

Dialysate CA125 levels after 5 years on continuous peritoneal dialysis

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Abstract The aim of this study was to evaluate longitudinal changes in dialysate cancer antigen 125 (dCA125) levels over time and to analyze relationships between dCA125 and peritoneal glucose exposure (PGE) in children undergoing long-term peritoneal dialysis (PD). The study group included seven boys and four girls (mean age 13 ± 5.1 years) with a mean PD duration of 84.0 ± 1.1 months. A peritoneal equilibration test (PET) was performed, and dCA125 levels were measured in all patients. Peritoneal appearance rates (AR) of dCA125, the velocity of the decrease in dCA125AR values, and annual PGE levels were also calculated. The final tests were performed at a mean of 63.3 ± 3.5 months after the initial ones. Both dCA125 and dCA125AR levels showed statistically significant decrements during the follow-up period ($p=0.003$), with the velocity of decrease in dCA125AR found to be $52.6 \pm 19.4\%$. There were no significant differences in peritoneal transport parameters between the beginning and end of the study period. PGE values were significantly higher in the last year of the study than in the first year ($p=0.014$), but the velocity of the decrease in dCA125AR levels was not related to total PGE. In conclusion, a significant decline was found in dCA125 and CA125 AR levels, reflecting mesothelial cell

mass, in children undergoing long-term PD (>5 years), but these were not related to PGE.

Keywords Peritoneal dialysis · Cancer antigen 125 · Mesothelium · Glucose exposure · Transport parameters

Introduction

Long-term peritoneal dialysis (PD) is associated with the development of various structural and functional alterations to the peritoneal membrane and may eventually lead to the loss of function of the dialysis membrane in some patients. These alterations include loss of mesothelial cells, thickening of the submesothelial compact zone, and changes in vascularization [1–5]. At least some of these effects are thought to be associated with chronic peritoneal glucose exposure (PGE) to non-physiological PD fluids. In addition, glucose degradation products formed during autoclaving of the glucose-based solutions seem to be strongly cytotoxic towards the peritoneal mesothelium [6–8]. On a cellular level, chronic PD is associated with the phenomenon of epithelial to mesothelial cell transformation as well as the premature aging and senescence of mesothelial cells [9].

Since peritoneal biopsy is not routinely performed due to its invasive nature, studies of peritoneal membrane structure have to rely on a number of biomarkers that are secreted by the peritoneal membrane and which can be assayed in the effluent of PD. Of these, the most important in terms of usefulness in studies and clinical practice are cancer antigen 125 (CA125), interleukin-6 and, to a lesser degree, vascular endothelial growth factor [10].

Effluent CA125 can be considered as a marker of the mass of viable mesothelial cells and their turnover, and is

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recommended as a tool for longitudinal membrane status evaluation [11, 12]. Dialysate CA125 levels have been shown in some studies to decrease in long-term PD treatment [13–16], but there are currently limited longitudinal data on children undergoing long-term PD [17]. The aim of the study reported here was to evaluate changes in dCA125 levels in peritoneal effluent over time and to analyze relationships between dCA125 and PGE in children treated with long-term PD.

Patients and methods

We previously published a cross-sectional study of dCA125 levels and peritoneal transport parameters in a group of 32 pediatric PD patients [18]. Of these children, 11 were still on PD at the time of writing this paper; these children comprised the patient group of this study. The values obtained from these patients in our earlier study were considered to be baseline values and were used to make a comparison with the results of the present study, which was performed 5 years later. The underlying renal diseases in these 11 children were: malformations of the urinary tract, including reflux nephropathy ($n=5$); miscellaneous hereditary nephropathies ($n=4$); chronic glomerulonephritis ($n=2$). Demographic data and clinical characteristics of the patients are listed in Table 1.

The patients were stable on PD and had been free of peritonitis for at least 3 months before the peritoneal equilibration test (PET) analysis. However, all patients had experienced at least two peritonitis episodes prior to inclusion in this study. All 11 patients were grouped at the beginning of the study according to their urinary volumes; only one patient was anuric, three had urinary volumes of <400 ml/m²/day, and the remaining seven had urinary volumes of >400 ml/m²/day. During the course of the study, a number of children became anuric: at the end of the first year of follow-up, two children; by the end of the second year, three children; by the end of the study, five children. It is sometimes difficult to get pediatric patients to cooperate

and they are occasionally hypertensive due to volume overload even if they have residual renal functions. Therefore, in our study, we had to prescribe hypertonic peritoneal dialysis solutions to our patients very often. A total of six patients had used hypertonic glucose solutions [2.27 g/dl glucose (395 mOsm/l) or 3.86 g/dl glucose (484 mOsm/l)] in the last 12 months prior to the present study, while four of these had used hypertonic glucose solutions from the very beginning of the initial study. The remaining five children were dialyzed with standard glucose-containing PD solutions.

Peritoneal transport characteristics

A standardized 4-h PET developed by the Pediatric Peritoneal Dialysis Study Consortium using an exchange volume of 1,100 ml/m² (2.27% dextrose) was performed [19]. Dialysate and blood glucose levels were measured by the hexokinase method and creatinine by the kinetic method (U-240 autoanalyzer; Tectron, Tokyo, Japan) on the same day as the PET. All serum values were expressed as concentrations per unit volume of plasma water by dividing the serum values by a factor of 0.93 [19]. Because of the very high glucose concentration of the dialysate samples, the measurements were performed after diluting the dialysate samples 1:10 with distilled water. The dialysate-to-plasma (D/P) ratio for creatinine and the ratio of dialysate glucose to initial dialysate glucose concentration (D/D0) and mass transfer area coefficient (MTAC) of creatinine were calculated using PD Adequest software [20].

CA125 measurements

Dialysate samples for the CA125 measurements were taken from a test bag after 4 h and stored at -70°C until CA125 analysis. All samples were assayed at the same time to avoid interbatch variation using a commercially available chemiluminescent enzyme immunometric assay (Immulite OM-MA; Siemens Healthcare Diagnostics, Plainfield, IN). The Immulite OM-MA assay is designed specifically for the quantitative measurement of CA125 antigen. The detection limit of the assay is approximately 0.2 U/ml, defined as the concentration two standard deviations above the signal response at zero dose. The antibody used in the Immulite OM-MA procedure is highly specific for CA125 with low cross-reactivity to other substances that may be present in patient samples.

The peritoneal appearance rates (AR) of dCA125 (dCA125 AR) were calculated as the dCA125 (units per milliliter) multiplied by the drained volume (in milliliters), divided by the dwell time (in minutes) [21] and corrected for body surface area [22].

Table 1 Demographic data and clinical characteristics of the patients

Parameters	Start of study	End of study
No. of patients	11	11
Age (years)	8.2±5.5	13.9±5.1
Gender (F/M)	4/7	4/7
PD modality (APD/CAPD)	8/3	8/3
Treatment time (months)	22.7±13.6	84.0±1.1
BSA (m ²)	0.78±0.29	1.04±0.33

F, Female; M, male; PD, peritoneal dialysis; APD, automated PD; CAPD, continuous ambulatory PD; BSA, body surface area

The velocity of the decrease in dCA125 AR was calculated as follows: $(dCA125AR)_{\text{first}} - (dCA125AR)_{\text{present}} / (dCA125AR)_{\text{first}}$

Peritoneal glucose exposure

Peritoneal glucose exposure was reviewed annually according to each patient’s PD prescription, and expressed as grams per square meter per day for each patient. The average 24-h peritoneal glucose exposure was calculated from the volume and glucose concentration of the prescribed PD fluid in automated PD (APD) patients, ignoring the percentage of glucose absorption and the dwell time (range 100–150 min). For example, for an APD patient who was using six 1-l exchanges, five of 1.36% and one of 2.27%, the PGE would be estimated as 90.7 g of glucose per day. However, this approach cannot be used for continuous ambulatory PD (CAPD) patients due to the long dwell time. Thus, in PGE calculations for CAPD patients, individual D_2/D_0 and D_4/D_0 glucose values from PET analysis were used, and the PGE was separately estimated for each 2 h of dwell time, as follows:

$$PGE_1 = V \times 13,6 \text{ for first } 2 - \text{ h of the dwell time}$$

$$PGE_2 = V \times 13,6 \times (D_2/D_0) \text{ for second } 2 - \text{ h of the dwell time}$$

$$PGE_3 = V \times 13,6 \times (D_4/D_0) \text{ for third } 2 - \text{ h of the dwell time}$$

For example, for a CAPD patient who was using four 1-l (1.36%) exchanges and who had $D_2/D_0=0,50$ and $D_4/D_0=0,30$, the PGE would be calculated as follows;

$$PGE_1 = 1 \times 13,6 \text{ for first } 2 - \text{ h of the dwell time}$$

$$PGE_2 = 1 \times 13,6 \times 0,50 \text{ for second } 2 - \text{ h of the dwell time}$$

$$PGE_3 = 1 \times 13,6 \times 0,30 \text{ for third } 2 - \text{ h of the dwell time}$$

$$PGE \text{ total} = 24,28\text{g of glucose per exchange, and } 4 \times 24,28 = 97,12\text{g of glucose per day.}$$

Statistics

Data are expressed as the mean±standard deviation (SD). Differences during the follow-up were estimated using the paired standard *t* test. Correlations between the different parameters were estimated using Pearson correlations. Calculations were made using SPSS ver. 15 statistical software for Windows (SPSS, Chicago, IL). *p* values <0.05 were considered to be significant.

Results

The final tests were performed on 11 children at a mean of 63.3 ± 3.5 (range 59.0–66.8) months after the initial tests, which in turn were carried out 22.7 ± 13.6 (range 1.5–47.7) months after the initiation of PD. dCA125, peritoneal transport properties, and glucose exposure values at the first and final measurement, respectively, are listed in Table 2. Both dCA125 and dCA125 AR levels were found to have significantly decreased during the follow-up period ($p=0.003$). However, no significant difference was found for the PET parameters.

Final dCA125 and dCA125 AR values were lower than the first values in all patients (Fig. 1), and the velocity of the decrease in dCA125 AR were found to be $52.6 \pm 19.4\%$ (range 13–73%).

PGE estimations tended to increase steadily during the study period, beginning at 100 ± 43 (initial measurement) and increasing to 104 ± 49 , 114 ± 42 , 118 ± 47 and 130 ± 56 g/m²/day for each subsequent year. PGE values were significantly higher in the last year than in the first year ($p=0.014$). The velocity of the decrease in dCA125 AR levels were not related to total peritoneal glucose exposure values ($r=0.34$, $p=0.30$) (Fig. 2).

Discussion

The peritoneal effluent of PD patients contains many substances. These can appear due to diffusion from the circulation, local peritoneal production, or both. The diffusion of a substance can be ignored when its local peritoneal production approaches or exceeds the serum concentration, such as CA125, for example, which is produced constitutively by mesothelial cells [10]. The concentration of CA125 increases linearly during a dwell of 4 h and is not influenced by the dialysis solution used. Consequently, CA125 can be a good marker to study in vivo peritoneal mesothelial cell mass or turn-over in PD patients. However, in this context, it has been recommended to express effluent CA125 as its dialysate appearance

Table 2 Dialysate CA125, peritoneal transport properties, and glucose exposures at baseline and final measurement

Parameters	First measurement (baseline)	Final measurement	<i>p</i>
CA125 (U/ml)	5.45±3.25	2.18±0.55	0.003
AR CA125 (U/ml/1.73 m ²)	47.84±28.92	19.40±7.59	0.003
D/P creatinine	0.71±0.11	0.68±0.18	0.732
D/D ₀ glucose	0.34±0.10	0.32±0.15	0.772
MTAC creatinine (ml/min/1.73 m ²)	5.53±3.52	7.53±3.70	0.198
Peritoneal glucose exposure (g/m ² /day)	100.1±43.2	130±55.9	0.014

CA, Cancer antigen 125; D/P, dialysate-to-plasma ratio; D/D₀, ratio of dialysate glucose to initial dialysate glucose concentration; MTAC, mass transfer area coefficient; AR, appearance rate

rate (CA125 AR) to avoid any influence of dwell time and ultrafiltration volume [11, 14, 15, 23]. In addition, the levels of CA125 should be corrected by the body surface area, especially in children, since they are physically more variable than adults [22].

The most important finding of our study is the observed significant decline in dCA125 concentrations and the dCA125 AR in children treated more than 5 years with PD. This result is in accordance with those from published longitudinal studies [15–17]. This downward trend with time suggests a decrease in mesothelial cell mass. In an earlier cross-sectional analysis [18], we failed to observe a correlation between dCA125 levels and the duration of PD and had speculated that significant mesothelial cell mass reduction is unlikely to occur within the first few years of PD treatment. On the other hand, in a longitudinal study, Rodrigues et al. showed a significant decrease in effluent CA125 levels after 3 years of PD treatment [16]. The children comprising our study cohort showed a large inter-individual variability in dCA125 concentrations, but these were <25 U/ml/1.73 m² in all patients at the end of the study. Pannekeet et al. [13] found both high and low

dCA125 concentrations during the first 3 years of peritoneal dialysis treatment, but after 5 years of treatment they were only able to detect low dCA125 levels [13]. Interestingly, not all mesothelial cells express CA125, and there are two populations of peritoneal mesothelial cells, namely CA125-positive and CA125-negative mesothelial cells [24]. However, the ratio of positive to negative CA125 mesothelial cells does not change with duration of PD, even though the mesothelial cell mass, similarly to CA125 concentration, decreases with time on PD [25]. This feature can partly explain inter-individual differences in the release of CA125 by mesothelial cells.

Using a one-point analysis to interpret CA125 levels in a group of patients is very difficult, since substantial inter-individual differences exist in both dCA125 AR and velocity of the decrease in dCA125 levels with the duration of PD treatment. dCA125 AR measurements may be more useful for the follow-up of individual patients than for comparisons of patient groups due to possible inter-individual differences in the release of CA125 by mesothelial cells. Our data confirm that serial determinations of dCA125 AR allow only the

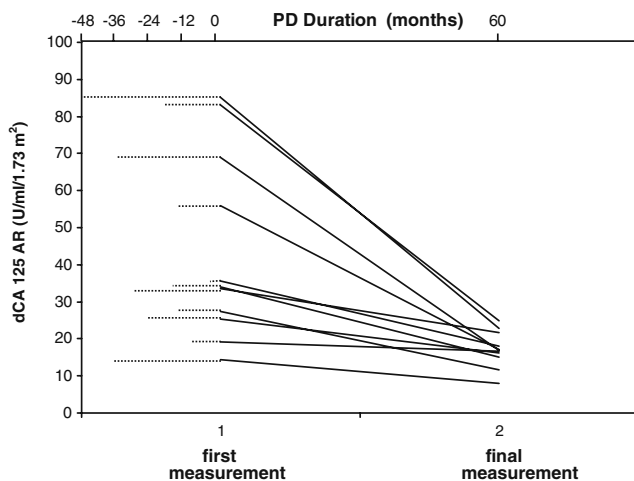


Fig. 1 Intra-individual changes in the appearance rate of cancer antigen 125 (CA125 AR) levels during follow-up

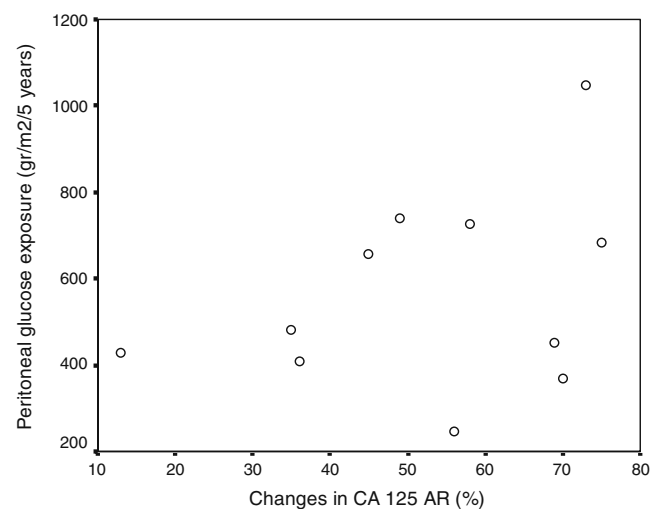


Fig. 2 No correlation was found between total peritoneal glucose exposure and changes in CA125 AR ($r=0.34$, $p=0.30$). PD, peritoneal dialysis

longitudinal follow-up of mesothelial cell mass in individual patients [14, 15].

However, there are a number of limitations to using dialysate CA125 as a clinical marker of mesothelial cell or membrane integrity [26]. It appears that the magnitude of CA125 release by mesothelial cells may depend not only on their number but also on their functional properties, which can be modulated by low pH, high lactate levels, and exposure to high glucose [7, 8]. The initial data on the relationship between dCA125 concentrations and PGE were obtained from PD biocompatibility studies [27–31]. The most consistent finding observed in all of these trials was that of an increased CA125 concentration in the effluent during dialysis with new biocompatible dialysis solutions. In a cross-over study in children, Haas et al. [31] reported that the peritoneal release of dCA125 increased twofold during bicarbonate APD compared with lactate APD. This finding was consistent with the recovery of the mesothelial cell layer, indicating improved *in vivo* mesothelial cell tolerance to high-dose glucose with the neutral pH PD solutions containing reduced glucose degradation products. In addition, previous studies confirmed that even the short-term exposure of mesothelial cells to acidic standard PD fluid results in a significant loss of cell viability and function [32, 33]. Schmitt et al. [33] found that with the standard lactate PD fluid, the peritoneal tissues were exposed to an acidic milieu for more than 1 h before lactate absorption and bicarbonate diffusion into the PD fluid resulted in peritoneal pH equilibration. In contrast, the pH remained in full equilibrium throughout the dialysis cycle when a bicarbonate-buffered solution was used. These results suggest that the pH of the dialysis fluid might be particularly relevant for APD, in which frequent short cycles continuously expose the peritoneal membrane to a cytotoxic acidic milieu [33]. The findings of the biocompatibility studies indicate that CA125 levels are a measure of mesothelial cell homeostasis because in a relatively short period, mesothelial cell mass is unlikely to change two- to four-fold; as such, the change in levels likely reflects synthesis by the resident mesothelial cell population, which are more sensitive to the less biocompatible standard fluid. Although Breborowicz et al. [34] reported limitations of CA125 as an index of peritoneal mesothelial cells in an *in vitro* study, they also showed a reduction of CA125 secretion and expression with chronic exposure to glucose solution. These divergent results emphasize the paucity of knowledge currently available on the control of CA125 synthesis, but they also reveal that CA125 synthesis can be up-regulated and down-regulated.

In our study, we found a significant increase in the PGE 5 years after the first measurement. However, no significant correlation was established between changes in the dCA125 AR levels and the total PGE. Inter-individual differences in

the velocity of the decrease in dCA125 AR levels might have led to insignificant results.

Functional changes in the peritoneal membrane after long-term PD have indeed been described. However, there is no evidence that the mesothelium is a size-selective barrier to solute transport. In our study, we were unable to establish a relationship between dCA125 AR values and peritoneal transport parameters, although the results do support the hypothesis that mesothelial cells are not likely to play a direct role in peritoneal transport during stable PD treatment [13]. PGE may not have had any influence on the peritoneal transport parameters of those patients with a longer duration of PD in our study. In a longitudinal study in adults, Davies et al. [6] showed that an increase in solute transport with time was preceded by increased peritoneal exposure to hypertonic glucose, and further increases in glucose exposure were observed as solute transport continued to rise. In our study, although we noted only obvious significant increases in glucose exposure rates in last 2 years of follow-up, no increments could be shown in D/P creatinine levels with time on PD. This finding could be attributed to our patients' multiple peritonitis episodes [35, 36]. On the other hand, a U-shaped curve of the D/P creatinine ratio was also present in a previous study on peritoneal transport [16].

In conclusion, based on our longitudinal results, dCA125 would appear to be a good marker for mesothelial cell mass or mesothelial cell turn over; as such, it can be used during a longitudinal follow-up of PD patients. However, dCA125 levels were found to vary considerably among the PD patients, and changes in the peritoneal mesothelial cell mass cannot be assessed using a single low value. Therefore, serial measurements of dCA125 might be a more valuable marker in the follow-up of individual patients. However, despite clinical experience with CA125, its current pre-eminent place as a marker of membrane integrity in PD needs to be confirmed by both *in vitro* investigations of CA125 regulation and studies to define longitudinal changes in large cohorts of PD patients and controls.

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