Effluent biomarkers in peritoneal dialysis: A captivating symphony from the peritoneal membrane

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CHAPTER 9

Clinical Relevance of Free Water Transport and Effluent Biomarkers in the Early Identification of Encapsulating Peritoneal Sclerosis

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ABSTRACT

Background Currently no diagnostic tool or methodology is available for the early detection of encapsulating peritoneal sclerosis (EPS). The objective of this study is to investigate and construct a panel of effluent biomarkers in conjunction with free water transport (FWT) to monitor peritoneal dialysis (PD) treatment and aid early identification of EPS.

Methods A case-control study nested in the longitudinal cohort of PD patients from our center was conducted. Time-specific areas under the ROC curve were calculated for FWT and various effluent biomarkers at a lag time up to three years before EPS diagnosis. Finally, FWT was combined with effluent appearance rates (AR) of CA125, IL-6 or PAI-1 to assess the clinical validity of the diagnostic panel.

Results The quantity of FWT and effluent biomarkers AR was investigated in 11 EPS patients and 34 long-term PD patients. The diagnostic performance was most favorable for FWT followed by PAI-1 AR. Throughout the diagnostic panels of FWT and AR of CA125, IL-6 or PAI-1 high specificity estimates above 84% were yielded. The combination of FWT and PAI-1 AR identified the largest proportion of EPS patients at one year prior to diagnosis.

Conclusions Measurement of effluent biomarkers complementary to peritoneal function test provides an all-round insight into the state of the peritoneal membrane. Our data indicate that an effluent biomarker panel including the quantity of FWT may aid in the early detection of EPS where high estimates of specificity are required to avoid unnecessary discontinuation of PD treatment.

INTRODUCTION

EPS is the most severe complication of peritoneal dialysis, which causes the peritoneum to become a thick fibrous membrane and forces to discontinue PD treatment. Mortality rates after the diagnosis of EPS ascend to 50%.[1] The long-term exposure of peritoneal dialysis (PD) solutions, high in glucose and glucose degradation products, has been described to be one the pivotal factors in the development of encapsulating peritoneal sclerosis (EPS).[1,2] However, only 3% of the PD patients eventually develop EPS.[1,3] At present the available diagnostic strategies comprise routine clinical assessments by means of symptoms of bowel obstruction and inefficacy of PD treatment. For confirmation of EPS diagnosis, laparoscopy or laparotomy is usually performed. Less invasive are radiologic assessments, but early detection of EPS is not possible since anatomical abnormalities are not observable.[4] Either way, in both appraisals the preclinical phase of EPS is far advanced. It is therefore essential that the discrepancies that lie at the origin of this harmful complication are elucidated and that novel non-invasive diagnostic instruments for the early detection of EPS are introduced.

Several methodologies are applied in assessing the effectiveness of PD treatment. From the effluent where the functionality of the peritoneal membrane is established by measuring transperitoneal transport and fluid removal, one can also detect markers that reflect pathophysiological processes as well as those associated with PD related clinical outcomes. Alongside the increased prevalence of late ultrafiltration failure EPS patients are characterized by impaired free water transport (FWT)[3] or a low osmotic conductance.[5] FWT is a parameter, which can be easily assessed by the modified peritoneal equilibration test whilst the osmotic conductance requires more extensive calculations.[6] FWT occurs through aquaporins, however, relative normal aquaporin expression levels has been described in one patient with ultrafiltration failure.[7] This suggests that a functional loss of the aquaporins can occur.

Histological studies have indicated that anatomical peritoneal membrane alterations associated with EPS evolve extensive abnormalities of the microvascular wall and fibrosis of interstitial tissues.[8,9] Also, the mesothelium is absent in approximately half of PD patients.[9] Potentially this is a consequence of the early onset of epithelial-to-mesenchymal transition of mesothelial cells. Interestingly, morphometric data did not reveal a relationship between the degree of fibrosis and inflammation.[9] The lack of correlation suggests deregulation of the local host response and production of vasoactive substances.

Over the past years a number of effluent markers have been related to the development of EPS.[10] To date only cancer antigen 125 (CA125) and interleukin-6 (IL-6) indicated clinical validity.[11] CA125 is considered as a representative of the mesothelial cell mass, IL-6 a reflectant of the degree of peritoneal inflammation and more recently plasminogen activator inhibitor-1 (PAI-1) as a marker for peritoneal fibrosis.[10] Hence, in this study optimal effluent biomarker combinations between CA125, IL-6 and PAI-1 are gauged in conjunction with FWT to investigate their clinical significance in PD treatment and the diagnosis of EPS.

PATIENTS AND METHODS

Study population and data collection

Data for the present study origins from the case-control studies that evaluated peritoneal transport parameters and effluent biomarkers[3,11] in 11 EPS cases and 34 long-term controls, nested in the longitudinal cohort of adult PD patients from our center. Clinical characteristics of the patients have therefore been reported previously.[11] The EPS cases represent the total number of EPS patients diagnosed within our PD unit from 1995 until 2008. No novel EPS patient has been identified ever since. Affirmation of EPS was by autopsy, laparotomy or radiologic examinations and reviewed by two experienced nephrologists and a radiologist. For each EPS case, three controls were randomly selected from the similar source population with a treatment duration of at least 57 months and remained EPS-free in the following three years.

To monitor the efficacy of PD treatment in terms of peritoneal membrane function, yearly standard peritoneal permeability analyses (SPA) were performed in all patients with a 3.86% glucose based dialysis solutions to which a volume marker was added.[12] Withdrawn dialysate specimens after this four-hour SPA were processed immediately and archived in a manual freezer at a temperature of at least -20°C. For biochemical determinations the dialysate samples were retrieved and defrosted. Homogenization of dialysate samples was followed by centrifugation prior to the biochemical determinations of CA125, IL-6, PAI-1 and vascular endothelial growth factor (VEGF) by means of enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, USA). The prospective collection of dialysate samples without verification of potential EPS diagnosis, allowed the retrospective longitudinal analysis of these promising effluent biomarkers.

Calculations and statistical analysis

The quantity of FWT was assessed by means of sodium (Na^+) kinetics after one hour of a standardized 3.86% dwell.[13,14] In brief, $FWT_{0\text{-}60}$ is calculated by subtracting the Na^+ transported through the small pores from the total net fluid transport. In addition, appearance rates of the markers were calculated to account for the drained effluent volume.

The association between the degree of inflammation and fibrosis was investigated by means of IL-6 AR and PAI-1 AR. Furthermore, time-specific ROC curves were computed for the quantity of $FWT_{0\text{-}60}$ and AR of CA125, IL-6, PAI-1 and VEGF with a lag time of maximum three years prior to the diagnosis of EPS. From these ROC curves, the area under the curve, including 95% confidence intervals were calculated as well as estimates of sensitivity and specificity. Threshold values for each parameter and effluent marker were based on the Youden's Index.[15] Consequently, these threshold values were used to assess the diagnostic accuracy of the combination between quantity of $FWT_{0\text{-}60}$ and the effluent biomarkers.

In a sensitivity analysis we isolated the PD patients who exhibit persistent low CA125 levels to investigate a potential effect on diagnostic accuracy measures with regard to PAI-1 AR. A persistent low level of CA125 was defined as two or more AR values below 100 U/min. Additionally, as EPS is a rare disease and unnecessary discontinuation of PD treatment is unwarranted, a second analysis was performed aimed at including EPS diagnosis. For this purpose the threshold values for the effluent biomarkers were based on pre-defined minimally acceptable true positive rates of 75%. The threshold of absolute $FWT_{0\text{-}60}$ was based on where the lower limit of $FWT_{0\text{-}60}$ was 55.0 mL in long-term (>5 years) PD patients with ultrafiltration failure.[16] All statistical analyses were performed within SPSS Statistics 21.0 and statistical significance was indicated by p-values below 0.05.

RESULTS

As morphological differences are present between patients who develop EPS and controls, we assessed correlations between peritoneal inflammation and fibrosis within these two patient groups. A positive correlation was present in long-term PD patients between IL-6 AR and PAI-1 AR (r=0.45, p=0.008). In contrast, this relationship was absent within patients who developed EPS (r=0.24, p=0.51).

Table 1 presents the time-specific area under the receiver operating characteristic

(ROC) curves for the quantity of FWT_{0-60} and various effluent markers. The diagnostic performance was the highest for quantity of FWT_{0-60}, which illustrated a maximum AUC of 0.94 (95% confidence interval 0.88-1.00). Based on the time-specific AUCs, AR of CA125, IL-6 and VEGF were unable to distinguish EPS patients from the long-term controls. PAI-1 AR showed reasonable capacity to discriminate between long-term PD patients and those who develop EPS from a lag time of three years onwards.

Table 1. Time-specific area under the receiver-operating characteristic curve for various effluent markers appearance rates at a maximum lag time of 3 years prior to the diagnosis of EPS.

	Area under the ROC curve (95% CI)		
Lag time[a] (years)	**1**	**2**	**3**
FWT_{0-60} (mL)	0.94 (0.88 - 1.00)***	0.87 (0.73 - 1.00)***	0.92 (0.81 - 1.00)***
CA125 AR (U/min)	0.63 (0.36 - 0.89)	0.47 (0.24 - 0.69)	0.70 (0.44 - 0.95)
IL-6 AR (pg/min)	0.62 (0.41 - 0.84)	0.65 (0.40 - 0.91)	0.67 (0.41 - 0.92)
PAI-1 AR (ng/min)	0.77 (0.63 - 0.91)**	0.72 (0.54 - 0.90)*	0.71 (0.52 - 0.91)
VEGF AR (pg/min)	0.68 (0.47 - 0.88)	0.59 (0.36 - 0.83)	0.63 (0.41 - 0.85)

AR: appearance rates; CA125: cancer antigen 125; CI: confidence interval; EPS: encapsulating peritoneal sclerosis; FWT_{0-60}: free water transport at 60 minutes; IL-6: interleukin-6; PAI-1: plasminogen activator inhibitor-1; ROC: receiver-operating characteristic; VEGF: vascular endothelial growth factor.
[a] Time from dialysate sampling to EPS diagnosis. * $p<0.05$, ** $p<0.01$, *** $p\leq0.001$.

Figure 2 depicts estimates of sensitivity and specificity for the quantity of FWT_{0-60} and the effluent markers AR at a lag time of one (panel A) and two (panel B) years before the diagnosis of EPS in which threshold values are based on Youden's Index. Throughout, estimates of sensitivity were the highest for VEGF AR accompanied by low specificity. The quantity of FWT_{0-60} indicated the most optimal balance between sensitivity and specificity estimates. Based on these data, a combination was made between the quantity of FWT_{0-60} and AR of CA125, IL-6 or PAI-1 at one year prior to the diagnosis of EPS (Table 2). A high specificity estimate was present within all panels. The panel with CA125 AR was positive for 63% of EPS patients whilst for the AR of IL-6 and PAI-1 respectively 70% and 100% of the EPS patients could be identified.

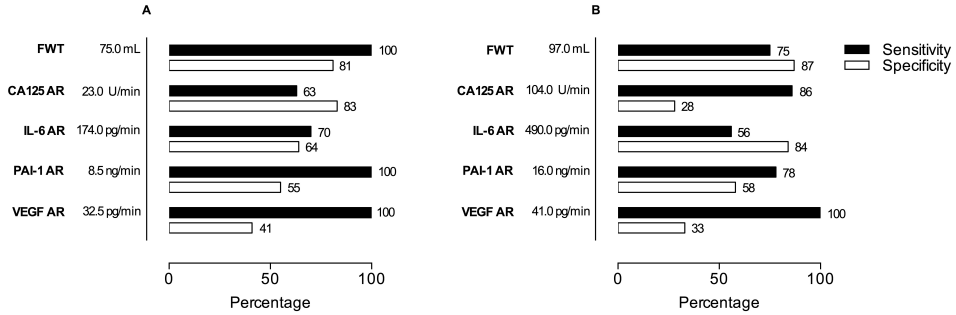

Figure 1. Diagnostic accuracy measures are depicted for quantity of $FWT_{0\text{-}60}$, CA125 AR, IL-6 AR, PAI-1 AR and VEGF AR. These graphs illustrate the threshold values for each parameter at a time lag of one year (Panel A) and two years (Panel B) accompanied by their corresponding estimates of sensitivity (solid bars) and specificity (open bars).

Table 2. Diagnostic accuracy measures for quantity of free water transport combined with effluent biomarkers at one year prior to EPS diagnosis.

	Sensitivity (%)	Specificity (%)
$FWT_{0\text{-}60}$ <75.0 mL & PAI-1 AR >8.5 ng/min	100	94
$FWT_{0\text{-}60}$ <75.0 mL & IL-6 AR >174.0 pg/min	70	94
$FWT_{0\text{-}60}$ <75.0 mL & CA125 AR <23.0 U/min	63	94

AR: appearance rates; CA125: cancer antigen 125; $FWT_{0\text{-}60}$: free water transport at 60 minutes; IL-6: interleukin-6; PAI-1: plasminogen activator inhibitor-1.

The sensitivity analysis in which the diagnostic accuracy of PAI-1 was re-evaluated, a total number of 32 patients was classified as PD patients exhibiting continuous low levels of CA125 AR. In this analysis the AUC for PAI-1 at one year prior to EPS diagnosis had improved to 0.82 (95% confidence interval 0.66-0.98).

The second sensitivity analysis revealed a marginal difference in estimates of sensitivity and specificity (Table 3). The proportion of identified EPS cases from the three panels ranged from 67-75%, accompanied by decent specificity. In this analysis a quantity of $FWT_{0\text{-}60}$ less than 55.0 mL indicated a positive test result. With regard to the effluent markers positive test results were CA125 AR values beneath 106.0 U/min, IL-6 AR above 93.5 pg/min or PAI-1 AR exceeding 9.0 ng/min.

Table 3. Diagnostic accuracy measures for quantity of free water transport combined with effluent biomarkers at one year prior to EPS diagnosis for a desired rule in policy.

					Sensitivity (%)	Specificity (%)
FWT_{0-60} <55.0 mL	**&**	**PAI-1 AR**	**>9.0**	**ng/min**	75	97
FWT_{0-60} <55.0 mL	**&**	**IL-6 AR**	**>93.5**	**pg/min**	67	94
FWT_{0-60} <55.0 mL	**&**	**CA125 AR**	**<106.0**	**U/min**	71	84

AR: appearance rates; CA125: cancer antigen 125; FWT_{0-60}: free water transport at 60 minutes; IL-6: interleukin-6; PAI-1: plasminogen activator inhibitor-1.

DISCUSSION

Currently no non-invasive methodology is available to detect EPS in a pre-clinical phase. In this study we constructed a diagnostic panel containing the amount of FWT during the first hour of a dialysis dwell with a 3.86/4.25% glucose-based solution as functional parameter and four-hour effluent biomarkers as indicators of morphological modifications. This was done by investigation of diagnostic accuracy measures. In the present study we were able to indicate the clinical relevance of FWT in conjunction with effluent CA125, IL-6 and PAI-1. We found that the panel comprising the quantity of FWT and PAI-1 AR is the most promising panel in making a prediction of imminent of EPS.

The diagnostic performance of CA125, IL-6 and VEGF in EPS has been studied previously by our group.[12] Nonetheless, the current analyses expanded our knowledge with regard to these effluent markers by the establishment of time-specific AUCs and threshold values based on the Youden's Index and pre-specified minimally acceptable true and false positive rates. Only a limited number of studies have investigated peritoneal transport parameters in the preceding years of EPS diagnosis in which solely FWT depicted a different time course.[3] No study has formerly reported measures of diagnostic accuracy for FWT. The present study showed clinically acceptable AUCs for quantities of FWT in the years prior to the diagnosis of EPS. It is noteworthy that the AUC for FWT remains high up to a lag time of three years. This indicates that potential therapies with steroids or tamoxifen might be induced at an early stage thus allowing suppression or treatment of EPS.[17-20] Estimates of sensitivity and specificity suggested an optimal threshold of 75.0 mL for FWT. Nevertheless, FWT is the only functional parameter that is indicative for EPS in which clinical experience suggest that a more stringent estimate of specificity is warranted. Hence, a FWT threshold of 55.0 mL was utilized in a sensitivity

analysis to compose a panel with either AR of CA125, IL-6 or PAI-1. This analysis had a marginal effect on the diagnostic accuracy measures.

As expected there was no differential ability for VEGF. Although local peritoneal production is present in all PD patients and strong correlations with small solute transport have been found.[21] The high sensitivity of VEGF AR is in accordance with morphometric data in which vascular abnormalities are present in all EPS patients.[9,10] Our findings are further supported by the non-divergent time course and effluent levels of VEGF.[12] Moreover, VEGF requires a concentration process of the dialysate specimens beforehand proper biochemical assessment due to its low appearance.

Interestingly, when CA125 AR were analyzed by the time-specific ROC curve a discriminative potential was absent one year before the diagnosis, although a higher AUC value was found at the longest lag time. This is probably due to the fact that some patients exhibit a persistent low level of dialysate CA125 or have marked reductions over time,[22,23] which contributes to coinciding dialysate levels between long-term PD patients, and patients who develop EPS. Additionally, the expression of CA125 by mesothelial cells varies per patient and may be even absent from the start of PD treatment.[24] Therefore, we further analyzed PAI-1 AR in patients who continuously exhibited CA125 AR levels of lower than 100 U/min. In this sensitivity analysis the discriminative capacity of PAI-1 AR was enhanced. The combination between CA125 AR and quantity of FWT yielded a good specificity estimate, which could detect more than half of the EPS cases. However, specificity decreased to 84% when FWT was set at a more stringent threshold of 55.0 mL.

Based on the AUCs, also no good distinction could be made with regard to IL-6 AR. However, previous research already reported elevated levels of IL-6 AR for those who developed EPS.[12] Furthermore, no relationship was present between the degree of inflammation and the extent of fibrosis as demonstrated by the Peritoneal Biopsy Study Group.[10] The latter was confirmed in the current analysis were no correlation was present between AR of IL-6 and PAI-1 in patients who developed EPS. High estimates for sensitivity and specificity were also observed for the panel including IL-6 AR. Apparently, the large inter-individual variability of IL-6 that is indicative for a better distinction between patients, might be the cause of the increased discriminative capacity when combined with FWT. However, the large intra-individual variability of 28% makes the interpretation and clinical utility of IL-6 problematic.[25]

The limitations of this study comprise the small number of EPS patients from our center. The low prevalence prevented multiple combinations for example between AR of

CA125, PAI-1 and the quantity of FWT. Furthermore, this hampered the construction of a prediction model where a validation cohort is essential for independent study verification. To overcome this general hindrance, multicenter studies are warranted, but not available. Lastly, the presented threshold values should not be interpreted as definitive but rather as an approximation and presentation of potential cut-off values, since this is the first study reporting on this subject. However, the strength lies in the fact that dialysate specimens were available long time before the onset of EPS and were collected prospectively and stored without ascertainment of EPS. This permitted the laboratory determinations of effluent CA125, IL-6, PAI-1 and VEGF in order to establish associations among the effluent markers and investigate them in the preceding years of EPS diagnosis. Moreover, the availability of standardized peritoneal function test as routine patient care allowed the assessment of functional losses of the peritoneal membrane that are most overt in EPS patients in terms of FWT.

To summarize, FWT indicated considerable clinical validity where the combination with PAI-1 AR is likely to be the most promising one. However, PAI-1 is a novel effluent marker that requires further validation by morphometric data and investigations by others. A potential strategy for the early detection of EPS could include prospective monitoring of FWT and retrospective determinations of effluent biomarkers. Due to the transdifferentiation of mesothelial cells during the initial phase of PD treatment,[26] effluent determinations of CA125 could be performed from two years after initiation of PD treatment and continued yearly thereafter. IL-6 could be measured alongside, however a single measurement should rarely lead to clinical decision-making. As peritoneal fibrosis has a longer lead-time, PAI-1 could be measured from serially archived dialysate specimens from four years after commencing PD treatment for time course assessment. In case storage of serial dialysate specimens is not feasible one could consider prospective measurements of PAI-1 after a treatment period of at least four years. We would like to highlight that FWT is simple to calculate from sodium removal by performing a modified PET including temporary drainage with a 3.86% glucose based dialysis solution followed by temporary drainage of the dialysate.[2] When combined with either effluent CA125, IL-6 or PAI-1 insight is gained at a functional level as well as on the morphological condition of the peritoneal tissues.

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