ORIGINAL ARTICLES

THE ASSOCIATION OF EFFLUENT CA125 WITH PERITONEAL DIALYSIS TECHNIQUE FAILURE

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◆ **Background and objectives:** Cancer antigen 125 (CA125) reflects the mesothelial cell mass lining the peritoneal membrane in individual patients. A decline or absence of mesothelial cells can be observed with duration of peritoneal dialysis (PD) therapy. Technique failure due to peritoneal membrane malfunction becomes of greater importance after 2 years of PD therapy in comparison to the initial period. In this study, we aimed to investigate the association between effluent CA125 and technique survival in incident PD patients with a PD therapy period of at least 2 years.

◆ **Methods:** Within the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a Dutch multicenter cohort including 2,000 incident dialysis patients, we identified all PD patients who developed technique failure after 2 years of PD therapy and randomly selected a number of them as cases in a nested case-control study. Controls were PD patients matched on follow-up time without technique failure. Cases and controls were included if they had a dialysate specimen available within 24 ± 6 months of PD therapy for retrospective CA125 determinations. Odds ratios for technique failure related to CA125 were estimated. We used a prospective cohort with incident PD patients from the Academic Medical Center–University of Amsterdam (AMC) for replication of effect estimates. In these patients,

absolute risk of technique failure was estimated and related to effluent CA125 levels.

◆ **Results:** A total of 38 PD patients were selected from the NECOSAD cohort. From the AMC cohort as replication cohort, 91 PD patients were included. Incidence rates of PD technique failure per 100 patient-years were 16.3 in the NECOSAD cohort and 12.9 in the AMC cohort. In both study populations CA125 levels below 12 – 14 kU/L were associated with an increased risk for technique failure. Technique survival rates in the AMC were 87% in patients with levels of CA125 above 12.1 kU/L and 65% for those with CA125 levels below this threshold after a maximum 5-year follow-up.

◆ **Conclusions:** Patients with high CA125 levels after at least 2 years of PD therapy tend to have better technique survival than patients with low CA125 levels. These results support the importance of effluent CA125 as a risk factor for dropout in long-term PD therapy.

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The continuous and long-term exposure of non-biological dialysis solutions to peritoneal tissues induces several alterations in peritoneal dialysis (PD) patients. An increased density of the peritoneal microvasculature, interstitial fibrosis, and loss of mesothelium are the main anatomic changes of the peritoneal membrane (1,2). The mesothelium is especially difficult to assess, because of

the possibility of mesothelial damage during peritoneal surgery. Nevertheless, data from the peritoneal biopsy registry show that absence of the mesothelium is found in 49% of PD patients compared with 17% of non-PD patients (2). Also, in encapsulating peritoneal sclerosis (EPS), absence or a significant reduction of mesothelial cells can be observed (3). Functionally, the peritoneal changes are reflected by an increase in low molecular weight solute transport and a decreased ultrafiltration capacity. Amongst other factors, these transport changes can contribute to the discontinuation of PD therapy. In general, PD technique failure often occurs in the first 6 months after commencing PD therapy due to abdominal, catheter, and infectious complications (4–6). However, discontinuation due to peritoneal membrane failure is usually observed after a therapy period of more than 2 years (4). At present, time-dependent risk factors attributing to technique failure have not yet been identified.

Cancer antigen 125 (CA125) in PD effluent is regarded as a biomarker that is proportional to the amount of mesothelial cells lining the peritoneal cavity in individual patients (7–9). As PD therapy progresses, effluent CA125 levels decrease with intra-individual coefficients of variation ranging from 7 – 17% (10,11). Associations between effluent levels of CA125 and the mass transfer area coefficient (MTAC) of creatinine are only present in the first 2 years of PD (12,13). The most likely driving force of this relationship is the production of vasoactive substances by mesothelial cells (12). This relationship disappears in the subsequent years (13) and can be explained by 2 opposing features that develop during long-term PD. First, by the increased degeneration of mesothelial cells compared to regeneration with time on PD therapy resulting in decreased effluent CA125 levels (10). The second feature is the increase in peritoneal transport of small solutes due to neoangiogenesis (1,12). A dysfunctional mesothelium may thus be a potential risk factor for the development of peritoneal membrane failure. We therefore postulate that low levels of effluent CA125 are associated with an increased risk for PD technique failure in patients on long-term PD therapy. The aim of the present study is to investigate the association between effluent CA125 and technique survival after 2 years of PD therapy.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

The population for this study originated from The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). NECOSAD is a multicenter prospective

cohort study that included adult end-stage renal disease patients at the initiation of dialysis therapy between January 1996 and December 2007 (end of study period June 2009). From the 38 participating centers, the local medical ethical committees gave approval and all patients participating in NECOSAD signed a written informed consent prior to inclusion. Clinical and demographic data, as well as blood and dialysate specimens, were prospectively collected and stored from all participating PD patients.

For logistic reasons, a nested case-control design was applied in which cases and controls were randomly selected by a computer-generated procedure. Patients who switched from PD to hemodialysis (HD) no less than 2 years after commencing PD therapy (cases) and for whom a dialysate sample was available within a timeframe of 24 ± 6 months were selected. The dialysis modality switch from PD to HD was considered permanent if this comprised a duration of more than 3 months. Two random control patients were matched to cases by month of modality switch (incidence density sampling). Due to incidence density sampling within a nested case-control design, the immortal time bias was avoided. For the controls, an available dialysate specimen within a timeframe of 24 ± 6 months of PD therapy was required as well (baseline of the analysis). The time difference between the case and time-matched controls with regard to the dialysate sampling withdrawal was not allowed to be greater than 1 month.

Clinical parameters such as demographic data, primary renal disease—according to the classification codes of the European Renal Association-European Dialysis and Transplantation Association (14)—, Davies comorbidity score (15), and primary choice of modality were recorded.

INDEPENDENT REPLICATION

Data from the Academic Medical Center–University of Amsterdam (AMC) cohort of PD patients were analyzed in order to independently replicate the study findings from the NECOSAD population. Peritoneal dialysis patients from the AMC who participated in NECOSAD were not included in this validation cohort ($n = 2$). All AMC-PD patients underwent a standardized peritoneal permeability analysis (SPA) (16). A SPA was performed within 12 months after commencing PD therapy and repeated once every year as routine patient care including effluent CA125 determinations. The presence of these predetermined effluent CA125 levels allows establishment of absolute risk estimates and technique survival curves.

In the present study, all incident adult patients without a history of renal replacement therapy were eligible if they commenced PD therapy in the AMC between January

1996 and December 2010. From this base population, a subset of patients with a minimum PD duration of 2 years and an available CA125 measurement within 24 ± 6 months were selected to assess the association between effluent CA125 and technique failure.

Follow-up of patients continued until one of the following events occurred: dialysis modality switch, renal transplantation, mortality, maximum follow-up duration of 3 years, or end of study period (January 2013). Demographic data, primary renal disease (14), Davies comorbidity score (15) and type of PD modality and dialysis solutions were collected at initiation of PD therapy and in subsequent years.

EFFLUENT CA125 ASSAY PROCEDURE

The collected and archived dialysate samples from the NECOSAD cohort were derived from the long dwell. Effluent samples were centrifuged at $1710 \times g$ for 10 minutes and stored at a minimum temperature of -20°C until biochemical analysis. The effluent CA125 levels were measured in triplicate and performed in the AMC by a radioimmunoassay technique using 2 monoclonal antibodies: OC125 and M11 (Fujirebio Diagnostics, Malvern, PA, USA). Acceptable coefficients of variation of within-assays were set at $\leq 20\%$. Coefficients of variation above 20% were omitted (1.5%).

In the AMC cohort, effluent samples obtained at the end of the 4-hour SPA were assayed immediately and in single for CA125 levels by means of a microparticle enzyme immunoassay in combination with a monoclonal antibody OC125 on an E170 autoanalyzer (Roche Diagnostics, Basel, Switzerland). An imprecision test revealed no systematic difference between the 2 laboratory techniques. Previous studies indicated no influence of acidity (17) and tonicity (10) of PD solutions during peritoneal function assessments on levels of effluent CA125.

STATISTICAL ANALYSES

Data on continuous characteristics are reported as median and interquartile range. Proportions (%) are expressed for categorical variables. Univariate comparisons between groups were performed, as appropriate, by means of Student's *t*-tests or Mann-Whitney U (continuous data) or chi-squared test (categorical data).

As central outcome, technique failure was defined as dialysis modality switch from PD to HD for at least 3 months. In addition, incidence rates per 100 patient-years (py) were calculated for PD technique failure in both cohorts for the period between January 1996 and

December 2007 from 2 years after the initiation of PD therapy with a maximum follow-up of 3 years.

The association between levels of effluent CA125 and technique failure in the NECOSAD study population was investigated by logistic regression adjusted for the potential confounders age, gender, comorbidity score and PD duration. The analysis was performed with effluent CA125 levels measured at 24 ± 6 months after initiation of PD therapy. Effluent levels of CA125 were investigated as a continuous variable, and dichotomous by means of low vs high based on the median CA125 level.

For the AMC population as validation cohort, competing risk analyses (18) were used to assess the difference in cumulative probability of technique failure. Renal transplantation and mortality were considered to be competing end points. Censored observations comprised lost to follow-up or a maximum follow-up duration of 5 years after commencing PD therapy. The main analysis consisted of a Cox proportional hazards model to calculate hazard ratios (HRs) for PD technique failure based on CA125 effluent levels measured within 24 ± 6 months after commencing PD. The HRs were adjusted for age, gender, and comorbidity score. Analyses were performed with CA125 as a continuous variable, as well as dichotomous by combining the 2 lowest tertiles vs the highest tertile of CA125 levels. Finally, in a sensitivity analysis, the above-described analyses were repeated based on the median CA125 value derived from the NECOSAD study population and appearance rates. The statistical software employed for all analyses was SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA) and *p* values less than 0.05 were considered statistically significant.

RESULTS

A total of 336 PD patients within the overall NECOSAD cohort were on PD for at least 2 years, with a cumulative incidence of 26.8% for technique failure. Furthermore, the incidence rate of technique failure was 16.3 per 100 py. For the present study, a total number of 13 cases vs 25 randomly selected controls were selected. Characteristics of these patients measured after 2 years of PD therapy are presented in Table 1. Overall, no overt differences were present between the cases and controls with the exception of effluent levels of CA125, which were significantly lower in the patients who experienced a modality switch from PD to HD. The main causes for a modality switch from PD to HD were peritonitis episodes (39%), catheter-related (15%), and ultrafiltration failure (8%).

The risk assessment of effluent CA125 for technique failure is shown in Table 2. When analyzed as continuous variable, an association was found between absolute

TABLE 1
Patient Characteristics of Cases and Controls Selected from the NECOSAD Cohort (*n*=38)

Factor	Cases (<i>n</i> =13)	Controls (<i>n</i> =25)	<i>p</i> value
Gender (% male)	54	76	0.16
Age at start of PD (years)	60 (38–68)	52 (36–69)	0.83
Primary Kidney Disease (%)			
Renovascular	8	4	0.44
Diabetic nephropathy	0	12	
Glomerulonephritis	0	8	
Other	82	76	
Davies comorbidity score (%)			
Low	54	56	0.90
Intermediate	46	44	
High	0	0	
PD modality (%)			
APD	15	32	0.38
CAPD	85	64	
NPD	0	4	
PD duration (months)	24 (23–24)	23 (23–24)	0.74
Effluent CA125 (kU/L)	10.5 (8.9–14.1)	15.5 (9.0–24.0)	0.01

NECOSAD = Netherlands Cooperative Study on the Adequacy of Dialysis; PD = peritoneal dialysis; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; NPD = night peritoneal dialysis; CA125 = cancer antigen 125.

Data are from 24 months after initiation of PD therapy and presented as median (interquartile range) or percentages.

TABLE 2
Odds Ratios with 95% Confidence Intervals for Effluent
CA125 Levels with PD Technique Failure

	Odds ratio	95% CI
CA125 (kU/L)		
Crude	0.89	0.79–1.00
Model 1	0.88	0.76–1.02
Model 2	0.87	0.75–1.02
CA125 low vs high ^a		
Crude	5.93	1.29–27.28
Model 1	6.71	1.09–41.09
Model 2	6.13	0.99–37.95

CA125 = cancer antigen 125; PD = peritoneal dialysis; CI = confidence interval.

Model 1: adjusted for age, gender, and month of switch.

Model 2: adjusted for age, gender, month of switch, and Davies comorbidity score.

^a Low CA125 ≤14.0 kU/L, high CA125 ≥14.0 kU/L.

levels of CA125 and technique failure. In this analysis, adjustment for the potential confounders did not attenuate the observed effect. Conversely, low CA125 levels of ≤ 14.0 kU/L vs effluent levels above this threshold identified a 5.9-fold increased risk for technique failure. This

association remained after adjustment for age, gender, and PD duration. Further adjustment for comorbidity score in the model resulted in a loss of statistical significance. Nonetheless, the effect was of similar magnitude.

INDEPENDENT REPLICATION

In the AMC PD population, 20.9% experienced a modality switch from PD to HD after the initiation of PD therapy. This resulted in an incidence rate for PD technique failure of 12.9 per 100 py.

The initial number of adult incident PD patients within the AMC population between 1996 and 2010 was 327. After applying the selection criteria, the final AMC study population consisted of 91 patients. The majority of the patients were male and continuous ambulatory peritoneal dialysis was used most often as the primary PD modality. Forty percent of the study population was treated with the more biocompatible dialysis solutions. Eighteen patients experienced a modality switch from PD to HD. Their baseline characteristics, together with those of the 73 PD patients who did not experience a modality switch, are presented in Table 3. With a survival period of at least 2 years since the initiation of PD therapy, discontinuation of PD therapy was due to renal transplantation (39%), mortality (29%), and technique

TABLE 3
Patient Characteristics AMC Cohort (n=91)

Factor	
Gender (% male)	63
Age at start PD (years)	52 (41–63)
Primary kidney disease (%)	
Renovascular	31
Diabetic nephropathy	22
Glomerulonephritis	11
Other	36
Davies comorbidity score (%)	
Low	31
Intermediate	58
High	11
PD modality (%)	
APD	32
CAPD	68
PD duration (months)	26 (23–27)
Effluent CA125 (kU/L)	9.0 (5.1–14.2)

AMC = Academic Medical Center–University of Amsterdam; PD = peritoneal dialysis; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; CA125 = cancer antigen 125.

Data are from 24 months after initiation of PD therapy and presented as median (interquartile range) or percentages.

failure (26%). Six percent of the patients were still on PD therapy or lost to follow-up. The main causes of technique failure were (repetitive) peritonitis episodes (50%) and ultrafiltration failure (28%).

Cumulative probability curves for technique failure are illustrated in Figure 1. The competing risk analysis revealed a 22% increased risk for technique failure in patients with CA125 levels below 12.1 kU/L vs patients with effluent CA125 levels above this threshold. The HR for CA125 levels for technique failure analyzed in a continuous manner did not point toward an association (Table 4). Dichotomously, the HRs indicated an increased risk for levels of CA125 below 12.1 kU/L, albeit not statistically significant. Furthermore, adjustment for age, gender, and comorbidity score did not attenuate the observed effect. The sensitivity analysis, where the CA125 cut-off value of 14.0 kU/L from the NECOSAD was used, indicated a relatively increased risk for technique failure with an unadjusted HR of 2.50 (95% CI: 0.57 – 10.86) and 2.65 (95% CI: 0.61 – 11.58) after adjustment for the confounders age, gender, and comorbidity score. Analyzing dialysate appearance rates of CA125 instead of concentrations could only be performed in the AMC cohort. Even though attenuated, the results were not substantially different (data not shown).

Figure 1 — Cumulative probability curves of low vs high effluent CA125 levels for technique failure. A cumulative probability curve illustrates technique failure of low (≤ 12.1 kU/L) vs high (≥ 12.1 kU/L) effluent CA125 levels considering mortality and renal transplantation as competing end points. The figures below the graph indicate the number of patients at risk. CA125 = cancer antigen 125; PD = peritoneal dialysis.

TABLE 4
Hazard Ratios with 95% Confidence Intervals for
Effluent CA125 Levels with PD Technique Failure

	Hazard ratio	95% CI
CA125 (kU/L)		
Crude	0.96	0.90–1.03
Adjusted ^a	0.97	0.90–1.04
CA125 low vs high ^b		
Crude	3.32	0.76–14.47
Adjusted ^a	3.36	0.77–14.64

CA125 = cancer antigen 125; PD = peritoneal dialysis; CI = confidence interval.

^a Adjusted for age, gender, and Davies comorbidity score.

^b Low CA125 ≤ 12.1 kU/L, high CA125 ≥ 12.1 kU/L.

DISCUSSION

The present analysis has shown that peritoneal effluent CA125 concentrations below 12 – 14 kU/L, which equals an appearance rate of about 100 U/min, are associated with reduced technique survival on PD in long-term patients, when compared with those who have higher levels after 2 years of PD therapy. These results strengthen the findings of a previous study in patients who developed EPS after a median PD therapy duration of 8.7 years, in whom a CA125 appearance rate below 33 U/min was indicative for the development of this

condition (19). Measurement of effluent CA125 in the first 2 years may not be very informative due to epithelial-to-mesenchymal transition of mesothelial cells (20) and the fact that technique failure in this period is mainly due to abdominal and catheter-related complications rather than peritoneal membrane failure (3).

In vitro studies have evidently shown that CA125 is constitutively produced by mesothelial cells and can therefore be considered as a measurement of mesothelial cell mass (7,8). Most mesothelial cells in peritoneal effluent express CA125 in the vast majority of PD patients (21). Cross-sectional studies on relationships between the number of mesothelial cells in peritoneal effluent and CA125 have been equivocal (7,8,22,23), probably because the expression is not 100% in all patients. Although peritoneal abnormalities can be induced in long-term rat models (24) that are similar to findings in humans, direct relationships between mesothelial cell mass and CA125 cannot be established because the antibody against CA125 is produced in mice and exhibits cross-reactivity with rat tissues and rat peritoneal effluent.

Clinical studies demonstrate intra-individual coefficients of variation of 17% in patients with a PD duration of more than 2 years (11) and a decreasing trend during longitudinal follow-up (10,13). The latter is in accordance with the sparse morphologic studies in long-term PD patients reporting a reduction of mesothelial cells (25,26). However, no direct proof is available because no CA125 has been measured in any morphologic study, even though, when all evidence is combined, it is conceivable that the results of the present and previous studies support the contention that effluent CA125 can be considered a biomarker for dropout of long-term PD patients due to peritoneal membrane damage and its consequences, such as ultrafiltration failure.

The low event rate in the AMC cohort might have prevented the detection of a statistically significant difference as reflected by the confidence intervals, even though both study populations showed an increased risk for technique failure in patients with a low CA125 level. The effect estimates from the AMC were less strong as compared with the NECOSAD. Potential reasons for this discrepancy could firstly be due to the origin of the case-mix. The multicenter NECOSAD cohort mainly consisted of patients included by non-academic dialysis centers. Additionally, analysis of peritoneal transport was not included in the NECOSAD questionnaire and it is unlikely that detailed information on, for instance, peritoneal ultrafiltration was available. Therefore, it is plausible that the decision for transfer to HD was merely taken on clinical grounds. The absence of peritoneal transport rates in this multi-center study cohort is considered

to be a limitation. The lack of these data disabled the potential to make inferences with regard to associations between effluent CA125 and peritoneal transport parameters. Additionally, the limited number of patients would probably hamper further analyses, even though previous studies have shown that no associations are present between effluent CA125 and parameters of peritoneal transport (27,28). In the AMC cohort, extensive peritoneal transport studies were done in all patients. Hence, the magnitude of peritoneal ultrafiltration capacity was known in all of them. As a consequence, automated PD was probably more often used during follow-up in the AMC patients, resulting in a lower technique failure rate. Furthermore, a larger proportion of PD patients within a center, leading to a greater level of experience, is associated with a decreased risk of technique failure (29). Together with the above-mentioned factors, this might have contributed to the lower incidence rate of technique failure in the university hospital than in the other centers.

In all NECOSAD patients, the decision to discontinue PD was taken by the treating nephrologists without any knowledge of the effluent CA125 concentration in that particular patient, because the determinations were done afterwards in effluent specimens collected from the NECOSAD biorepository. Although in the AMC, the effluent CA125 levels were known, it is unlikely that such bias was present in the majority of the patients as these results were not used to ascertain a clinical outcome. Also, effluent CA125 concentrations were lower in the AMC patients, probably because the dwell time of the instilled dialysis solution was strictly standardized to 240 minutes, while the effluent of the long dwell was used in the NECOSAD cohort. However, the sensitivity analysis in which the AMC effluent CA125 cut-off value of 12.1 kU/L was amended to 14.0 kU/L (threshold NECOSAD study population) yielded a non-statistically significant difference with similar effect sizes.

To the best of our knowledge, this study is the first to explore and quantify the association between dialysate CA125 levels and PD technique failure. Hence, the present effect size is considered to be the best estimate available in which the strong association did not disappear after adjustment for several variables. The current study confirms our postulation that low dialysate CA125 levels are associated with long-term PD technique failure, even in the absence of regular peritoneal transport assessments. Nevertheless, for reinforcement of this hypothesis further investigations with a larger study population including detailed clinical information are essential.

Serial measurements of effluent CA125 allow assessment of individual time-courses, which in turn allows for monitoring of the integrity of the peritoneal mesothelium.

In interpreting isolated dialysate CA125 determinations, inter-individual variations should be considered, due to differences in CA125 expression on mesothelial cells between patients, especially in the rare ones who have a low expression and therefore present with persistently low dialysate levels of CA125. However, a single high effluent CA125 value is indicative of a low risk for dropout in long-term PD due to peritoneal membrane failure.

DISCLOSURE

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