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ORIGINAL ARTICLES

STUDY OF CA-125 AND VEGF BIOMARKERS IN DRAINED PERITONEAL SOLUTION IN PERITONEAL DIALYSIS PATIENTS

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ABSTRACT

INTRODUCTION: During long-term treatment with peritoneal dialysis, structural and functional changes occur in the peritoneal membrane (PM). Peritoneal biopsy is the gold standard for detecting histopathological changes in the peritoneum, but as an invasive procedure it is not applied routinely. In the clinical practice, noninvasive Peritoneal Equilibration Test is used, but as it is not completely informative, new noninvasive methods are needed.

AIM: The aim of this article is to evaluate the applicability of new non-invasive carbohydrate antigen 125 (CA-125) and vascular endothelial growth factor (VEGF) biomarkers in drained peritoneal dialysate for assessment of the functional status of the peritoneal membrane in peritoneal dialysis (PD) patients.

MATERIALS AND METHODS: A total of 35 patients (22 men and 13 women; aged 28 to 78 years) on peritoneal dialysis were included in the study. Creatinine ratio between dialysate and plasma was measured by Jaffe's method both at the beginning and at the end of the study. CA-125 and VEGF in drained peritoneal dialysate were determined by ELISA at 4h and 12h dwell time both at the beginning and at the end of the study. Standard statistical methods were used and $p<0.05$ was accepted as statistically significant.

RESULTS: During follow-up we observed significant decrease in D/P-creatinine values, significant decrease in drained peritoneal dialysate volume, significant decrease of CA-125 appearance rates, and no significant change in the appearance rate of VEGF. We observed large interindividual variations of the CA-125 biomarker in both at the beginning and at follow-up.

CONCLUSIONS: In our study, CA-125 was more informative for the functional state of the PM as we found a significant decrease of the CA-125 levels which parallels the conventional biomarkers used. Our study did not confirm VEGF as a suitable biomarker for assessment of the PM function as we did not observe significant changes in the VEGF levels during PD treatment. CA-125 testing in PD would have advantages as addition to classical tests.

Keywords: *peritoneal dialysis, peritoneal membrane, CA-125 and VEGF biomarkers*

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INTRODUCTION

Peritoneal dialysis (PD) is a method of renal function replacement therapy that is performed at home. The exchange of substances between the blood and the dialysis fluid takes place through the peritoneum, which acts as a dialysis membrane. Many different factors influence the clinical outcomes of PD treatment, but one of the main ones is the peritoneal

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membrane (PM). It plays a key role in the removal of metabolic waste products and in achieving ultrafiltration sufficient to restore and maintain water balance in PD-treated patients.

The PM is composed of two layers—a mesothelial and a submesothelial (interstitial layer) one (1,2). The mesothelium is a continuous surface layer formed by a single row of mononuclear polygonal cells (1,2). They are thought to be involved in preventing the formation of fibrinous adhesions in the peritoneum (3) by secreting phospholipids and phosphatidylcholine, providing a lubricating surface for the movement of abdominal organs (3,4). Mesothelial cells have multiple microvilli, increasing the total membrane surface area many folds. They play an important role in the transport of anionic molecules such as proteins (1,2). Mesothelial cells can release cytokines and growth factors such as IL-1, IL-6, fibrinolysis factors, TGF-β, and growth factors affecting peritoneal transport, such as VEGF. The submesothelial interstitial layer is composed of hyaluronan, glycosaminoglycans, and a fibrous collagen network that provides a scaffold for the embedded structures (1,2). Blood and lymphatic vessels, as well as cells such as fibroblasts, fat cells, macrophages (1,2), etc., are located within it and enter into complex interactions with each other. Structural and functional changes occur in PM with prolonged PD treatment (1,5–10). Peritoneal membrane dysfunction (inadequate solute transport or inadequate water removal) is an emerging factor for PD failure, requiring transfer to hemodialysis. The key factors are (2) repeated episodes of inflammation associated with peritonitis and (1) long-term exposure to bioincompatible PD fluids. Ultrafiltration failure is the most important manifestation. Assessment of the PD membrane is usually done by investigating the transport of small solutes and fluid. The peritoneal equilibration test (PET) is a standardized functional test to assess the transport status of the PM. In PET, peritoneal solute transport is determined by the ratio of the concentrations of substances in the drained dialysate (D) and in the plasma (P)—D/P for creatinine (D/P Cr), and the ratio D/D0 for glucose (D—concentration of glucose at a certain time, D0—baseline concentration of glucose). Changes in the PM affect both layers and are characterized by: mesothelial cell loss, mesothelial-mesenchymal transformation (MMT), thickening of the submesothelial compact zone, fibrosis, neoangiogenesis, and angiopathy (10,11,12). Mesothelial-mesenchymal transformation is accompanied by high carbohydrate antigen 125 (CA-125) concentrations and acceleration of transmembrane transfer, increased glucose absorption, and loss of ultrafiltration capacity of the PM (11).

Peritoneal biopsy is the gold standard for detecting histopathological changes in the peritoneum, but it is not applied as a routine procedure in clinical practice. It is invasive—complications requiring temporary interruption of PD are possible, it carries a risk of adhesions (12,13), and there is uncertainty about sampling errors and reproducibility of results (14). Novel noninvasive methods to assess PM are needed, and cytokines, growth factors, and other candidate biomarkers in drained peritoneal fluid have been investigated in recent years with the idea of routine application for noninvasive assessment and monitoring of PM in PD patients.

CA-125 was discovered in 1981 (14) and is a transmembrane mucin-type glycoprotein (15,16) with a negatively charged structure and the ability to bind to specific cellular receptors (18,19). Mesothelial cells of PM produce CA-125, which is thought to form a protective barrier on mucosal surfaces (20) and protect against adhesion of pathogens to the apical zone of cells. In patients treated by PD, the potential CA-125 biomarker has been studied in drained peritoneal solution (10,21,22). In some studies, CA-125 in drained peritoneal solution is used as a biomarker of mesothelial cell mass (14,23,11) and PM remodeling (23). Some authors, Lai et al. (27) and Breborowicz et al. (28), concluded that CA-125 does not reflect the mesothelial cell mass. They found that it did not correlate with the number of cells in the monolayer of mesothelial cultures. Factors such as patient age, inflammatory state and a history of exposure to high glucose content, rather than just the number of mesothelial cells, were found to influence the level of CA-125. The observations mentioned lead to uncertainty about the biological and diagnostic importance of CA-125 in peritoneal dialysis effluent (PDE). Despite extensive research, our understanding of this biomarker remains limited, and the clinical relevance of elevated CA-125 levels in PDE is still unknown (30).

Vascular endothelial growth factor (VEGF) is a glycoprotein that stimulates blood vessel formation during embryogenesis and wound healing (24). It is also involved in angiogenesis in pathological processes such as tumor growth, diabetic retinopathy, etc., and in MMT of the PM in PD. VEGF is produced locally and can be measured in drained peritoneal solution (24). Normal (as well as malignant) mesothelial cells express VEGF receptors and co-receptors (25). VEGF and its receptors are key factors in almost all stages of neoangiogenesis in PD (25). Mesothelial-mesenchymal transformation is accompanied by acceleration of transmembrane transfer, increased glucose absorption, and loss of peritoneal membrane ultrafiltration capacity (11), and target therapy options are being explored to prevent VEGF-mediated peritoneal neoangiogenesis (25). Elevated VEGF level significantly correlates with peritoneal membrane function (D/P Cr) and moreover, effluent VEGF can predict the peritoneal solute transport rate in clinical practice (25). In patients undergoing PD, VEGF levels in the peritoneal dialysate tend to increase. This increase is mainly a response to the inflammation and hypoxia that occur in the PM during dialysis. The continuous contact of PM with the dialysis solution, especially when using high-glucose-based solutions, can create an inflammatory environment that triggers the release of VEGF (25).

AIM

The aim of this study was to evaluate the applicability of new non-invasive biomarkers CA-125 and VEGF in drained peritoneal dialysate for assessment of the functional status of the PM in PD patients.

DESIGN, PATIENTS AND METHODS

The study was prospective, included 35 patients (22 men and 13 women; aged 28 to 78 years) who signed informed consent to participate in the study and last from 2021 to 2023. The research was approved through protocol number 101 dated 24/03/2021 of the local Ethics Committee. All patients were dialyzed with conventional glucose-based, low pH dialysis solutions and followed up at two university hospitals in Bulgaria. Information about treatment with erythropoietin or statins was extracted from the medical records.

Peritoneal equilibration test (PET) was assessed as paired creatinine measurement by Jaffe's method in drained peritoneal dialysate (DPD) and blood plasma and calculated as D/P Cr ratio. The CA-125 and VEGF biomarkers in DPD were examined at study initiation and followed up after one year, both at the 4-hour stay (within the PET) and at the 12-hour stay of the dialysis solution in the peritoneal cavity. Sampled DPD was centrifuged at 1500×g for 10 minutes at room temperature and supernatant was stored at -80°C until analysis. CA-125 in DPD was analyzed with Quantikine ELISA Human CA125/MUC16 Immunoassay, Catalog No. DCA125, R&D Systems, USA according to manufacturer's instructions. VEGF in DPD was analyzed with Quantikine ELISA Human VEGF Immunoassay, Catalog No. DVE00, R&D Systems, USA according to manufacturer's instructions.

Effluent samples were obtained during regular outpatient visits and appearance rates (ARs) were calculated. The AR is the amount of CA-125 or VEGF present in the total drained effluent divided by the duration of the dwell time in minutes according to the following equation:

AR = ([Protein] × Volume effluent) / Dwell time (26)

Statistical analysis was performed by Jamovi v2.6 and descriptive statistics, paired samples T-test, Wilcoxon rank W-test, Pearson correlation matrix, and Spearman's rank correlation tests were used and $p<0.05$ was accepted as statistically significant.

RESULTS AND DISCUSSION

On conventional PM examination, we found a significant decrease in D/P Cr values, presented as average ± standard deviation, (0.728 ± 0.105 vs. 0.700 ± 0.116, n = 35, W = 435, p = 0.05, respectively) and a significant decrease in DPD volume (3157 mL ± 3106 mL vs. 3120 mL ± 3063 mL, n=35, W= 66, p=0.002, respectively) during the follow-up period.

In Table 1 are presented D/P Cr and Drained dialysate/12h determined at the beginning and at the end of the study.

When PM was examined by biomarkers in DPD, we observed large interindividual variations of the CA-125 biomarker in DPD, also found in other studies (26): 14.44÷383.86 U/mL for the beginning of the study and 46.67÷3267.91 U/mL after one year.

Table 1. D/P Cr and Drained dialysate [mL]/12h.

	N	Average	Median	Standard Deviation	Wilcoxon Rank Test
D/P Cr in the beginning	35	0.728	0.730	0.105	W = 435, p = 0.05
D/P Cr in the end	35	0.700	0.720	0.116	
Drained dialysate [mL] in the beginning	35	3157	2400	3106	W = 66, p = 0.002
Drained dialysate [mL] in the end	35	3120	2300	3063	

The results of AR CA-125 [U/min] in drained peritoneal solution at 12 h of solution residence in the peritoneal cavity at the beginning of the study (AR V1 CA-125) and after 1 year (AR V3 CA-125) are presented in Table 2.

At the end of the study, we found a statistically significant positive correlation between AR CA-125 levels and DPD/24h volume: r=0.579 (p<0.001) (Table 3).

The relationship between AR CA-125 and administered medications, statins and erythropoietin (EPO), was analyzed by Spearman's correlation. There was no significant association of AR CA-125 with the indicated medications (Table 4).

Table 2. AR CA-125 [U/min] in drained peritoneal solution at 12h at the beginning of the study and after 1 year.

	N	Average	Median	Standard Deviation	Wilcoxon Rank Test
AR CA-125 [U/min] in the beginning of the study	35	152.1	130.5	124.8	W = 489, p = 0.004
AR CA-125 [U/min] after 1 year	35	89.2	72.6	75.9	

During follow-up, biomarker CA-125 in DPD significantly decreased (152.1±124.8 U/mL vs. 89.2 ± 75.9 U/mL; n=35, W=489, p=0.004) (Fig. 1).

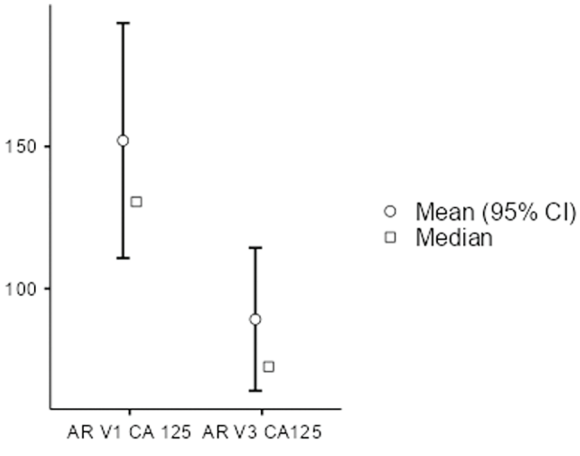

Fig. 1. Changes in AR CA-125 [U/min] over the 1-year follow-up period.

In the cross-sectional study, the mean AR VEGF in drained peritoneal solution was 357 ± 666 pg/min (AR VEGF V1 [pg/min]) at 12 h of dialysis solution residence in the peritoneal cavity and 459 ± 268 pg/min (AR VEGF V2) at 4 h of residence. We found no significant change in the VEGF biomarker in the DPD at follow-up (W = 361, p = 0.461). At study entry, we found no correlation between duration of PD treatment and VEGF biomarker in DPD. We found no correlation between therapy with statins (r=0.064, p=0.767), EPO (r=0.329, p=0.066), and changes in VEGF. In some studies, serum VEGF concentrations were significantly higher in long-term PD patients, and peritoneal effluent VEGF concentrations were

Table 3. AR CA-125 and dialysate volume drained—Pearson's coefficient.

		AR CA-125 at 12 h Dwell	AR CA-125 at 4 h Dwell
Drained dialysate/24 h	Pearson's r	0.579***	-0.218
	p-value	p < 0.001	p = 0.208

*Note. * p < .05, ** p < .01, *** p < .00; p<0.05 is considered statistically significant.*

Table 4. AR CA-125 [U/min] and administered medications—Spearman's coefficient.*

		AR V1 CA-125 [U/min] (12h Dwell at the Beginning of the Study)	AR V2 CA-125 [U/min] (4h Dwell at the Beginning of the Study)	AR V3 CA-125 [U/min] (12h Dwell at the End of the Study)	AR V4 CA-125 [U/min] (4h Dwell at the End of the Study)
Statins	Spearman's rho	0.027	0.173	-0.246	-0.082
	p-value	0.899	0.419	0.247	0.704
EPO	Spearman's rho	-0.047	0.000	0.087	0.063
	p-value	0.802	0.999	0.640	0.736

Table 5. Spearman's correlation coefficient (rho) for the association between AR VEGF [pg/min] and duration of PD and medical treatment with statins and EPO.*

		AR V1 VEGF [pg/min] (12h Dwell at the Beginning of the Study)	AR V2 VEGF [pg/min] (4h Dwell at the Beginning of the Study)	AR V3 VEGF [pg/min] (12h Dwell at the End of the Study)	AR V4 VEGF [pg/min] (4h Dwell at the End of the Study)
PD treatment time	Spearman's rho	-0.124	-0.198	-0.211	-0.405*
	p-value	0.476	0.255	0.223	0.016
Statins	Spearman's rho	-0.027	0.355	0.046	-0.064
	p-value	0.899	0.089	0.833	0.767
EPO	Spearman's rho	-0.059	-0.000	-0.076	-0.329
	p-value	0.750	0.998	0.679	0.066

significantly lower in patients receiving statins, suggesting a protective effect of those drugs on peritoneal membrane (29). In one Spanish study, patients treated with EPO showed significantly higher serum levels of VEGF than non-treated patients (30).

When Spearman's correlation coefficient (rho) was determined for the relationship between AR VEGF and duration of PD and medical treatment with statins and EPO, none was found (Table 5).

We attributed the VEGF results to the small group of patients and the relatively short follow-up period.

Table 6. VEGF in drained peritoneal dialysate at the beginning (AR V1 VEGF [pg/min]) and at the end of the study (AR V3 VEGF [pg/min]) with 12h stay of dialysis solution in the peritoneal cavity.

	N	Average	Median	Standard Deviation	Wilcoxon Rank Test
AR V1 VEGF [pg/min]	35	357	171	666	W = 361, p = 0.461
AR V3 VEGF [pg/min]	35	350	136	640	

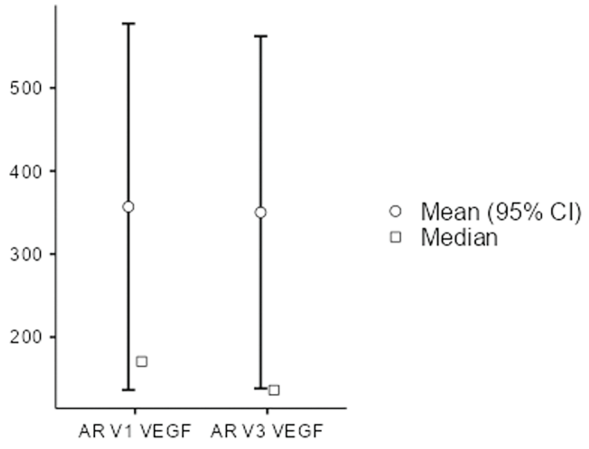

Fig. 2. Changes in AR VEGF [pg/min] over the 1-year follow-up period.

CONCLUSION

In our study, CA-125 was more informative for the functional state of the PM as we found a significant decrease of the CA-125 levels which parallels the conventional biomarkers used. In contrast, our study did not confirm VEGF as a suitable biomarker for assessment of the PM function as we did not observe significant changes in the VEGF levels during PD treatment.

CA-125 testing in PD would have advantages vs. transmembrane transport of low-molecular-weight substances and ultrafiltration capacity as it is less labor-intensive, does not require calculations after the results are received from the laboratory, does not require a four-hour patient stay at the PD center and the test is non-invasive and can be repeated multiple times, making it suitable for PM monitoring.

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