Kidney International, Vol. 51 (1997), pp. 888–893

Longitudinal follow-up of CA125 in peritoneal effluent

MARJA M. HO-DAC-PANNEKEET, JOHAN K. HIRALALL, DIRK G. STRUIJK, and RAYMOND T. KREDIET

Departments of Nephrology and Clinical Chemistry, Academic Medical Center, Amsterdam, and Foundation for Home-dialysis Midden-West Nederland, Utrecht, the Netherlands

Longitudinal follow-up of CA125 in peritoneal effluent. Mesothelial changes occur during peritoneal dialysis. CA125 provides a way to study the mesothelial cells in the *in vivo* situation. In the present study longitudinal changes of CA125 were analyzed. In addition, the appearance of CA125 in peritoneal effluent and day-to-day variability were studied. CA125 was measured in the effluent of five stable CAPD patients during four hour dwells with 1.36% glucose, with 3.86% glucose and with 7.5% icodextrin. In addition, CA125 was determined on six consecutive days in four hour effluents of three patients and appearance rates (AR) were calculated. Longitudinal follow-up was performed in 31 patients in whom three to seven yearly observations had been made. Linear appearance of CA125 was present in all dwells. No difference was found between the appearance rates of CA125 with 3.86% glucose, compared to either 1.36% glucose or icodextrin. Mean day-to-day coefficient of variation was 6.4% for CA125 AR, but a wide variation existed in stable CA125 values among patients (mean 22.1, range 2 to 48 U/ml). A negative trend with duration of CAPD was present in the longitudinal study. A mean decrease of 2.2% per year could be calculated, but substantial interindividual differences existed. Sudden decreases of CA125 AR were found in five patients. Possible causes were found in all of them and included a severe or recurrent peritonitis, and temporary cessation of peritoneal dialysis. In one patient a sudden decrease preceded the manifestation of peritoneal sclerosis. It can be concluded that CA125 can be used for the *in vivo* follow-up of the mesothelium in peritoneal dialysis patients. The appearance of CA125 in effluent is linear in time and not influenced by the initial lysis of mesothelial cells. A gradual loss of mesothelial cells is likely to occur, although interindividual variability is substantial. An acceleration of the process may be caused by severe peritonitis and perhaps by temporary cessation of peritoneal dialysis. A sudden decrease in CA125 may be an alarming sign for the development or manifestation of peritoneal sclerosis.

Changes in the mesothelial cells lining the peritoneal cavity have been described in peritoneal dialysis patients. These data were mainly derived from studies on peritoneal biopsies taken at catheter removal or reinsertion [1–4], or from animal studies investigating either peritoneal tissue specimens [3, 5] or mesothelial cells obtained by an imprint technique [6]. The reported changes in the mesothelium can be summarized as glucose-induced degenerative changes in isolated cells [6], activation in stable patients, loss of mesothelial cells in some patients treated with CAPD for a long period of time, and temporary loss of mesothelial cells during uncomplicated peritonitis [1–4]. In addition, in peritoneal sclerosis a lack of remesothelialization has been described [7]. A pivotal role of the mesothelial cells in peritoneal host defense has been made likely based on *in vitro* studies on human peritoneal mesothelial cells [reviewed in 8], and in an *in vivo* study of our group showing a relation between mesothelial cell count in peritoneal effluent and peritonitis incidence [9]. A loss of, or dysfunctional mesothelium may therefore be a potential risk factor in the elimination of micro-organisms and regulation of the inflammatory reaction.

The *in vivo* study of the mesothelium has become possible by the discovery of cancer antigen (CA) 125 as a marker of mesothelial cell mass or cell turnover in stable CAPD patients [10, 11]. Originally used as a tumor-marker for non-mucous ovarian carcinomas [12], further studies using the OC125 antibody against CA125 [13] reported that this 220 kDa glycoprotein was not only expressed by ovarian neoplasms, but was present also in mesothelial cells of both pleural and peritoneal tissue. Subsequently, it was demonstrated in mesothelial cells in peritoneal effluent of peritoneal dialysis patients [10], and proved to be expressed at a constant rate by confluent mesothelial cell monolayers *in vitro*, without any effect of stimulation with interleukin-1, TNFα, or interferon-γ [11]. This implied that CA125 in peritoneal effluent can possibly be used to study the reported changes in mesothelial cells of peritoneal dialysis patients. In a previous cross-sectional study, no relation between CA125 in the effluent of CAPD patients and peritoneal permeability characteristics could be found [14]. A negative relation was present with the duration of CAPD treatment [14]. This suggests a possible loss of mesothelial cells during CAPD treatment in individual patients. At present, no data are available on the follow-up of the mesothelium *in vivo* by CA125 concentrations in peritoneal effluent. Also, the extent to which CA125 can be used as a marker of mesothelial integrity, as well as the inter- and intraindividual variabilities have not been established.

In the present study, we attempted to answer these questions by a longitudinal study in which CA125 was followed over three to seven years in a large group of patients. The influence of different intercurrent complications of PD on the mesothelium in these patients was studied. Furthermore, analysis of the appearance of CA125 in peritoneal effluent during four hour dwells, as well as day-to-day variability of CA125 in standardized dwells was performed.

Methods

Patients were included who had been treated with peritoneal dialysis for at least one year, except for the longitudinal study. All patients were free of peritonitis at the time of and during the month prior to the studies.

Received for publication July 8, 1996
and in revised form September 26, 1996
Accepted for publication September 26, 1996

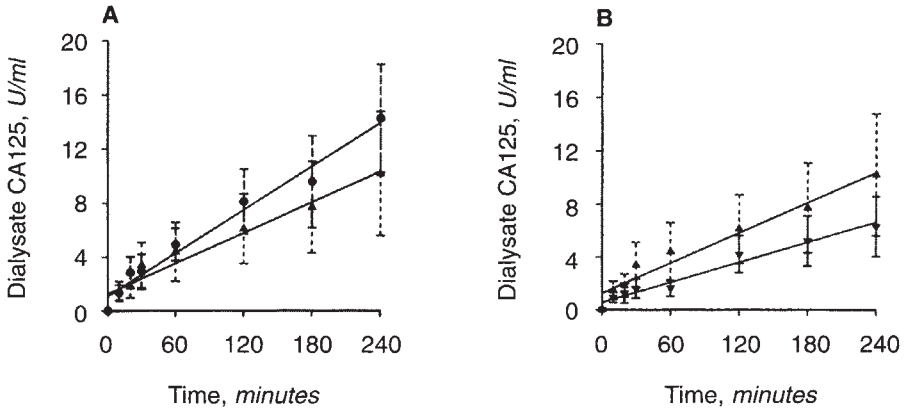

Fig. 1. *Linear CA125 release in the effluent during four-hour dwells in five stable CAPD patients.* In **A**, 3.86% glucose (●) is compared to 1.36% glucose (▲), and in **B**, 3.86% glucose is compared to icodextrin (▼). Data are expressed as mean ± SEM.

Appearance of CA125 in peritoneal effluent

CA125 was measured in effluent during standardized four-hour dwells at 0, 10, 20, 30, 60, 120, 180 and 240 minutes. Dwells with 3.86% glucose (Dianeal; Baxter NL, Utrecht, the Netherlands) were compared to 1.36% glucose (Dianeal, Baxter NL) and to 7.5% icodextrin (Icodial; ML Laboratories, St Albans, UK), both in five patients.

Day-to-day variability

Three stable CAPD patients were studied on a daily basis for six days. The patients performed standardized four-hour dwells with 1.36% glucose-based dialysate solutions at the beginning of each day. The exact dwell times and volumes of the bags were recorded. CA125 was measured in the six bags on consecutive days, and appearance rates (AR) were calculated by multiplication with the dwell volume and dividing by the dwell time. Intra-individual coefficients of variation were calculated as the SD divided by the mean data from the six days, multiplied by 100. The overall coefficient of variation was obtained from the overall SD. The latter was calculated as the square root of the mean of the squares of the SD data of each patient.

Longitudinal follow-up of CA125

In 31 patients CA125 was determined in four-hour dwells with 1.36% glucose on a yearly basis during the standard peritoneal permeability analyses [15]. The minimum number of determinations was 3 (11 patients). The interval between the subsequent determinations had to be at least one year apart. Ten patients were studied four times, in four patients five investigations were performed, and six investigations were made in four patients. Maximum follow-up was seven years (2 patients). This resulted in a total of 131 studies. The observation period did not necessarily include the first year of treatment. The mean cross-sectional age was 49 years, range 21 to 78 years, and the mean peritonitis incidence 0.30 (0 to 4.5) episodes/year. Duration of peritoneal dialysis ranged from 0.4 to 10.5 years.

Assays

CA125 was determined using a microparticle enzyme immunoassay, in combination with a commercially available monoclonal antibody OC125 (Cis Bio International, France) on an IMx autoanalyzer (Abbott Laboratories, North Chicago, IL, USA). Measuring range was 1.8 to 800 U/ml, with normal serum values < 35 U/ml. Interassay variability was 2.3%. The method was validated for determinations in peritoneal effluents in our laboratory [10]. Samples of one patient were always measured within the same run, to avoid interassay variability.

Statistical analysis

Data are expressed as mean ± SEM for data with a normal distribution, and medians and ranges are given for asymmetrically distributed data. Linear regression analysis was performed for individual patients using the method of least squares. Analysis of trend was performed according to Yellin [16]. For correlations, Spearman rank correlation analysis was used and the Wilcoxon's rank-sum test was applied for comparisons of two samples [17].

Results

Appearance of CA125 in peritoneal effluent

CA125 appearance in the effluent was linear in time during dwells with 1.36% and 3.86% glucose based dialysate and with icodextrin (mean regression coefficient 0.97, range 0.93 to 0.99 for all). The comparison of 3.86% glucose dwells with either 1.36% glucose (Fig. 1A) or icodextrin (Fig. 1B) revealed no difference in CA125 concentrations at any time point ($P > 0.30$).

Day-to-day variability

The median CA125 appearance rates were: patient 1, 179 U/min, range 165 to 198; and patient 2, 155 U/min, range 131 to 173. Patient 3 showed median values 148 U/min (range 129 to 167). The mean day-to-day coefficient of variation was 6.4% (5.5 to 8.1) for CA125 appearance rates. The overall coefficient of variation for CA125 appearance rate was 7.7%.

Longitudinal follow up

Median cross sectional CA125 concentration was 13.8 U/ml, range 1.1 to 96.5. CA125 appearance rate was 108 U/min, range 10 to 610. The second year of treatment was assumed to represent the stable CAPD situation. In 26 patients observations had been made within this year of treatment. Mean values were 22.1 ± 2.1 U/ml/four hours for CA125 concentrations and 170 ± 15 U/min for the appearance rate. Both CA125 concentrations ($r = -0.51$, $P < 0.0001$) and appearance rates ($r = -0.49$, $P < 0.0001$) were inversely related to the duration of CAPD treatment (Fig. 2 for

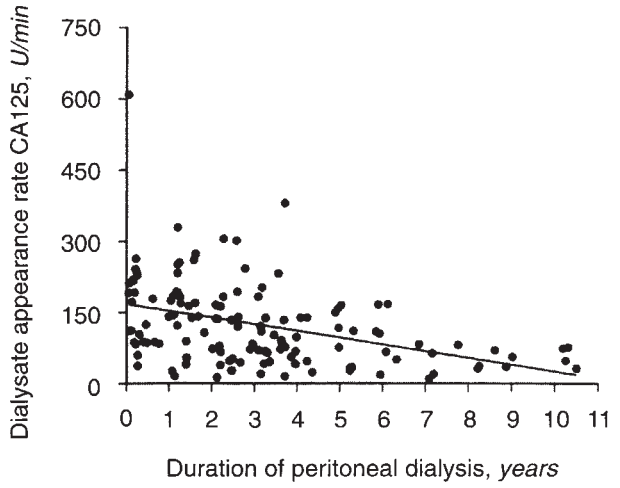

Fig. 2. *CA125 appearance rates were inversely related to duration of PD treatment* (r = −0.49, P < 0.001).

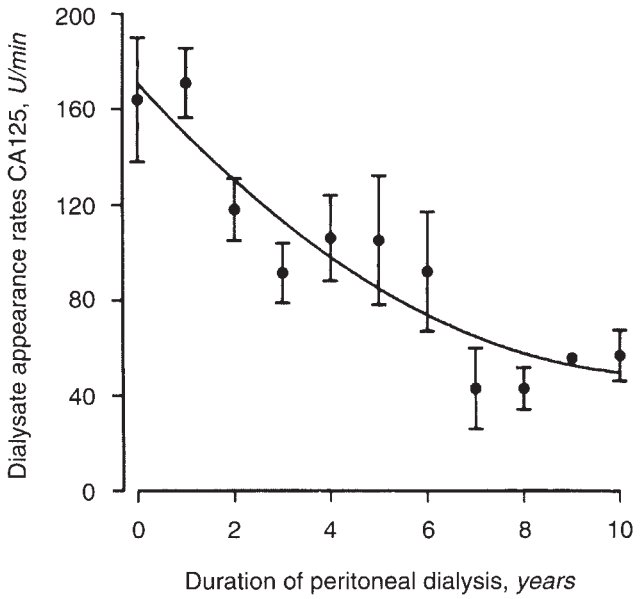

Fig. 3. *Analysis of trend, based on the individual regression coefficients, of CA125 versus duration of PD treatment (mean regression coefficient −3.80, SEM 2.38,* P < 0.01).

AR), and very weakly to peritonitis incidence ($r = -0.21, P = 0.02$ for AR).

After analysis of the trend, based on individual regression coefficients, a significant negative trend in time was found, with a mean regression coefficient of -3.80 ± 2.38, $P < 0.01$, which is shown in Figure 3. Using this trend, a median decrease of 2.2% (1.1 to 24.8) per year could be calculated. None of the patients showed a significant increase of CA125 (regression coefficient > −3.80 + 1 SEM). The appearance rate of CA125 remained stable (regression coefficient −3.80 ± 1 SEM) over the years in 11 patients, 4 of whom had values below the 10th percentile of the whole group thoughout their PD treatment (example given in Fig. 4A). In 20 other patients a significant decrease of the appearance rate of CA125 was found, which was defined as a regression coefficient lower than −3.80 to 1 SEM.

Sudden decreases were defined as values < 50% of the expected value according to the individual regression line of a patient. Five patients met these criteria, with a range of decrease of 50 to 97%. An example of a patient from this group in shown in Figure 4B. The clinical records of these patients were searched for possible etiological moments. The sudden decrease was preceded by treatment resistant peritonitis with *S. epidermidis* in one patient, and *Pseudomonas aeruginosa* peritonitis in a second patient, in whom the diagnosis peritoneal sclerosis was made shortly afterwards. Multiple peritonitis episodes (5) within one year occurred in the third patient. A temporary cessation of peritoneal dialysis preceded the change in CA125 in the last two patients, in one because of a fascia defect (2 months). In the second patient the reason was a chronic exit site infection (*S. aureus*) that required catheter replacement and temporary cessation of peritoneal dialysis for two weeks. No peritonitis episodes occurred shortly prior to the decrease in CA125 in these last two patients.

Discussion

The linear appearance of CA125 in peritoneal effluent of stable CAPD patients and its small coefficient of intra-individual variation, as found in the present study, support its use as a marker of peritoneal mesothelial cell mass or stable mesothelial cell turnover. These findings extend previous data based on the relation of dialysate CA125 with the mesothelial cell count [10], and on *in vitro* studies with cultured mesothelial cells [11].

In the present longitudinal study, a negative trend for the dialysate CA125 appearance rate with time on dialysis treatment was found. This provides evidence for loss of mesothelial cell mass during long duration peritoneal dialysis. Such a phenomenon is supported by scattered morphological studies, both under stable conditions [1], during peritonitis [2–4] and in the infrequent complication of peritoneal sclerosis [7]. In theory, loss of mesothelial cells could lead to an increased susceptibility to peritonitis or to impaired inflammatory control, because the mesothelial cells are important providers of inflammatory mediators. However, CA125 was only very weakly related to peritonitis incidence in the present study, and we are not aware of any reports on increased peritonitis incidence or severity in long-term CAPD patients. Although late peritonitis [18] and bouts of repeated episodes of peritonitis [19] may have some influence on membrane permeability, no data on mesothelial integrity were available in these studies. An alternative explanation for the negative trend of CA125 with duration of peritoneal dialysis could be that stabilization of the mesothelial cell population might result in a decline in CA125 appearance rates. Under those circumstances, a constant number of mesothelial cells would release a lower amount of CA125 into the peritoneal effluent after long-term peritoneal dialysis. In our opinion, this is not the most plausible explanation, because rather than stabilization, activation of mesothelial cells is induced by peritoneal dialysis [1]. It has further been shown that activation of a continous monolayer of cultured mesothelial cells with known stimuli does not lead to an increase of CA125 release [11]. Therefore, it is not very likely that even if

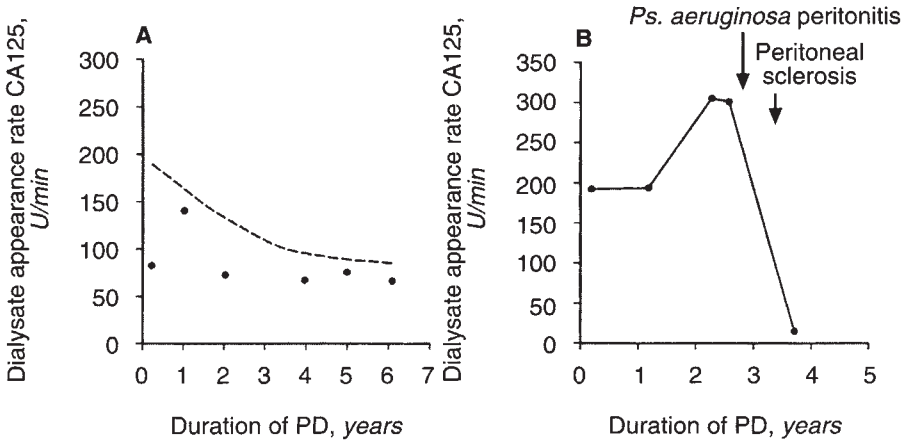

Fig. 4. *Representative examples of interindividual differences in CA125 follow-up between patients.* A patient with extremely low CA125 appearance rates throughout treatment is depicted in **A**. In **B** a patient with a sudden decrease in CA125 in shown.

stabilization of previously stimulated mesothelial cells would occur, this would affect CA125 appearance rates in the effluent.

Serial determinations of dialysate CA125 allow longitudinal follow-up of mesothelial cell mass in individual patients, which is impossible in morphological studies. Our data suggest a gradual loss of mesothelial cells in most patients on peritoneal dialysis. However, substantial interindividual differences existed in both CA125 appearance rates and the velocity of the decrease in CA125 with the duration of peritoneal dialysis treatment. Therefore, it seems appropriate to obtain normal values for each patient and to compare subsequent values to the individual regression line of a patient. In the follow-up of patients, changes in CA125 concentrations exceeding 10% from day-to-day can be considered as mesothelial alterations. These data were obtained by the Abbott IMx CA125 assay, which was validated for measurements in peritoneal effluents in our laboratory [10]. The IMx assay gives highly reproducible results, and stability proved to be good after three years at −20°C and in repeated thawing and freezing cycles (coefficients of variation 7 to 10%). Measurements in serum using this method have shown better reproducibility when compared to the Abbott RIA for CA125, as well as better results after sample dilution [20, 21]. The very low detection limit of the assay also is an advantage for the determination of CA125 concentrations in dialysis solutions. Data on comparisons of determinations of CA125 in serum by different assays point to distinct differences in results, and therefore it is advisable to always use the same method for follow-up of patients.

Sudden diversions from the regression line of CA125 in an individual patient should be considered an alarming sign for mesothelial damage. Individual susceptibility and interfering events seem to influence this process of loss of mesothelial cell mass. Possible events causing an acute decrease of mesothelial cell mass found in the present study were severe peritonitis episodes and temporary cessation of peritoneal dialysis. However, as shown in a previous study [22], uncomplicated peritonitis does not lead to changes in dialysate CA125 after recovery. This was supported the very weak relation between peritonitis incidence and CA125 appearance rates in the present study. It is, however, possible that distinct microorganisms, such as *Pseudomonas* species [23] or *S. aureus* [24, 25] are either more harmful to the mesothelium, or do cause more damage to an already injured peritoneum.

In four of our patients CA125 values below the 10th percentile of the group were found thoughout treatment. Two possibilities exist for this finding. Firstly, these patients may have a low number of mesothelial cells from the start, or alternatively, they may have continous low expression of CA125 in their mesothelial cells. This last possibility seems to be the most likely, because the percentage of mesothelial cells that express CA125 can vary between patients, but is constant in time in cultured mesothelial cells [11]. In addition, these four patients did not have a higher peritonitis incidence than the others, which would have pointed to the possibility of a lower number of mesothelial cells.

In the extreme situation of peritoneal fibrosis, the absence of mesothelial cells has been described [7]. The sudden development of extremely low CA125 concentrations in the only patient who developed peritoneal sclerosis in this series, indicates a massive loss of mesothelial cells, probably provoked by the severe peritonitis epidsode with *Pseudomonas aeruginosa* that may have accelerated the process of fibrosis. It suggests that these sudden decreases in CA125 should be considered as an alarming sign for the manifestation of peritoneal sclerosis. This contension is supported by extremely low CA125 concentrations in the effluent of six patients with peritoneal sclerosis that were found in a retrospective study [26]. The observation that cessation of peritoneal dialysis seemed to induce loss of mesothelial cells in two patients is rather confusing, because "peritoneal rest" has been proposed as a method of treatment of peritoneal membrane failure in the past [27, 28]. However, no effects of this treatment on mesothelial cell mass has been reported in these studies.

The actual cause of the loss of mesothelial cell mass that occurs remains speculative, but the unphysiological composition of dialysis solutions may be involved. Adverse effects of peritoneal dialysis solutions on cultured mesothelial cells have been described extensively [reviewed in 8]. Lysis of mesothelial cells can be caused by high glucose concentrations, high osmolality, and low pH in combination with lactate *in vitro*. The extent to which these data can be extrapolated to the *in vivo* situation remains uncertain. It should be appreciated that pH is almost immediately normalized by the residual volume in the peritoneal cavity [29]. Therefore, in the *in vivo* setting, high glucose and hyperosmolality are probably more important. If acute lysis of mesothelial cells would occur *in vivo*, this is likely to happen during the initial phase

of a dwell. In theory, this could be reflected in a marked release of CA125 during this phase. However, no such release of CA125 was found, indicating that the unphysiological composition of the dialysate does not cause lysis of mesothelial cells to such extent that it influences CA125 concentrations. It implies that the contribution of acute mesothelial cell loss to four-hour dwell concentrations of CA125 is negligible.

The detrimental effects of high glucose concentrations on cultured mesothelial cells could not be confirmed in the present *in vivo* study. No effect of dialysate glucose concentration on CA125 appearance rates was found at any time point during the four hour dwells. Similarly, no effect of hyperosmolality on acute mesothelial cell damage could be established, because CA125 release was similar during glucose 3.86% (osmolality 486 mOsm/kg H_2O) and 7.5% icodextrin (282 mOsm/kg H_2O). It can not, however, be excluded based on the results of the present study, that chronic exposure to unphysiological dialysis solutions causes changes in the peritoneal membrane. Glucose may especially be harmful, since the continuous exposition to unphysiologically high concentrations can lead to non-enzymatic glycosylation [30]. Such effects are also suggested by a recent finding that glucose exposition may be an additional risk factor for peritoneal sclerosis in peritoneal dialysis patients [31]. The effect of chronic exposure of the mesothelial cells to high glucose concentrations still has to be determined, and can only be answered when randomized long-term studies with different osmotic agents will become possible.

It can be concluded that dialysate CA125 is a useful marker for the follow-up of mesothelial cell mass or stable mesothelial cell turnover in individual peritoneal dialysis patients. A gradual loss of mesothelial cell mass occurs in most patients on peritoneal dialysis. Interindividual differences exist in the velocity of this process. Events causing a sudden loss of mesothelial cells include severe peritonitis episodes and possibly temporary cessation of peritoneal dialysis. A sudden decrease in CA125 must be considered as an alarming sign for the manifestation of peritoneal sclerosis. Prospective analysis of CA125 in PD effluent will be needed to determine the relevance of CA125 as a diagnostic tool for peritoneal sclerosis.

Acknowledgment

This study was supported by the Dutch Kidney Foundation (Grant 93/1302).

Reprint requests to Dr. Marja M. Ho-dac-Pannekeet, Department of Nephrology, F4-215, Academic Medical Center, P.O. Box 22700, 1100 ED Amsterdam, The Netherlands.

References

1. Dobbie JW, Zaki MA, Wilson MS: Ultrastructural studies on the peritoneum with special reference to chronic ambulatory peritoneal dialyis. *Scott Med J* 26:213–223, 1981
2. Di Paolo N, Sacchi G, De Mia M, Gaggiotti E, Capotondo L, Rossi P, Bernini M, Pucci AM, Ibba L, Sabatelli P, Alessandrini C: Morphology of the peritoneal membrane during continuous ambulatory peritoneal dialysis. *Nephron* 44:204–211, 1986
3. Gotloib L, Shostack A, Bar-Sella P, Cohen R: Continuous mesothelial injury and regeneration during long term peritoneal dialysis. *Perit Dial Bull* 7:148–155, 1987
4. Pollock CA, Ibels LS, Eckstein RP, Graham JC, Ceterson RJ, Mahony JF, Ross Sheil AG: Peritoneal morphology on maintenance dialysis. *Am J Nephrol* 9:198–204, 1989
5. Slater ND, Cope GH, Raferty AT: Mesothelial hyperplasia after chronic intraperitoneal fluid administration. A light miocroscopy study in the rat, in *Ambulatory Peritoneal Dialysis*, Avram MH, Giodano C, New York, Plenum, 1990, pp 110–112
6. Gotloib L, Wajsbrot V, Shostak A, Kushnier R: Experimental approach to peritoneal morphology. *Perit Dial Int* 14(Suppl 3):S6–S11, 1994
7. Dobbie JW, Henderson L, Wilson LS: New evidence on the pathogensis of sclerosing encapsulating peritonitis (SEP) obtained from serial biopsies, in *Advances in Contiuous Peritoneal Dialysis*, edited by Khanna, Nolph, Prowant, Twardowski, Oreopoulos, Toronto, University of Toronto Press, 1987, pp 138–149
8. Topley N, Williams JD: Role of the peritoneal membrane in the control of inflammation in the peritoneal cavity. *Kidney Int* 46(Suppl 48):S71–S78, 1994
9. Betjes MGH, Bos HJ, Krediet RT, Arisz L: The mesothelial cells in CAPD effluent and their relation to peritonitis incidence. *Perit Dial Int* 11:22–26, 1991
10. Koomen GCM, Betjes MGH, Zemel D, Krediet RT, Hoek FJ: Cancer antigen 125 is locally produced in the peritoneal cavity during continuous ambulatory peritoneal dialysis. *Perit Dial Int* 14:132–136, 1994
11. Visser CE, Brouwer-Steenbergen JJE, Betjes MGH, Koomen GCM, Beelen RHJ, Krediet RT: Cancer antigen 125: A bulk marker for the mesothelial mass in stable peritoneal dialyis patients. *Nephrol Dial Transplant* 10:64–69, 1995
12. Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths T, Parker L, Zurawksi VR Jr, Knapp RC: A radioimmunoassay using a monovclonal antibody to monitor the course of epithela ovarian cancer. *N Engl J Med* 309:883–887, 1983
13. Kabawat SE, Bast RC Jr, Bhan AK, Welchh WR, Knapp RC, Colvin RB: Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. *Int J Gynecol Pathol* 2:275–285, 1983
14. Pannekeet MM, Koomen GCM, Struijk DG, Krediet RT: Dialysate CA125 in stable CAPD patients: No relation with transport parameters. *Clin Nephrol* 44:248–254, 1995
15. Pannekeet MM, Imholz ALT, Struijk DG, Koomen GCM, Langedijk MJ, Schouten N, de Waart R, Hiralall J, Krediet RT: The standard peritoneal permeability analysis: A tool for the assessment of peritoneal permeability characteristics in CAPD patients. *Kidney Int* 48:866–875, 1995
16. Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in circulation research. *Circ Res* 47:1–9, 1990
17. Altman DG: *Practical Statistics for Medical Research*. London, Chapman and Hall, 1991, pp 179–228
18. Selgas R, Muñoz J, Cigarran S, Ramos P, L-Revuelta K, Escuin F, Miquel JL: Peritoneal functional parameters after five years on continuous ambulatory periotneal dialysis (CAPD): The effect of late peritonitis. *Perit Dial Int* 9:329–332, 1989
19. Davies SJ, Bryan J, Phillips L, Russell GI: Longitudinal changes in peritoneal kinetics: The effects of peritoneal dialysis and peritonitis. *Nephrol Dial Transplant* 11:498–506, 1996
20. Thomas CMG, Massuger LFAG, Segers MFG, Schijf CPT, Doesburg WH, Wobbes T: Analytical and clinical performance of improved Abbott IMx assay: Comparison with Abbott CA125 RIA. *Clin Chem* 41:211–216, 1995
21. Wong ECC: Difficulties in analysis of CA125 in diluted samples. (letter) *Clin Chem* 41:1543–1544, 1995
22. Pannekeet MM, Zemel D, Koomen GCM, Struijk DG, Krediet RT: Dialysate markers of peritoneal tissue during peritonitis and in stable CAPD. *Perit Dial Int* 15:217–225, 1995
23. Bunke M, Brier ME, Golper TA: Pseudomonas peritonitis in peritoneal dialysis patients: The network #9 peritonitis study. *Am J Kidney Dis* 25:769–774, 1995
24. Selgas R, Munoz J, Ramos P, L-Revuelta K, Escuin F, Miguel JL: Peritoneal functional parameters after five years on continuous ambulatory peritoneal dialysis (CAPD): The effects of late peritonitis. *Perit Dial Int* 9:329–332, 1989

25. DOBBIE JW, KREDIET RT, TWARDOWSKI ZJ, NICHOLS WK: A 39-year old man with loss of ultrafiltration. *Perit Dial Int* 14:384–394, 1994
26. KREDIET RT, PANNEKEET MM, STEGEMAN G, STRUIJK DG: Markers of peritoneal tissue in stable CAPD patients and patients with sclerosing peritonitis. *Perit Dial Int* 15(Suppl 2):S43, 1995
27. MACTIER RA: Investigation and management of ultrafiltration failure in CAPD. *Adv Perit Dial* 7:57–62, 1991
28. DE ALVARO F, CASTRO MJ, DAPEANA F, BAJO MA, FERNANDEZ-REYES MJ, ROMERO JR, JIMENEZ C, MIRANDA B, SELGAS R: Peritoneal resting is beneficial in peritoneal hyperpermeability and ultrafiltration failure. *Adv Perit Dial* 9:56–61, 1993
29. PEDERSEN FB, RYTTOR N, DELURAN P, DRAGSHOLT C, KILDEBERG P: Acatate versus lactate in peritoneal dialysis solutions. *Nephron* 39:55–58, 1985
30. YAMADA K, MIYAHARA Y, HAMAGUCHI K, NAKAYAMA M, NAKANO H, NOZAKI O, MIURA Y, SUZUKI S, TUCHIDA H, MIMURA N, ARAKI N, HORIUCHI S: Immunohistochemical study of human advanced glycosylation end-products (AGE) in chronic renal failure. *Clin Nephrol* 42:354–361, 1994
31. HENDRIKS PMEM, HO-DAC-PANNEKEET MM, VAN GULIK THM, STRUIJK DG, PHOA SSKS, SIE LH, KOX C, KREDIET RT: Peritoneal sclerosis in chronic peritoneal dialysis patients. Analysis of clinical presentation, riskfactors and peritoneal transport kinetics. *Perit Dial Int* (in press)