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Kinetics of peritoneal protein loss during CAPD: I. Different characteristics for low and high molecular weight proteins

ALEXANDER KAGAN, YAACOV BAR-KHAYIM, ZEHAVA SCHAFER, and MENAHEM FAINARU

Lipid Research Laboratory, Department of Medicine 'A', and Division of Nephrology, Kaplan Hospital, Rehovot, Israel

Kinetics of peritoneal protein loss during CAPD: I. Different characteristics for low and high molecular weight proteins. We studied the peritoneal protein loss in 13 patients during CAPD using 2 liters of 1.5% dextrose dialysis solutions. We compared the kinetic characteristics of the peritoneal mass transfer and clearance of proteins over a wide range of molecular size, to those of small molecular weight solutes. The peritoneal clearance of all studied proteins and solutes correlated strongly and negatively with their molecular mass. No changes were observed in these clearances during 58 months of dialysis. Unlike the peritoneal mass transfer and clearance of small molecular weight solutes (< 200) which revealed a remarkable progressive drop after the first hour of an eight-hour dialysis cycle, the mass transfer and clearance of proteins of large molecular weight (> 68,000) was continuous throughout the eight hours. The clearance of proteins of small molecular weight (< 15,000) showed similar kinetics to small solutes (< 200). These results indicate that long dwell times (6 or 8 hr) of peritoneal dialysis are detrimental for the loss of large molecular weight proteins (such as albumin and immunoglobulins) in view of the negligible dialysance of both small solutes (creatinine and potassium) and "intermediate molecules" (represented by the small molecular weight proteins) during the latter hours of long dwell cycles. Thus we suggest that substituting CAPD (3 × 8 hr or 4 × 6 hr) with CCPD (6 × 1 hr) may limit protein loss in these patients.

Since its introduction in 1976 [1], continuous ambulatory peritoneal dialysis (CAPD) has been widely accepted as a treatment for end-stage renal disease [2] resulting in a survival similar to that obtained in patients maintained on hemodialysis [3]. One of the major disadvantages of CAPD is protein loss in the nephrotic range: 5 to 15 g/day [4]. Such a loss of plasma proteins into the dialysis fluid may lead to depletion of the visceral protein pool unless replenished by an adequate dietary intake [5].

In the present study we investigated the kinetics of protein loss as a function of molecular weight, dwell-time and duration of dialysis, and compared it to the kinetics of small solutes clearance. These results may be used for planning of alternative regimens for peritoneal dialysis that will preserve the dialysis efficiency while minimizing the loss of high molecular weight proteins.

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Methods

Patients

Thirteen patients, (5 females and 8 males, aged 18 to 73 years) with end-stage renal failure and undergoing continuous ambulatory peritoneal dialysis were studied. The etiology of their kidney disease and other clinical characteristics are detailed in Table 1. None of the patients was obese, suffered from diabetes mellitus, nephrotic syndrome or overt liver disease. None of the patients has been previously treated by hemodialysis or had a kidney transplant. Five patients (prospective group, patients 1 to 5) had been recruited before the start of CAPD treatment and were studied during their training period, at one, three and six months on CAPD. The other eight patients (6 to 13, Table 1) were studied at 6 to 58 months on CAPD. None of the studies was conducted within one month of a peritonitis episode. The study was approved by the Human Studies Committee of the Hospital, and an informed consent was obtained from each subject.

Dialysis procedure

All patients had a Tenckhoff peritoneal catheter and were on CAPD for one day to 58 months. They were dialyzed continuously with three to four exchanges daily using 2 liter plastic bags of Travenol® Dianeal, 1.5% Dextrose (Travenol Laboratories, Ashdod, Israel). Dehydrating solutions (4.25% Dextrose), were used intermittently when indicated. The daily energy intake was about 30 Kcal/kg in addition to calories derived from dextrose in the dialysis fluid. The mean daily protein intake was 1.5 g/kg of body weight, and their diet was supplemented with vitamins, calcium and aluminium hydroxide.

Study protocol

Two liter bags of Travenol® Dianeal 1.5% dextrose solutions were used for the exchanges. Calculations were based on our own determinations of volume 2.1 ± 0.005 liter and dextrose concentration 67.3 ± 0.9 mmol/liter (mean ± SD, $N = 12$). The effluents were collected in each study following sequential cycles of varying dwell time: eight hours (usually from midnight to 8 a.m.), four hours and one hour, respectively, without disruption of CAPD. No study was performed if the eight hour effluent contained more than 100 cells per μl. All patients were recumbent and fasting during collection of samples (17 hr).

Table 1. Clinical characteristics and initial[a] blood analysis in CAPD patients

No.	Age *yr*	Sex	Etiology of kidney disease	Drug therapy	Duration of CAPD *months*	Blood pressure *mm Hg*	Weight *kg*	Height *m*	Hct %	Glucose	Urea	Creatinine	Albumin *g/liter*
										mmol/liter			
1	40	F	UNK	—	0-6	190/100	51	1.52	26.8	4.9	23.3	0.70	44.0
2	58	F	CGN	Aten	0-6	190/120	71	1.66	28.5	5.6	27.7	1.21	42.0
3	42	F	UNK	—	0-6	170/100	45	1.64	27.5	4.8	17.5	0.57	38.0
4	18	M	CGN	—	0-3	170/100	52	1.76	25.1	4.2	25.5	0.70	37.0
5	73	M	HT	Nif, Clon	0-3	180/80	66	1.68	32.4	5.8	25.5	0.92	44.0
6	59	M	HT	MD, Ver	6	165/80	84	1.72	29.8	4.9	28.3	1.09	40.0
7	35	M	CPN	—	14, 32	110/70	71	1.78	30.1	5.3	27.7	1.13	41.0
8	56	M	UNK	—	18	140/90	56	1.38	35.8	5.2	25.3	0.88	40.0
9	66	F	UNK	—	9	130/85	45	1.45	30.4	6.1	15.3	0.74	39.0
10	50	M	UNK	—	16	145/80	50	1.59	31.2	5.1	13.5	1.14	46.0
11	53	M	UNK	—	58	165/85	62	1.70	38.1	4.9	26.2	1.32	43.0
12	38	F	UNK	—	28	100/70	54	1.54	28.9	5.3	18.0	1.01	38.0
13	39	M	CGN	—	32	160/110	69	1.77	30.5	4.8	28.2	1.16	42.0

[a] Before the start of CAPD treatment

Abbreviations are: Hct, hematocrit; UNK, unknown; CGN, chronic glomerulonephritis; HT, hypertension; CPN, chronic pyelonephritis; Aten, atenolol; Nif, nifedipine; Clon, clonidine; MD, alpha methyldopa; Ver, verapamil.

Sample collection and analysis

During each study two venous blood samples were obtained at 8 a.m. and 12 noon. The dialysate effluents were collected into cooled bags on ice and processed at 4°C. Their volume was determined and centrifuged together with the blood samples at 2500 × g for 20 minutes. One to two liter aliquots were concentrated to 10 to 30 ml (30- to 100-fold) by means of membrane ultrafiltration using an YM-10 membrane and a 300 ml cell (Amicon Corp., Danvers, Massachusetts, USA), using N_2 at 4 kg/cm^2 at 4°C. The concentrated dialysate and the ultrafiltrate were collected separately.

The protein concentration on original, concentrates and ultrafiltrates of effluent samples was quantified by the method of Lowry et al using bovine serum albumin as standard [6]. Total protein and albumin levels in serum, and albumin level in concentrated effluents were analyzed by standard autoanalyzer techniques (Technicon Corp. Tarrytown, New York, USA). As the molecular cutoff of the YM-10 membrane is 10,000 daltons the proteins determined in the concentrate consisted of high molecular weight proteins (HMWP), and the ultrafiltrate contained the low molecular weight proteins (LMWP). This separation was verified by electrophoresis on sodium dodecyl sulfate polyacrylamide gel. Samples of serum and unconcentrated effluent were analyzed for urea, creatinine, uric acid, phosphorus, potassium, glucose, by standard autoanalyzer techniques (Technicon Corp.). Concentrations of IgG, IgA, IgM and complement components C_3 and C_4 in serum and concentrated dialysate were measured by nephelometric methods [7]. Lysozyme activity was determined on serum and dialysate samples by a turbidometric method [8]. The sensitivities of the protein determination methods were as follows: protein by the method of Lowry et al [6] — 4 mg/liter; albumin by the autoanalyzer technique was 1 g/liter; IgG, IgA and IgM — 10 mg/liter; C_3 — 14 mg/liter; C_4 — 2.2 mg/liter and for lysozyme 0.5 mg/liter.

Calculations and data analysis

The optimal design for studying the kinetics of protein loss during CAPD calls for sampling of small aliquots from the peritoneal effluent at regular intervals from initiation of an eight hour dialysis cycle. Such a study was not feasible in our patients because of ethical and methodological reasons. We were concerned that such samplings might have added to the propensity of peritonitis in these patients. The sensitivity of our methods used for the determinations of various protein concentrations in the effluent necessitated sampling of large volumes of dialysate, which would have perturbed the kinetics of protein loss. Therefore, we preferred to study three consecutive cycles of varying length (8,4, and 1 hr) in each individual, and calculate the kinetics at different time intervals by subtractions as explained below. We were concerned about the possible diurnal effects and the order of studies. In preliminary studies (not shown) we have validated our study protocol both by showing no diurnal effect on the kinetics of protein loss (3 × 8 hr daily cycles in five patients, each studied twice) and by showing no appreciable effect to randomization of the order of cycles studied (8,4,1 when compared to both 8,1,4 and 1,4,8). Furthermore, the results detailed in the present article show no effect of the duration of CAPD treatment in five patients studied prospectively for six months (N = 18), corroborating the validity and reproducibility of the study protocol.

Peritoneal mass transfer (mass/hr) and clearance of solutes (ml/min) were calculated as follows: $Ve \cdot Ce/T$ and $Ve \cdot Ce/t \cdot P$, respectively, where: Ve = total dialysate effluent volume (ml); Ce = dialysate effluent concentration of solutes; T and t = dwell time in hours and minutes, respectively, and P = serum concentration (average of the two determinations). For glucose mass transfer and clearance the following formulas were used: $(Vi \cdot Ci - Ve \cdot Ce)/T$ and $(Vi \cdot Ci - Ve \cdot Ce)/t \cdot Ci$, respectively, where Vi = total dialysate influent volume (ml) and Ci = influent dialysate glucose concentration. These calculations were used for estimation of both mass transfer and clearance during the studied dwell times of one, four and eight hours. For one to four hour and four to eight hour periods of an eight-hour dwell time the mass transfer and clearance of solutes were calculated for each study separately using the following formulas: $(Ce_2 \cdot Ve_2 - Ce_1 \cdot Ve_1)/(T_2 - T_1)$ and $(Ce_2 \cdot Ve_2 - Ce_1 \cdot Ve_1)/(t_2 - t_1) \cdot P$, respectively, where the subscript 2

Table 2. Peritoneal loss of solutes during an 8 hour cycle of CAPD[a]

	Mass transfer *mg/hr/1.73 m²*	Clearance *ml/min/1.73 m²*
Potassium	1.11 ± 0.04[b]	3.95 ± 0.13
Urea	396.2 ± 24.6	4.95 ± 0.18
Creatinine	23.7 ± 1.35	3.87 ± 0.10
Uric acid	15.4 ± 0.47	3.53 ± 0.10
Inorganic phosphorus	11.3 ± 0.62	3.71 ± 0.13
Glucose (absorbed)	2177.0 ± 94.4	2.99 ± 0.13
Total protein	609.1 ± 38.6	0.166 ± 0.013
LMWP[c]	80.9 ± 5.14	—
Lysozyme	0.9 ± 0.08	0.685 ± 0.06
HMWP[c]	462.2 ± 37.45	—
Albumin	255.7 ± 15.19	0.121 ± 0.009
IgG	51.7 ± 4.41	0.090 ± 0.009
IgA	9.8 ± 0.89	0.073 ± 0.007
C_3	5.4 ± 0.58	0.089 ± 0.010
C_4	1.3 ± 0.10	0.075 ± 0.006
IgM	2.7 ± 0.43	0.052 ± 0.007

[a] The results represent 27 studies performed in 13 patients and are expressed as mean ± SEM. All patients were recumbent and fasting. Two liters of Dianeal 1.5% were used for 8 hr exchanges.

[b] The results are expressed as mEq/hr/1.73 m^2

[c] LMWP–low molecular weight proteins (< 10.000), HMWP–high molecular weight proteins (> 10.000). These fractions were obtained by ultrafiltration through a YM-10 (Amicon) membrane.

represents the longer cycle (4 and 8 hr) and the subscript 1 represents the shorter cycles (1 and 4 hr, respectively).

All data were normalized for a body surface area of 1.73 m^2 and evaluated by Student's *t*-test, analysis of variance and linear regression [9].

Results

Effect of the molecular mass and cycle length on peritoneal clearance

The peritoneal loss, calculated both as mass transfer and clearance, of solutes having a wide range of molecular sizes during eight hours of an uninterrupted CAPD cycle is detailed in Table 2. From this table and Figure 1A it is evident that the peritoneal clearance of these solutes is inversely correlated to their respective molecular mass. For the small molecular weight solutes (< 200) this was $r = -0.696$, $P < 0.05$ and for the large molecular weight solutes (> 68,000) $r = -0.912$, $P < 0.0005$.

When these losses during a regular cycle of eight hours were divided into time intervals: (0 to 1, 1 to 4 and 4 to 8 hr) a major difference was observed between the behavior of small and large molecular weight solutes (Table 3). The mass transfer of small molecular weight solutes revealed a remarkable drop with the progress of the cycle duration, whereas the mass transfer of large molecular weight solutes did not change much (Table 3, Fig. 2). A similar difference between small and large molecular weight solutes was also observed when the peritoneal clearance was calculated (Table 3). The peritoneal mass transfer and clearance of the large solutes (molecular weight > 68,000) showed a biphasic pattern during the eight hour exchange. Their loss decreased significantly during the mid-interval (1 to 4 hours) when compared to 0 to 1 and 4 to 8 hour periods ($P <$ 0.05; Table 3, Fig. 2).

As a result of the differential behavior between small and large molecular weight solutes, the linear regression between their peritoneal clearances and their respective molecular weights varied among the different dwell time periods (Fig. 1B). Unlike the large molecular weight solutes which showed similar slopes during the various time intervals (−10.7, −14.1 and −14.6 for 0 to 1, 1 to 4 and 4 to 8 hr periods, respectively), the clearance of small molecular weight solutes revealed a remarkable change in these slopes during the different time periods (−0.05, −0.33, and +0.58, for 0 to 1, 1 to 4 and 4 to 8 hr, respectively; Fig. 1B). One may calculate from Table 3 that for a peritoneal loss of 1 g of urea at intervals 0 to 1, 1 to 4 and 4 to 8 hours of the cycle, 0.18, 0.55 and 2.51 g of albumin are lost, respectively.

It is of special interest that proteins of small molecular weight, such as lysozyme (molecular wt 14580), and the proteins that underwent ultrafiltration during concentration of the peritoneal effluent (molecular wt < 10,000) showed a kinetic pattern similar to that of small molecular weight solutes (< 200) rather than that observed in plasma proteins of higher molecular mass (Table 3, Fig. 2). The clearance of these "middle" molecular weight proteins decreased with the prolongation of dwell time. Therefore, we may conclude that during long cycles the loss of high molecular weight proteins is not accompanied by efficient dialysis.

Effect of duration of CAPD treatment on peritoneal clearance and serum levels of solutes

No statistically significant changes were observed in the peritoneal clearance (8 hr dwell) of all studied solutes, of either small, intermediate or large molecular weight, during 58 months of dialysis (Table 4; F value for analysis of variance <1.0, $P >$ 0.5). Similar results were observed also for the initial rate during the first hour of dwell (not shown). Nonetheless, we have observed a tendency for changes in the serum level of some of the studied solutes during the 58 months (Table 5). Mean serum creatinine concentration increased from 0.8 to 1.2 mmol/liter during three years of CAPD, without a parallel drop in its peritoneal clearance during this period (Tables 4, 5). Lysozyme showed a tendency to lower serum levels at one to six months of dialysis without a concomitant increase of its peritoneal clearance during this period. Serum albumin showed a tendency for a drop of about 5 g/liter during three years of dialysis without a remarkable change in its clearance.

Most solutes studied revealed a positive significant linear correlation between their peritoneal loss and their respective blood levels (Table 6, Fig. 3). The mass transfer of albumin was negatively correlated to its plasma levels, unlike all other studied solutes of both small and large molecular weight, which showed a positive correlation (Table 6).

Discussion

In the present study we investigated the possible contribution of some factors to the kinetic characteristics of protein loss into peritoneal fluid during CAPD. We have followed prospectively five patients for six months and examined another eight patients up to 58 months on CAPD. Few studies have been performed to date on the peritoneal transport kinetics in CAPD patients followed for more than one year [10–14]. These studies have shown that in most patients no significant changes occur with duration of dialysis in the peritoneal mass transfer of low,

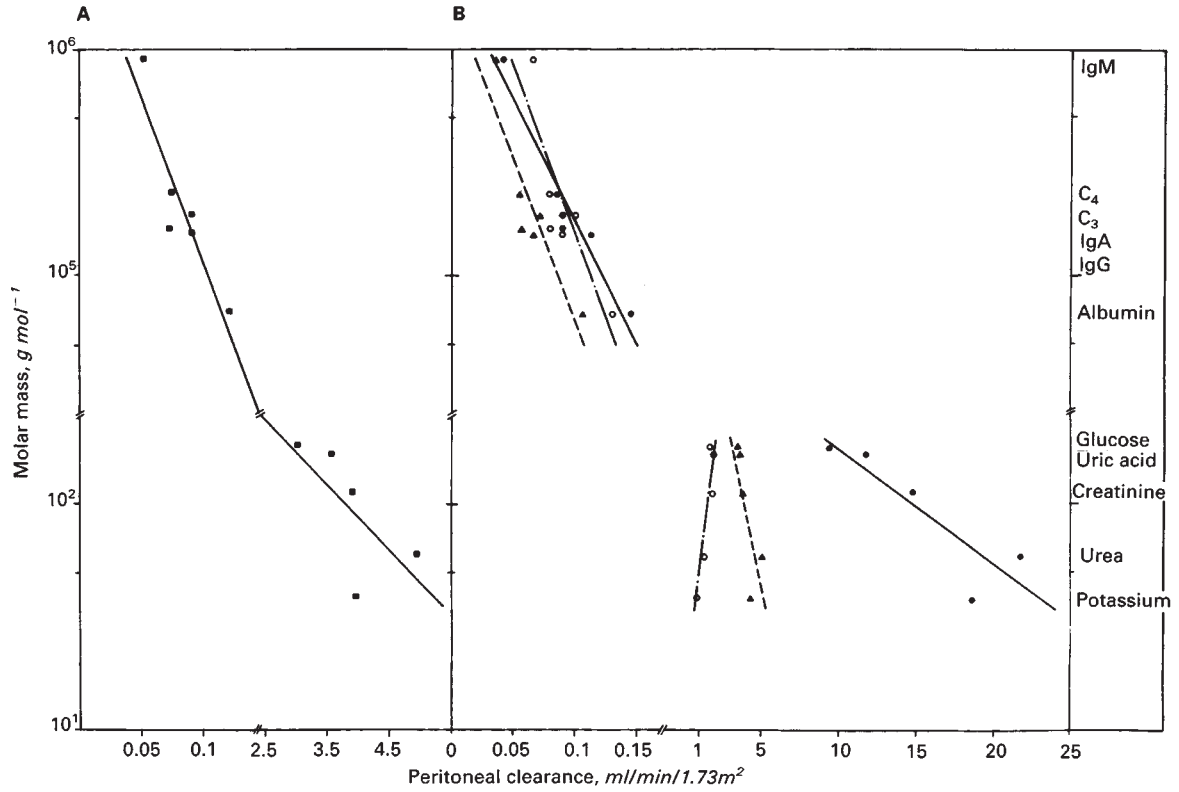

Fig. 1. *Effect of molecular mass on the peritoneal clearance of solutes during 0–8 hours (■) (A) and 0–1 hr (●——●), 1–4 hr (▲----▲) and 4–8 hr (○–·–○) (B) of an 8 hour CAPD cycle.* The clearance of each solute was calculated from the average serum levels of two determinations during the study, and the mass recovered sequentially in the peritoneal effluent at following dwell times: 8 hr, 4 hr and 1 hr (27 studies in 13 patients). The mass lost during 1–4 hr and 4–8 hr periods were calculated by subtracting the 1 hr from 4 hr, and 4 hr from 8 hr values, respectively. The regression equations obtained were as follows: A. Small solutes (molecular < 200): Log y = 3.065 − 0.281x, $r = -0.696$, $P < 0.05$; large solutes (molecular wt > 68000): Log y = 6.507 − 14.44x, $r = 0.912$, $P < 0.0005$. B. Small solutes 0–1 hr: Log y = 2.754 − 0.05x, $r = -0.884$, $P < 0.025$; 1–4 hr: Log y = 3.3 −0.331x, $r = -0.743$, $P < 0.05$; 4–8 hr: Log y = 1.112 + 0.579x, $r = +0.898$, $P < 0.01$; large solutes 0–1 hr, Log y = 6.311 − 10.716x, $r = -0.968$, $P < 0.005$; 1–4 hr: Log y = 6.213 − 14.085x, $r = -0.885$, $P < 0.005$; 4–8 hr: Log y = 6.631 − 14.582x, $r = -0.857$, $P < 0.01$.

Table 3. Effect of dwell time on peritoneal loss of solutes during CAPD[a]

	Mass transfer *mg/hr/1.73 m²*			Clearance *ml/min/1.73 m²*		
Dwell time, *hours*	0–1	1–4	4–8	0–1	1–4	4–8
Potassium	5.1 ± 0.2[b]	1.2 ± 0.1[b,d]	0.2 ± 0.04[b,d,e]	18.47 ± 0.95	4.18 ± 0.22[d]	0.78 ± 0.15[d,e]
Urea	1676.7 ± 91.5	381.1 ± 23.1	108.7 ± 17.3[d,e]	21.71 ± 0.98	5.01 ± 0.28[d]	1.36 ± 0.20[d,e]
Creatinine	84.3 ± 4.7	21.9 ± 1.3[d]	11.2 ± 1.1[d,e]	14.72 ± 1.04	3.69 ± 0.20[d]	1.82 ± 0.15[d,e]
Uric acid	49.8 ± 3.9	16.1 ± 1.0[d]	8.3 ± 0.6[d,e]	11.59 ± 0.94	3.67 ± 0.22[d]	1.87 ± 0.13[d,e]
Inorganic phosphorus	35.5 ± 2.5	10.1 ± 0.9[d]	7.2 ± 0.6[d,e]	11.85 ± 0.81	3.30 ± 0.23[d]	2.34 ± 0.16[d,e]
Glucose (absorbed)	6822.9 ± 890.9	2443.3 ± 274.9[d]	1205.8 ± 120.8[d,e]	9.38 ± 1.22	3.35 ± 0.37[d]	1.65 ± 0.16[d,e]
Total protein	1297.8 ± 109.4	454.2 ± 50.5[d]	567.0 ± 53.7[d]	0.35 ± 0.04	0.13 ± 0.02[d]	0.16 ± 0.02[d]
LMWP[c]	522.3 ± 48.0	36.5 ± 5.0[d]	29.9 ± 5.1[d]	—	—	—
Lysozyme	7.0 ± 2.0	1.0 ± 0.3[d]	0.4 ± 0.1[d,e]	5.14 ± 1.53	0.57 ± 0.18[d]	0.31 ± 0.09[d]
HMWP[c]	587.1 ± 62.5	382.0 ± 39.4[d]	487.9 ± 54.4	—	—	—
Albumin	303.5 ± 33.0	211.6 ± 16.7[d]	273.3 ± 21.2[e]	0.14 ± 0.02	0.1 ± 0.01[d]	0.13 ± 0.01
IgG	68.1 ± 9.3	38.5 ± 3.4[d]	53.4 ± 5.8[e]	0.12 ± 0.01	0.07 ± 0.01[d]	0.09 ± 0.01[e]
IgA	13.4 ± 2.2	7.4 ± 0.8[d]	10.6 ± 1.2[e]	0.09 ± 0.01	0.06 ± 0.01[d]	0.08 ± 0.01[e]
C_3	5.3 ± 0.6	4.1 ± 0.5	5.9 ± 0.9[e]	0.09 ± 0.01	0.070 ± 0.01	0.10 ± 0.01
C_4	1.9 ± 0.5	0.9 ± 0.1[d]	1.4 ± 0.2[e]	0.09 ± 0.01	0.05 ± 0.01[d]	0.08 ± 0.01[e]
IgM	2.3 ± 0.4	1.9 ± 0.3	3.6 ± 0.8[e]	0.04 ± 0.01	0.03 ± 0.01	0.06 ± 0.01[e]

[a] The results represent 26 studies performed in 13 patients and are expressed as mean ± SEM. Two liters of Dianeal[R] 1.5% were used for three consecutive exchanges of 8, 4 and 1 hours. The solute loss during the dwell times of 1–4 and 4–8 hours were calculated from the 0–1, 0–4 and 0–8 hr losses.

[b] The mass transfer of potassium is expressed in mEq/hr/1.73 m²

[c] LMWP-low molecular weight and HMWP-high molecular weight proteins, see Table 2

[d] $P < 0.05$ when compared to 0–1 hr time interval

[e] $P < 0.05$ when compared to 1–4 hr time interval

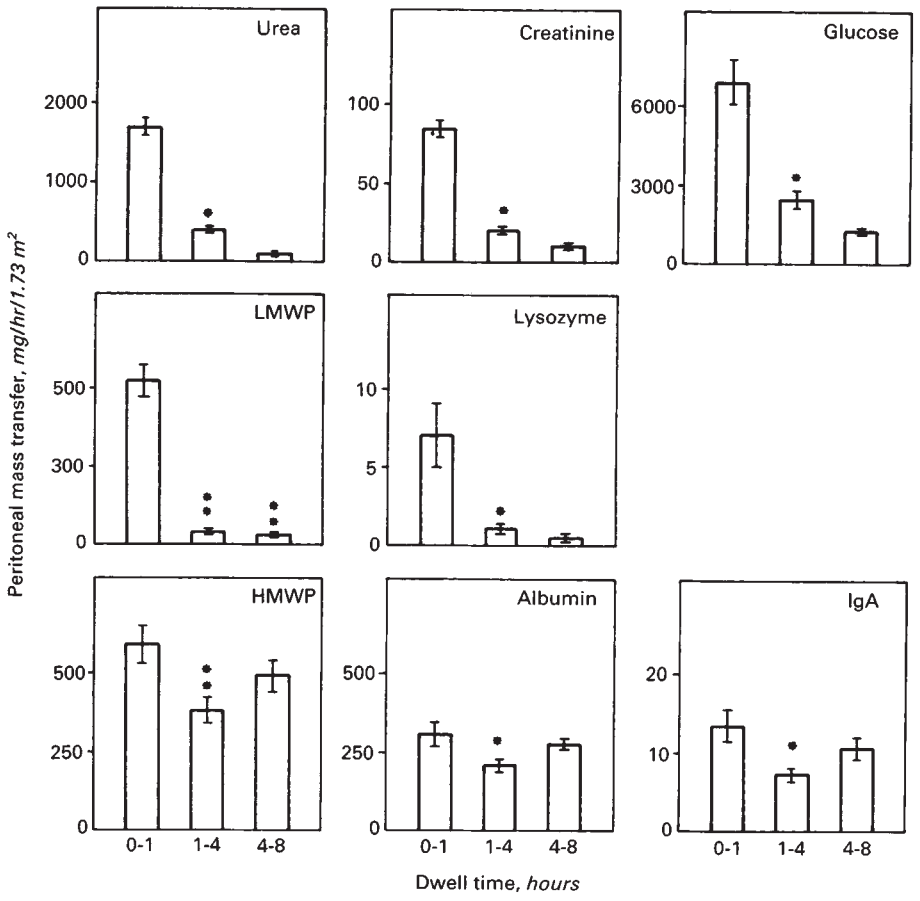

Fig. 2. *Effect of dwell time on the peritoneal mass transfer of small* (molecular wt < 200, upper panels), intermediate size (middle panels) and large molecular weight solutes (molecular wt > 68,000, lower panels), in 13 patients on CAPD. The bars represent mean ± SEM of 27 studies. The individual data were calculated for the various time intervals as detailed in the legend to Figure 1. * represents statistical significance ($P < 0.05$) by paired Student's *t*-test compared with both 0–1 hr and 4–8 hr intervals; **$P < 0.05$ by paired *t* test compared with 0–1 h interval.

Table 4. Effect of duration of CAPD treatment on peritoneal clearance of solutes during an 8 hour cycle[a]

Months on dialysis	0 (5)[b]	1 (5)	3 (5)	6 (4)	9–18 (4)	28–58 (4)
	ml/min/1.73 m²					
Potassium	3.97 ± 0.32	3.83 ± 0.24	3.96 ± 0.40	3.94 ± 0.44	4.16 ± 0.13	3.89 ± 0.29
Urea	5.30 ± 0.30	5.18 ± 0.42	5.21 ± 0.58	4.65 ± 0.55	4.79 ± 0.15	4.33 ± 0.33
Creatinine	3.66 ± 0.24	3.92 ± 0.08	4.00 ± 0.35	3.70 ± 0.26	4.08 ± 0.21	3.84 ± 0.23
Uric acid	3.21 ± 0.31	3.54 ± 0.06	3.59 ± 0.28	3.42 ± 0.20	3.80 ± 0.23	3.67 ± 0.24
Inorganic phosphorus	3.24 ± 0.33	3.77 ± 0.15	3.88 ± 0.37	3.63 ± 0.16	4.18 ± 0.33	3.66 ± 0.41
Glucose (absorbed)	2.68 ± 0.44	3.01 ± 0.19	2.99 ± 0.11	2.68 ± 0.08	3.37 ± 0.48	3.31 ± 0.15
Total protein	0.14 ± 0.03	0.17 ± 0.02	0.16 ± 0.02	0.18 ± 0.03	0.20 ± 0.05	0.16 ± 0.01
Lysozyme	0.67 ± 0.06	0.70 ± 0.13	0.84 ± 0.22	0.70 ± 0.16	0.68 ± 0.03	0.48 ± 0.06
Albumin	0.10 ± 0.02	0.13 ± 0.02	0.13 ± 0.02	0.14 ± 0.02	0.12 ± 0.02	0.12 ± 0.01
IgG	0.07 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.02	0.09 ± 0.03	0.12 ± 0.03
IgA	0.06 ± 0.01	0.08 ± 0.02	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.02	0.07 ± 0.01
C_3	0.08 ± 0.02	0.09 ± 0.02	0.09 ± 0.01	0.10 ± 0.02	0.10 ± 0.04	0.09 ± 0.01
C_4	0.07 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01
IgM	0.03 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.02	0.08 ± 0.03

[a] The results represent 27 studies performed in 13 patients according to the duration of CAPD and are expressed as mean ± SEM. 0, 1 and 3 months represent repeated studies in the prospective group-patients No. 1–5 (Table 1) and the 6 months determination are studies performed in patients No. 1–3 and 6. The remainder were studied once at the time stated in Table 1, in addition to patient No. 7 who was restudied at 32 months. None of the differences were statistically significant by analysis of variance ($F < 1.0$).

[b] Figures in parentheses represent number of patients studied at each time period

middle and large molecular weight solutes. Our study confirms these findings, that is, no major changes were observed in the clearance of all investigated solutes from smallest molecules, such as potassium, up to the largest, such as IgM, during 58 months of CAPD. Moreover, no consistent differences in the peritoneal transport kinetics were observed with age, sex or number of peritonitis episodes [14–18].

The most important single factor found to affect the perito-

Table 5. Effect of duration of CAPD treatment on plasma levels of solutes[a]

Months on dialysis	0 (5)[b]	1 (5)	3 (5)	6 (4)	9–18 (4)	28–58 (4)	F[c]
Potassium *mmol/liter*	5.1 ± 0.3	4.8 ± 0.3	4.8 ± 0.3	4.5 ± 0.2	4.4 ± 0.6	4.7 ± 0.4	0.38
Urea *mmol/liter*	23.9 ± 1.54	19.8 ± 1.7	22.0 ± 3.5	21.2 ± 2.5	20.5 ± 3.1	26.5 ± 2.8	0.69
Creatinine *mmol/liter*	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	2.32
Uric acid *mmol/liter*	0.5 ± 0.03	0.4 ± 0.03	0.4 ± 0.02	0.5 ± 0.02	0.4 ± 0.02	0.4 ± 0.02	0.62
Inorganic phosporous *mmol/liter*	1.7 ± 0.2	1.4 ± 0.03	1.6 ± 0.2	1.6 ± 0.1	1.5 ± 0.2	2.2 ± 0.2	1.83
Glucose *mmol/liter*	5.1 ± 0.3	5.5 ± 0.2	5.0 ± 0.1	5.1 ± 0.1	5.4 ± 0.2	5.1 ± 0.1	1.06
Total protein *g/liter*	67.0 ± 3.0	62.9 ± 2.0	60.5 ± 3.5	60.1 ± 3.9	64.7 ± 4.0	62.7 ± 1.0	0.55
Lysozyme *mg/liter*	23.4 ± 1.2	16.4 ± 1.5	17.6 ± 2.2	25.5 ± 1.8	26.0 ± 1.9	28.4 ± 3.8	4.05[c]
Albumin *g/liter*	40.3 ± 1.6	37.0 ± 1.7	36.0 ± 2.0	35.5 ± 0.4	36.3 ± 2.9	35.5 ± 2.4	0.46
IgG *g/liter*	10.1 ± 1.5	9.9 ± 1.2	9.6 ± 1.3	9.6 ± 0.6	11.5 ± 1.6	9.3 ± 0.9	0.26
IgA *g/liter*	2.1 ± 0.2	2.3 ± 0.3	2.2 ± 0.2	2.2 ± 0.2	3.0 ± 0.6	2.2 ± 0.3	0.69
C_3 *g/liter*	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.2	1.2 ± 0.1	1.2 ± 0.3	1.92
C_4 *g/liter*	0.3 ± 0.03	0.3 ± 0.02	0.2 ± 0.02	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.04	2.16
IgM *g/liter*	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.8 ± 0.2	1.1 ± 0.1	0.9 ± 0.2	0.17

[a] The studies were performed on patients detailed in Table 5 and are expressed as mean ± SEM.
[b] Figures in parentheses represent number of patients studied at each time period.
[c] Analysis of variance, $P < 0.05$ when the value for F is greater than 2.8.

Table 6. Pearson's correlation coefficients between plasma level and 8 hour peritoneal mass transfer of solutes in patients undergoing CAPD

	r	*P*
Potassium	0.370	<0.05
Urea	0.818	<0.0005
Creatinine	0.872	<0.0005
Uric acid	0.419	<0.05
Inorganic phosphorus	0.626	<0.0025
Glucose	−0.275	NS
Lysozyme	0.388	<0.05
Albumin	−0.609	<0.005
IgG	0.371	<0.05
IgA	0.416	<0.05
C_3	0.113	NS
C_4	0.123	NS
IgM	0.334	<0.05

The correlation was computed from 18 studies performed in 5 patients studied prospectively for 6 months (patients 1–5, Table 1). NS, not significant, $P > 0.05$

neal clearance kinetics of solutes and proteins was the molecular mass, suggesting membrane restriction based on size exclusion, in accordance with results observed by previous investigators [19–26]. Although the negative exponential relationship between clearance and molecular mass was maintained during an eight hour dwell, the mass transfer and clearance of individual molecules were affected in a different manner during the cycle duration. The mass transfer of small molecular weight solutes (<200) decreased remarkably with increasing dwell time (0 to 1 > 1 to 4 > 4 to 8 hr), confirming previous reports [27–29]. Unlike small molecules, large molecular weight solutes (> 68,000) showed a continuous loss. This discrepancy between small and large solutes has also been observed by other investigators, and it was concluded that the net removal of proteins was independent of the dwell time [28].

The peritoneal mass transfer and clearance of high molecular weight proteins (large solutes) showed biphasic changes during an eight hour cycle in our CAPD patients, demonstrating a small but significant temporary decrease of these parameters after the first hour of dialysis (1 to 4 hr) with a subsequent increase to the initial rate. Blumenkrantz et al [14] and Miller et al [30] showed that the protein loss during maintenance intermittent peritoneal dialysis was greatest during the initial hours of dialysis, and progressively decreased with subsequent exchanges. These authors suggested that this phenomenon is caused by a washout of the residual protein present in the peritoneal cavity. Our results, which were obtained from consecutive uninterrupted cycles of CAPD, cannot be explained by this suggestion. Alternatively, the biphasic pattern observed in the clearance of proteins of high molecular weight across the peritoneal membrane throughout an eight hour cycle, may be attributed to an early irritant effect of the hypertonic dialysate solution [31, 32], with a subsequent brief and transient peritoneal interstitial dehydration [33] resulting in a delayed passage of large molecules to the peritoneal fluid [34, 35]. The late increase in the clearance of high molecular weight proteins (4 to 8 hr) may be explained by the progressive drop in the dialysate tonicity caused by glucose absorption. The possible effect of the peritoneal lymphatic absorption as suggested recently [36] has not been addressed in the present study. The effect of the circadian rhythm on the kinetics of protein loss has been excluded in our study by changing the order of cycles and conducting some experiments during daytime without affecting the results. These latter findings are supported by the findings of Young, Brownjohn and Parsons [25]. The fact that peritoneal protein losses may be dependent on dwell time has been also demonstrated by other authors [37–40].

It is interesting that the peritoneal mass transfer and clearance of low molecular weight proteins (< 15,000) were similar to those observed with small solutes, showing a remarkable drop after the first hour of dialysis, unlike the peritoneal mass transfer and clearance of high molecular weight proteins which were continuous during an 8h dialysis cycle. Therefore, when studying factors affecting the kinetics of peritoneal excretion of proteins they should not be pooled, but divided into low and high molecular weight proteins. Our results indicate that the daily peritoneal loss of low molecular weight proteins as with small molecular weight solutes (<200) was mainly during the first hour of three eight-hour cycles (>50% of the daily loss) and less than 17 percent of the daily loss during the four to

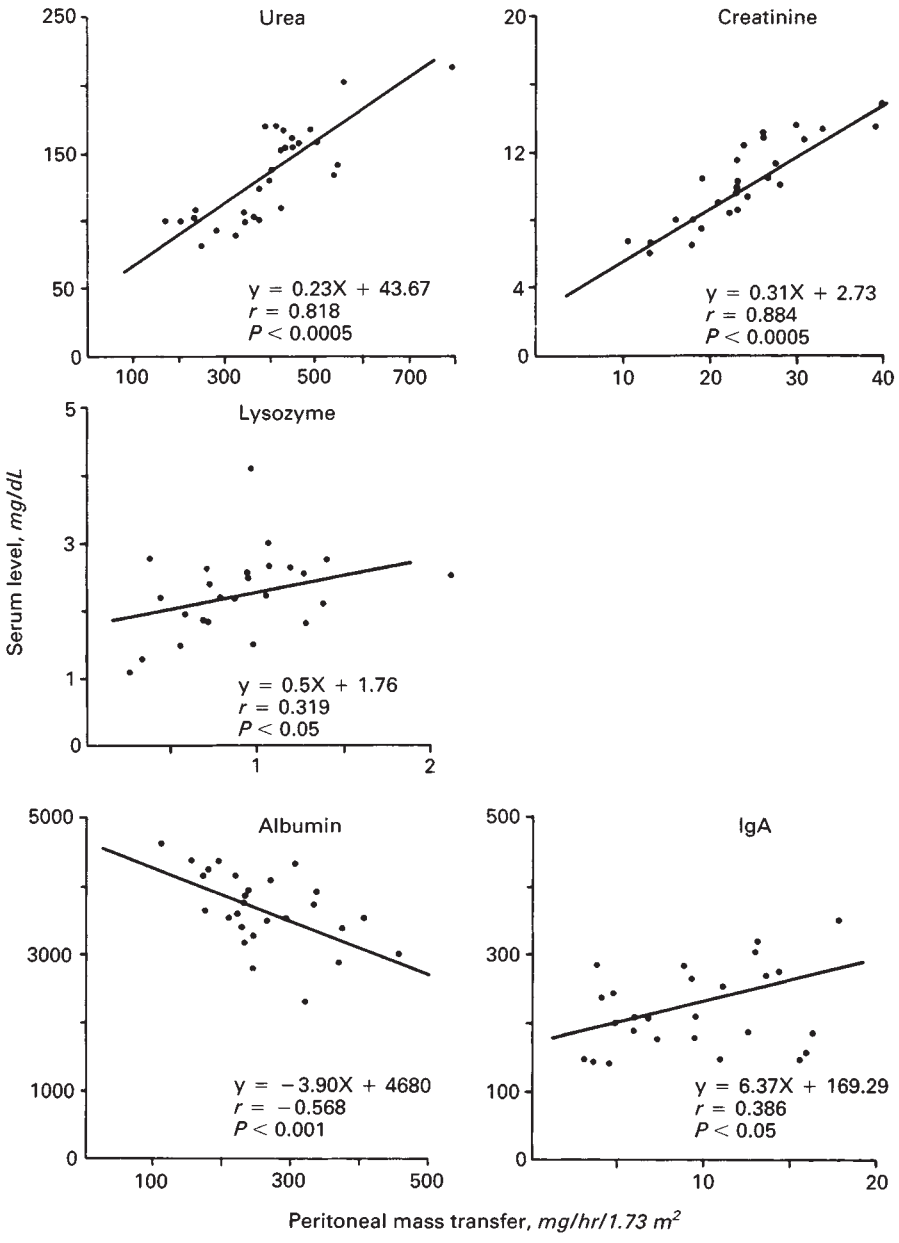

Fig. 3. *Correlation between the serum levels and 8 hour peritoneal mass transfer of small (upper panel) intermediate size (middle panel) and large (lower panel) molecular weight solutes in 13 CAPD patients (N = 26 studies).* All correlations were statistically significant at $P < 0.05$ as indicated in the figure.

eight-hour intervals of the eight-hour dwell time. On the other hand the daily peritoneal loss of high molecular weight proteins (> 68,000) occurred mainly during the last four hours of dwell (more than 50% of daily loss at 4 to 8 hr intervals). As low molecular weight proteins may represent the excretion of intermediate molecular weight solutes (uremic toxins [22]) and their kinetic characteristics are similar to those of small solutes, we suggest that increasing the number of short dialysis cycles is more effective in the removal of both small solutes and "uremic toxins" ("middle molecules") than three to four daily exchanges of long (6 to 8 hr) cycles. In our opinion, the prolonged dialysis cycles may be detrimental, particularly after four hours of dwell, when the increased peritoneal loss of high molecular weight proteins is not accompanied by significant dialysance of small and "middle" molecules.

Blumenkrantz et al in IPD patients [14] and Young et al in CAPD patients [25] demonstrated that the rate of peritoneal loss of all investigated proteins were positively correlated to their respective serum concentrations. We observed a similar correlation for the clearance of lysozyme and immunoglobulins, but no such correlation could be demonstrated in the clearance of complement components. This lack of correlation may reflect a too small interpatient variation in the serum levels of C_3 and C_4 as noted also by other investigators [14, 41]. In contrast to most plasma proteins, we observed a negative correlation between the clearance of serum albumin to its serum concentration, in agreement with the study reported by Kaysen and Schoenfeld [34]. This negative correlation may indicate to an inadequate compensation in the synthetic rate of albumin to replace the peritoneal loss.

Recent data suggest that patients undergoing CAPD may be prone to protein depletion [4, 41] and demonstrate abnormal (lower) "nutritional parameters" such as total body nitrogen [42, 43]. A significant decrease in total serum protein, albumin, IgG, IgA, C_3 and other proteins has been reported during CAPD treatment [4, 14, 41, 44, 45]. In other studies the serum levels of proteins in patients on CAPD were maintained at the lower normal limits [46, 47]. Our results support these latter findings, demonstrating the lack of statistically significant changes in serum levels of proteins during long-term CAPD treatment. The only exception was serum lysozyme, which serum activity decreased significantly with the start of CAPD treatment, increased to the initial levels at six months and remained stable for three years on CAPD. These changes occurred without a parallel change in its peritoneal clearance. The initial drop in serum lysozyme could be explained by effective dialysis, whereas the latter increase correlated to an increase in serum creatinine levels and therefore can be ascribed to deterioration of residual renal function occurring during long-term dialysis treatment [48].

From this study we may conclude that during CAPD the peritoneal protein transport of low and high molecular weight proteins reveal different kinetic characteristics. Their loss is dependent on their molecular mass and their serum concentration, but are not influenced by duration of CAPD. It is conceivable that substitution to 1 hour × 6 cycles/day peritoneal dialysis regimen, as practiced during CCPD for the standard 8 hour × 3 or 6 hour × 4 cycles of CAPD, may result in reduction of protein loss without affecting the clearance of small and middle molecular weight solutes.

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Reprint requests to M. Fainaru, M.D., Beilinson Medical Center, Petah-Tiqva, 49100 Israel.

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