrations of sVEGF at the beginning of chronic PD treatment directly significantly correlated with serum fibrinogen, and after six months with fibrinogen and glycemia. In patients receiving erythropoiesis-stimulating agent (ESA), levels of sVEGF and ddVEGF were lower at baseline, while after six months of PD ddVEGF increased. In patients not receiving ESA, sVEGF increased more prominently, while ddVEGF decreased. The changes were not statistically significant. Patients receiving angiotensin-converting-enzyme inhibitor (ACEi) had sVEGF and ddVEGF levels insignificantly lower than those not using ACEi, however sVEGF significantly increased during six months of PD. After six months of PD, ddVEGF was significantly higher compared to those not using ACEi. Treatment with statins did not significantly influence levels of sVEGF and ddVEGF during the follow-up. Concentrations of sVEGF were continually lower than those of ddVEGF and increased more, while concentrations of ddVEGF were higher in patients using statins.

Conclusion Serum and drained dialysate concentrations of VEGF in PD patients were connected with poorer metabolic profile, while the role of inflammation and treatment agents should be studied further.

Keywords: peritoneal dialysis; VEGF; statins; erythropoietin stimulating agents; angiotensin converting enzyme inhibitors

INTRODUCTION

Chronic uremic inflammation, peritoneal exposure to high glucose and glucose degradation products and high lactate concentration in conventional peritoneal dialysis (PD) solutions increases intracellular lactate concentration, inhibits nicotinamide adenine dinucleotide (NAD^+) regeneration and increases NADH/NAD^+ ratio. This state mimics intracellular hypoxia, which induces synthesis of vascular endothelial growth factor (VEGF), a powerful angiogenic factor [1, 2]. VEGF plays the key role in peritoneal hyperpermeability, while monoclonal anti-VEGF antibodies decrease neoangiogenesis [3].

Patients on PD are treated with erythropoiesis-stimulating agents (ESA), inhibitors of angiotensin-converting enzyme (ACEi) and statins which might modulate the PD treatment quality.

OBJECTIVE

The aims of this study were to evaluate serum (s) and drained dialysate (dd) VEGF concentration during the first six months of chronic PD treatment, to assess relationships between these concentrations and demographic characteristics of patients, standard biochemical parameters, presence of diabetes mellitus or peritonitis episodes, and use of certain therapeutic agents.

Table 1. Demographic data and diabetes mellitus in patients on chronic peritoneal dialysis treatment

Parameter		Number	%
Gender	Male	11	55.0
	Female	9	45.0
Age (years)	≤65	13	65.0
	>65	7	35.0
Diabetes mellitus	No	9	45.0
	Yes	11	55.0

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METHODS

This prospective study included 20 incident patients (11 men, nine women) affected by end-stage renal failure of different leading diseases during the first six months of chronic PD treatment. The mean age of our patients was 62.9±12.69 years. Eleven of the patients were affected by diabetes mellitus (Table 1). The patients used at least eight liters of conventional lactate-buffered acidic (pH 5.5) PD fluid daily, with glucose concentration of 1.25–2.76%. PD was performed as continuous treatment with four to five two-liter dwells with lowest glucose concentration, with a sporadic use of higher glucose concentration bags, and the mean daily glucose load was 120.84±20.43 g/day. PD fluid was produced by Baxter Medical Product, USA. Patients were free of clinical and laboratory signs of peritonitis and/or other infections within four weeks prior to the examinations. At the beginning and after six months of PD treatment, after overnight fasting, venous blood samples were taken in tri-potassium ethylenediaminetetraacetic acid (K_3EDTA) vacutainer tubes to determine the complete blood count (CBC) and in biochemistry vacutainer vials to assess serum levels of glucose, urea, creatinine, albumin, cholesterol, iron, ferritin, fibrinogen and C-reactive protein (CRP). The blood samples were centrifuged at 3,000 rotations per minute for 10 minutes. CBC was determined with the Beckman Coulter® HmX Hematology Analyzer. Hemoglobin was determined using cyanmethemoglobin method. Biochemical analyzer ARCHITECT ci8200, Abbott Diagnostics, Wiesbaden, Germany, was used to determine concentrations of biochemical parameters in serum.

VEGF

Sandwich enzyme-linked immunoadsorbent assay (ELISA) kits Quantikine® Human VEGF, R&D Systems, USA & Canada, were used to determine concentrations of sVEGF and ddVEGF. The human VEGF kit is a quantitative sandwich enzyme immune assay. A monoclonal antibody specific for VEGF is pre-coated onto a microplate. Standards and samples, including standards of known human VEGF content, control specimens, and unknown, are pipetted into these wells, and any VEGF present is bound by the immobilized (capture) antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for VEGF is added to the wells. Following a wash to remove any unbound antibody enzyme reagent a substrate solution is added to the wells and color develops in proportion to the concentration of VEGF bound in the initial step. The color development is stopped and its intensity is measured. In our study, intra- and inter-essay coefficient of variation was 2.6% and 9.8%. Lower limit of detectability was 3.5 pg/mL.

Blood and dialysate samples taken after an eight-hour overnight dialysis dwell to determine concentrations of VEGF were immediately stored at -70°C, before the estimation.

Some of the patients were on chronic treatment with ESA, angiotensin-converting enzyme inhibitors (ACEi) and/or statins. Data concerning the use of previously reported therapeutic agents and data about peritonitis occurrence were collected in our out-patient clinic and/or from medical history.

Statistical analysis

Statistical analysis of the data was performed with SPSS Statistics software package, version 20.0. Data with non-normal distribution were expressed as mean values ± median, while other data were expressed as means ± SD. Differences between groups were analyzed with Student's t-test, χ^2 test and Mann–Whitney test. The Pearson product-moment correlation coefficient and Spearman's rank correlation coefficient were used to analyze correlations. Concentrations of sVEGF and ddVEGF were analyzed with non-parametric tests due to non-normal distribution (CV>30%). Statistically significant difference was p-value less than 0.05.

The Ethical Committee of the School of Medicine, University of Belgrade, approved this study and the patients gave informed consent for participation.

Table 2. Biochemical parameters at the beginning (0) and after six months (6) of peritoneal dialysis

Serum concentration		Mean	SD	Median	Z-test/ F-test
Urea (mmol/L)	0	18.94	5.47	18.10	Z=0.632 p=0.819
	6	18.99	6.11	18.45	
Glycemia (mmol/L)	0	6.25	2.38	5.20	Z=0.316 p=1.000
	6	6.09	2.48	5.25	
Creatinine (μmol/L)	0	661.25	177.65	610.00	Z=0.316 p=1.000
	6	698.85	243.30	642.00	
Albumin (g/L)	0	31.30	5.20	32.00	F=0.159 p=0.692
	6	32.00	5.87	34.00	
Fibrinogen (g/L)	0	5.50	1.41	5.65	F=0.556 p=0.460
	6	5.16	1.50	4.95	
C-reactive protein (IU/L)	0	6.30	6.04	4.10	Z=0.474 p=0.978
	6	6.64	5.63	7.00	
Iron (μmol/L)	0	10.77	5.00	10.00	Z=0.632 p=0.819
	6	10.30	3.68	10.45	
Ferritin (mmol/L)	0	248.23	223.40	201.50	Z=0.632 p=0.819
	6	295.09	253.00	186.50	
Hemoglobin (g/L)	0	99.15	14.52	96.50	F=0.876 p=0.355
	6	102.95	10.90	104.50	
Transferrin saturation (%)	0	30.50	14.09	28.00	Z=0.632 p=0.819
	6	26.50	7.72	28.00	
Cholesterol (mmol/L)	0	5.58	1.71	5.90	Z=0.474 p=0.978
	6	5.97	2.07	5.60	
Triglyceride (mmol/L)	0	1.86	0.95	1.41	Z=0.949 p=0.329
	6	2.10	1.00	1.80	
Total proteins (g/L)	0	63.20	7.33	63.50	F=0.022 p=0.883
	6	62.85	7.65	62.00	

SD – standard deviation

RESULTS

During the follow-up, biochemical parameters corresponded to adequate dialysis according to Kidney Disease Outcomes Quality Initiative guideline recommendations for PD treatment [4]. CBC and iron stores were satisfactory. After six months of PD, serum fibrinogen, total protein, iron, and transferrin saturation insignificantly declined, while mean serum urea, creatinine, albumin, cholesterol, CRP, ferritin and hemoglobin insignificantly increased (Table 2).

The patients' gender and age and diabetes mellitus did not influence sVEGF and ddVEGF at the beginning of chronic PD treatment, as shown in Tables 1 and 3.

After six months of PD, sVEGF concentration increased significantly from 149.33±116.71 pg/mL to 239.36±102.23 pg/mL, p=0.012, while ddVEGF levels showed no significant change (43.55±51.15 vs. 38.44±50.47 pg/mL).

At baseline sVEGF levels significantly correlated with fibrinogen, and after the six-month follow-up they correlated with glycemia. At the beginning and after six months of PD no other significant correlation of sVEGF and investigated biochemical parameters was found. Concentrations of ddVEGF showed no significant correlation with any of the investigated parameters at baseline; after the six-month follow-up a significant correlation was found with serum cholesterol (Table 3).

Concentrations of sVEGF and ddVEGF were lower in patients receiving statins at the beginning (Table 4) and after six months of PD than in patients who were not receiving statin therapy (Table 5). During the first six months of PD treatment, sVEGF and ddVEGF concentrations slightly increased in all patients.

At baseline, the levels of sVEGF and ddVEGF in patients receiving ESA were lower than those in patients not

Table 3. Concentrations of serum (s) and drained dialysate (dd) vascular endothelial growth factor (VEGF) related to gender, age and diabetes mellitus (DM) at the beginning of peritoneal dialysis

Variable		N	Mean	SD	p
sVEGF (pg/mL)	Male	11	166.57	112.10	0.486
	Female	9	128.25	125.43	
ddVEGF (pg/mL)	Male	11	37.52	46.36	0.933
	Female	9	39.57	57.96	
sVEGF (pg/mL)	≤65 years	13	119.96	113.29	0.132
	>65 years	7	203.86	110.12	
ddVEGF (pg/mL)	≤65 years	13	35.82	43.59	0.790
	>65 years	7	43.31	64.98	
sVEGF (pg/mL)	DM no	9	178.48	115.36	0.325
	DM yes	11	125.47	117.66	
ddVEGF (pg/mL)	DM no	9	37.15	57.58	0.923
	DM yes	11	39.49	46.73	

N – number of patients

Table 4. Correlation of concentrations of serum (s) and drained dialysate (dd) vascular endothelial growth factor (VEGF) and biochemical parameters at the beginning of peritoneal dialysis treatment

Parameters at the beginning	sVEGF		ddVEGF	
	R	p	R	p
Cholesterol	-0.046	0.849	-0.038	0.874
Triglyceride	0.259	0.270	0.100	0.675
Urea	0.042	0.861	-0.181	0.445
Glycemia	-0.029	0.905	0.120	0.615
Total proteins	-0.092	0.699	-0.211	0.372
Albumin	-0.101	0.671	-0.037	0.878
Fibrinogen	0.566	0.009*	0.159	0.503
C-reactive protein	0.403	0.078	0.046	0.849

* – statistically significant

Table 5. Correlation of concentrations of serum (s) and drained dialysate (dd) vascular endothelial growth factor (VEGF) and biochemical parameters after six months of peritoneal dialysis

Parameters after six months	sVEGF		ddVEGF	
	R	p	R	p
Cholesterol	0.012	0.960	0.586	0.007*
Triglyceride	0.015	0.949	0.156	0.511
Urea	0.268	0.254	0.191	0.420
Glycemia	0.569	0.009*	0.280	0.232
Total proteins	-0.092	0.699	-0.211	0.372
Albumin	-0.101	0.671	-0.037	0.878
Fibrinogen	0.566	0.009*	0.159	0.503
C-reactive protein	0.403	0.078	0.046	0.849

* – statistically significant

Table 6. Concentrations of vascular endothelial growth factor (VEGF) in serum (s) and drained dialysate (dd) at the baseline of peritoneal dialysis treatment

Drugs at the baseline			N	Mean	SD	p
ESA	sVEGF (pg/mL)	No	8	166.27	115.30	0.607
		Yes	12	138.03	121.33	
	ddVEGF (pg/mL)	No	8	42.56	61.21	0.790
		Yes	12	35.69	44.66	
ACEi	sVEGF (pg/mL)	No	2	266.29	141.44	0.408
		Yes	18	136.33	110.72	
	ddVEGF (pg/mL)	No	2	93.35	109.96	0.576
		Yes	18	32.34	41.73	
Statins	sVEGF (pg/mL)	No	14	157.33	108.50	0.304
		Yes	6	130.65	143.20	
	ddVEGF (pg/mL)	No	14	37.12	46.54	0.867
		Yes	6	41.52	63.48	

ESA – erythropoietin-stimulating agents; ACEi – inhibitors of angiotensin-converting enzyme

Table 7. Concentrations of vascular endothelial growth factor (VEGF) in serum (s) and drained dialysate (dd) after six months of peritoneal dialysis treatment

Drugs after six months			N	Mean	SD	p
ESA	sVEGF (pg/mL)	No	8	262.13	71.06	0.385
		Yes	12	224.19	119.21	
	ddVEGF (pg/mL)	No	8	26.59	19.05	0.166
		Yes	12	54.85	62.76	
ACEi	sVEGF (pg/mL)	No	2	272.94	107.11	0.709
		Yes	18	235.63	104.21	
	ddVEGF (pg/mL)	No	2	15.60	0	0.024*
		Yes	18	46.65	53.12	
Statins	sVEGF (pg/mL)	No	14	239.54	75.01	0.993
		Yes	6	238.96	158.39	
	ddVEGF (pg/mL)	No	14	41.12	41.93	0.827
		Yes	6	49.21	72.91	

* – statistically significant

receiving it (Table 6). After six months of PD treatment, ddVEGF was higher and sVEGF was lower in patients receiving ESA than in patients not receiving it (Table 7). After six months of PD treatment sVEGF increased both in patients on and in those not on ESA. After six months of PD treatment ddVEGF increased in patients receiving ESA, while it decreased in those not receiving ESA. The changes were not statistically significant (Tables 6 and 7).

Patients using ACEi had lower sVEGF levels at the beginning and after six months of PD than those not receiving ACEi (Tables 6 and 7). Patients who received ACEi had lower ddVEGF at the beginning of PD and higher after six months of PD, compared to those not using ACEi (Tables 6 and 7). During the first six months of PD sVEGF increased in all patients, while concentrations of ddVEGF rose in those treated with ACEi, and it decreased in patients not using ACEi.

DISCUSSION

Vasopermeabile and powerful angiogenic VEGF is a glycoprotein with high affinity for endothelial cells. Ischemia, hypo- and hyperglycemia, cytokines and hormones up-regulate VEGF in different cell types and tissues [5]. The VEGF is present on mesothelial cells of peritoneal layer in humans [6], and these cells produce VEGF in vitro [7]. During chronic PD treatment VEGF is up-regulated in peritoneal layer and it is found in drained dialysate [8].

Serum VEGF levels

Concentrations of sVEGF in our patients were similar to those found in other studies [8, 9, 10]. At the beginning of PD treatment they were 149.33±116.71 pg/mL, and after six months of PD they rose up significantly to 239.36±102.23 pg/mL [11].

Key role of VEGF in the development of microvascular hyperpermeability and neoangiogenesis of peritoneal layer on chronic PD has been proved [12]. Neoangiogenesis is responsible for enlargement of effective peritoneal membrane vascular surface and consequently for increase of small molecular solute transport rates [13].

Concentrations of sVEGF at the beginning of PD directly and statistically significantly correlated with fibrinogen serum levels, suggesting contribution of inflammatory state to higher VEGF levels, but after six months of PD the correlation was not found (Table 3). Other investigators found direct correlations between sVEGF levels and chronic inflammatory state defined with plasma concentrations of interleukin-1 (IL-1), CRP and fibrinogen [13].

Concentrations of sVEGF at the beginning of peritoneal dialysis were not affected by gender, age and diabetes mellitus (Table 3).

After six months of PD, sVEGF concentrations correlated directly with glycemia (Table 3), suggesting that higher VEGF concentrations are present in patients with poor metabolic conditions. This is in agreement with other investigators findings that hyperglycemia up-regulates VEGF [6].

Drained dialysate VEGF levels

Referent ranges for ddVEGF concentration during chronic PD are not established. Trace VEGF quantity is present in dialysate, it is partly filtered from systemic circulation and partly synthesized locally in peritoneal layer tissue [7]. Studies have confirmed higher ddVEGF levels than expected if VEGF was only filtered from plasma. It has been suggested that local production contributes to its dialysate level [14]. It is possible that local VEGF production is more substantial than assumed, since two types of receptors with high affinity for VEGF [7] are present in the peritoneal membrane and because neovascularization eliminates VEGF from dialysate [14]. In our study, levels of ddVEGF fell slightly during the first six months of PD treatment (43.55±51.15 vs. 38.44±50.47 pg/ml). As in our group, a wide range of ddVEGF levels is reported in literature [9, 14].

Concentration of ddVEGF after six months of PD treatment correlated with cholesterol (Table 4) suggesting that patients with poorer metabolic characteristics had higher VEGF concentration.

Concentrations of ddVEGF at the beginning of peritoneal dialysis were not affected by gender, age and diabetes mellitus (Table 3).

Influence of ESA treatment on serum and drained dialysate VEGF levels

In our study, treatment with ESA did not significantly influence levels of sVEGF and ddVEGF (Tables 6 and 7).

Our findings are not in agreement with other investigators', reporting significantly higher sVEGF concentrations in patients on ESA compared to those not using ESA (375±220 pg/ml vs. 251±75 pg/mL) [15]. A recent study also found a positive correlation between ESA therapy and plasma concentrations of VEGF and angiogenin – the VEGF mediator of neoangiogenesis, proving that erythropoietin (EPO) dose may affect plasma VEGF levels in chronic hemodialysis patients [16].

There are no data on the relationship between ddVEGF levels and EPO therapy in human pathology, but in a rat experimental model of chlorhexidine-induced fibrosis the beneficial effect of high intra-peritoneal EPO doses was demonstrated [17].

EPO enhances proliferation of endothelial cells in vitro. In bovine aorta culture EPO and VEGF synergistically promote erythropoiesis and endothelial cells proliferation [18], and EPO is a co-mitogen of VEGF. Molecules of EPO and VEGF are similar, hypoxia induces expression of their genes and they both express action on target cells through tyrosine kinase receptors [19].

Influence of ACEi treatment on serum and drained dialysate VEGF levels

In our study, patients receiving ACEi at baseline had sVEGF and ddVEGF levels insignificantly lower than those not using ACEi (Table 6). After six months of PD patients using ACEi had significant sVEGF increase (p=0.007), and ddVEGF was insignificantly higher compared to those not using ACEi (Table 7).

There are no sufficient literature data about the relationship between ACEi therapy and sVEGF and ddVEGF concentrations. Our findings are partly in agreement with experimental and clinical findings that during long term PD treatment ACEi act as protectors of the peritoneal layer and have positive influence on dialysis quality [20]. Experimental data have proved that ACEi protect peritoneal membrane from hyperosmolar glucose-based PD solutions [21] blocking angiotensin II, which stimulates synthesis of inflammatory cytokines and thus promotes angiogenesis and fibrosis [22].

An in vitro study demonstrated that incubation of human mesothelial cells, the major source of intraperitoneal VEGF, with captopril led to concentration-dependent decrease of VEGF synthesis, suggesting that inhibition of angiotensin II in the peritoneal membrane could be a therapeutic option for membrane preservation during long-term PD treatment [21].

In human pathophysiology, one of the potential mechanisms of peritoneal membrane damage is the presence of local renin-angiotensin-aldosterone system (RAAS) by which angiotensin II from injured peritoneal mesothelial cells activates VEGF and other cytokines' expression and enhances epithelial-to-mesenchymal transition, which leads to fibrosis and neoangiogenesis in submesothelial tissue [22]. Recent data seem to demonstrate the benefit of RAAS blockade on preservation of functional characteristics of peritoneal membrane on long-term PD [23, 24].

Studies in humans proved that chronic PD patients using ACEi and/or blockers of angiotensin receptors (ARB) had lower small molecules peritoneal transport rate [23] and higher urea and creatinine clearances compared to group using placebo [24]. In our study lower rise of ddVEGF levels in patients using ACEi compared to rise of sVEGF levels during the first six months of PD could implicate some protective effect of ACEi therapy on peritoneal layer.

Influence of statins treatment on serum and drained dialysate VEGF levels

Treatment with statins did not significantly influence levels of sVEGF and ddVEGF during the follow up (Tables 6 and 7). In our study, sVEGF concentrations were continually lower and increased more, while concentrations of ddVEGF were higher in patients using statins. The inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase, the so-called statins, are effective in controlling hypercholesterolemia and they have antioxidant, anti-inflammatory, immunomodulatory, antiatherosclerotic, renoprotective and antithrombotic effects [25]. Different statins significantly reduce VEGF synthesis in human smooth muscle cells and in microvascular endothelial cells, although in the same doses statins up-regulate the VEGF synthesis in macrovascular human endothelial cells [26]. It has been found that statins reduce risk of all-cause mortality in patients on chronic PD treatment and have theoretically beneficial effects on peritoneal membrane remodeling during long-term PD treatment [27]. There are no data about the influence of statin therapy on serum and effluent VEGF concentrations in patients on chronic PD treatment. In an experimental rat model of PD, addition of atorvastatin to drinking water resulted in significant preservation of membrane function and significantly lower effluent VEGF concentrations [28].

Limitation of the study

The limitation of our study was the small size of our study sample and relatively short observation period.

CONCLUSION

Concentrations of VEGF in serum and drained dialysate in patients on chronic PD treatment were influenced with worsening of metabolic profile. More patients and a longer follow-up are advisory to assess other factors influencing the serum and drained dialysate VEGF concentrations and to find agents reducing concentrations of VEGF in PD patients.

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Васкуларни ендотелни фактор раста у серуму и дијализату у првих шест месеци перитонеумске дијализе

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КРАТАК САДРЖАЈ

Увод Хронична перитонеумска дијализа (ПД) стимулише стварање васкуларног ендотелног фактора раста (*VEGF*).

Циљ рада Циљ ове проспективне студије био је да се одреде концентрације *VEGF* у серуму (*s*) и изливеном дијализату (*dd*) у првих шест месеци примене ПД и процени однос између ових концентрација и демографских одлика, биохемијских параметара, коморбидитета, појава перитонитиса и примене појединих лекова код болесника на ПД.

Методе рада Истраживањем је обухваћено 20 болесника просечне старости од 62,9±12,69 година, од којих је 11 имало дијабетес. Концентрације *VEGF* и биохемијских параметара одређиване су у узорцима венске крви узетим наташте на почетку и после шест месеци лечења применом ПД.

Резултати Концентрација *VEGF* у серуму (*sVEGF*) била је статистички значајно виша после шест месеци примене ПД, док се концентрација у дијализату није значајно променила. На почетку ПД *sVEGF* је била статистички значајно повезана с нивоом фибриногена у серуму, а после шест месеци са нивоом фибриногена у серуму и гликемијом. Код болесника који су примали стимулаторе еритропоезе (*ESA*) концентрација *ddVEGF* је порасла после шест месеци примене ПД, док се код оних који нису примали *ESA* ниво *ddVEGF* смањио. Насупрот томе, концентрација *sVEGF* се повећала током шест месеци примене ПД код болесника који нису добијали *ESA*. Нивои *sVEGF* и *ddVEGF* били су безначајно нижи код болесника који су узимали *ACE*-инхибиторе него код оних који их нису користили. Код болесника који су узимали *ACE*-инхибиторе забележен је значајан пораст концентрације *sVEGF* и *ddVEGF*. Примена статина није значајно утицала на нивое ових параметара.

Закључак Концентрација *VEGF* у серуму и дијализату код болесника на ПД је повезана с лошијим метаболичким профилом, док ће улога инфламације и терапије бити предмет наших будућих истраживања.

Кључне речи: перитонеумска дијализа; *VEGF*; статини; еритропоетин-стимулишући фактори; инхибитори ангиотензин-конвертујућег ензима

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