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CLINICAL INVESTIGATION

Protein and energy intake, nitrogen balance and nitrogen losses in patients treated with continuous ambulatory peritoneal dialysis

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Protein and energy intake, nitrogen balance and nitrogen losses in patients treated with continuous ambulatory peritoneal dialysis. The aim of this investigation was to analyze factors which influence the dietary protein intake (DPI), the energy intake and the utilization of ingested protein, and to determine the relationship between various types of nitrogen losses in stable continuous ambulatory peritoneal dialysis (CAPD) patients. We performed 23 nitrogen balance (NB) studies of 6 to 11 days duration in 12 CAPD patients. One study was performed in all patients 3.4 ± 1.2 months after starting CAPD (early studies). The study was then repeated in nine patients after 12.1 ± 2.6 months, and two of these patients were studied again after 16 and 24 months, respectively (late studies). Before each NB study, the dietary intakes prior to the study were assessed in diaries and interviews. During a few days preceding the NB periods and during the NB periods each patient received an individualized diet composed so as to resemble the patients' spontaneously chosen diet regarding DPI and dietary energy intake (DEI). Total nitrogen, protein, urea and creatinine were analyzed in the dialysate and urine collected daily. Total nitrogen was also analyzed in the feces, collected over the whole NB period. Total nitrogen appearance (TNA), non-protein nitrogen appearance (NPNA) and urea nitrogen appearance (UNA) were calculated by correcting total nitrogen output, non-protein nitrogen output, that is, TNA minus the total protein losses (PL) and urea nitrogen output for changes in total body urea nitrogen. Glucose was determined in the collected dialysate and the daily glucose absorption was calculated. DPI varied between 0.62 and 2.09 g/kg/day, DEI between 21 and 42 kcal/kg/day and the peritoneal energy (glucose) intake (PEI) between 4 and 13 kcal/kg/day. DPI (but not DEI) correlated with Kt/V_{urea} and Kt/V_{Cr} and with total and renal clearances for urea and creatinine. NB (not corrected for "unmeasured" nitrogen losses) was positive in most studies, and it correlated with DPI and the total energy intake (TEI) in the early studies, but only with TEI in the late studies. DPI correlated with TNA, NPNA, UNA, non-protein-non-urea nitrogen loss and fecal nitrogen loss. UNA was highly correlated with TNA and NPNA ($r = 0.95$). We used data from 33 NB studies in CAPD patients (our present data combined with data from the literature) to calculate regression equations describing the relationship between TNA and NPNA, respectively, and UNA. Equations were derived by which the protein equivalent of TNA (PNA), that is, 6.25 TNA, and the protein equivalent of NPNA (PNPNA), that is, 6.25 NPNA, may be calculated from UNA which is directly measured. In stable CAPD patients, who are not strongly catabolic or anabolic, PNA may be used to estimate DPI and PNPNA may be used to estimate the net protein intake (DPI − PL).

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Protein-energy malnutrition is common in patients with chronic renal failure (CRF) are treated with continuous ambulatory peritoneal dialysis (CAPD) [1–4]. Anorexia, biochemical abnormalities, loss of protein and amino acids into dialysis fluid, peritonitis and other superimposed catabolic illnesses may be contributory factors [5]. There is evidence that the protein requirements in CAPD patients are higher than in normal individuals and patients with chronic renal failure who are not undergoing dialysis treatment. The dietary protein and energy intakes of CAPD patients have been reported to decline over time and a concurrent decrease in total body nitrogen, as an indicator of total body protein mass, has been observed during the first two years of CAPD [6, 7].

Adequate protein and energy intakes are essential to the maintenance of nitrogen equilibrium and prevention of protein-wasting. The assessment of protein and energy intakes is therefore important in the clinical evaluation of CAPD patients. On the basis of data from nitrogen balance (NB) studies in non-dialyzed CRF patients and maintenance hemodialysis (HD) patients [8–10], it has been demonstrated that there is a linear relationship between the urea nitrogen appearance (UNA) (that is, the urea nitrogen output in urine and dialysate, corrected for changes in the body urea nitrogen) and the total nitrogen appearance (TNA) (the nitrogen output in urine, feces and dialysate, corrected for changes in body urea nitrogen). TNA × 6.25 may be considered to represent the protein equivalent of the nitrogen appearance (PNA), earlier called the protein catabolic rate (PCR). Hence, after determining the relationship between UNA and TNA, equations can be derived which permit the estimation of PNA from UNA. In patients who are metabolically stable, that is, neither strongly catabolic nor anabolic, PNA reflects the dietary protein intake (DPI), and UNA, either determined directly or computed by urea kinetic modeling, may be used as a tool for evaluating DPI.

Patients treated with CAPD have substantial protein loss in the dialysate, varying between 5 and 15 g protein per day in different studies [5], and considerably higher losses during and after episodes of peritonitis [11]. In addition, CAPD patients lose amino acids and other nitrogenous compounds continuously [12–14]. The relationship between TNA and UNA in CAPD patients therefore differs from that in HD patients and non-dialyzed patients with CRF [14]. However, no equations

for calculation of TNA or PNA from UNA, based on data obtained by actual measurements of nitrogen and urea losses in CAPD patients, have previously been available. Equations derived from the relationship observed between UNA and TNA in HD patients or non-dialyzed CRF patients were therefore used to calculate PNA (PCR) in CAPD patients, taking the loss of protein in the dialysate into consideration [15]. It was demonstrated both in HD and CAPD patients that PNA (PCR) correlates with the efficacy of small molecule removal (by dialysis + residual renal excretion) expressed as Kt/V_{urea}, suggesting that underdialysis leads to a lowering of the protein intake [7, 16–19]. Recent evidence suggests that it is possible to increase PNA (PCR) by increasing the amount of dialysis [20, 21].

In the present study we have investigated the extent to which requirements for protein and energy are met in patients undergoing CAPD, and have attempted to evaluate the importance of various factors which might influence the intakes of protein and energy and the utilization of dietary protein. For this purpose the dietary protein and energy intakes were assessed in a group of CAPD patients during treatment, and the NB was measured in the hospital while the patients were following a diet containing their usual intakes of protein and energy. The study also enabled us to determine the unique relationship between TNA and NPNA (non-protein nitrogen appearance), respectively, and UNA in CAPD patients, and to derive equations which can be used to estimate the protein intake in stable CAPD patients.

Methods

Demographics

We studied 12 patients, 10 men and 2 women, who had end-stage chronic renal failure, with a mean age of 50 ± 13 years (range 27 to 60 years). All patients were in good clinical condition at the time of the metabolic studies and had been free from peritonitis for one month or more before this study. None had an intercurrent illness, active liver disease, diabetes mellitus or other systemic diseases, and none was treated with corticosteroids, androgenic steroids or lipid-lowering agents. The patients were prescribed aluminum hydroxide, calcium carbonate and sodium bicarbonate, as required to maintain mineral and acid-base balance, and all were given supplements of vitamins B and C with no major change in the doses during the study period. Several of the patients worked full-time or part-time and all were able to manage housework. The degree of the patients' activity was generally low; none was doing endurance training. Patients 3 and 8 had been treated with maintenance HD for one year and 13 years, respectively, before starting CAPD. In all patients, a short period of intermittent peritoneal dialysis preceded the start of CAPD.

In all patients, NB studies were conducted early after the start of CAPD, that is, after 3.4 ± 11.2 (2 to 6) months ("early studies"). In nine patients the studies were repeated after 12 ± 3 (9 to 17) months on CAPD ("late studies"). Two of them were also studied a third time after 16 and 24 months, respectively, on CAPD; these were also included among the late studies (all late studies after 13.4 ± 4.3 months on CAPD). During the NB studies the patients were encouraged to perform their usual amount of daily exercise.

Age, sex, body weight and body mass index (BMI), that is, weight (kg)/[height (m)]^2, serum biochemistries, renal, dialysis and total clearances of urea and creatinine, Kt/V_{urea} and Kt/V for creatinine (Kt/V_{Cr}) are presented in Table 1. BMI was below the normal range in two patients (No. 2 and 4) at the time of the early study. Body weights increased from 63.6 ± 5.5 kg to 66.8 ± 5.4 kg ($P = 0.0023$) and BMI increased from 20.7 ± 2.2 to 21.7 ± 2.1 ($P = 0.0034$) in the nine patients studied both early and late (second time). The renal urea clearance was less than 0.5 ml/min during 11 of the studies and the renal creatinine clearance was less than 0.5 ml/min during eight of the studies. Daily Kt/V_{urea} is a measure of the dose of dialysis (+ residual renal function) regarding urea elimination in relation to the distribution volume of urea (V). V is generally assumed to be equal to total body water, and is approximately equal to 60% of the body weight. In the formula Kt/V_{urea}, K = total (renal + dialysate) urea clearance (ml/min), t = 1440 (min) and V (ml) = 0.6 × body wt (g). Kt/V_{Cr} was calculated in a similar way, except that K = total creatinine clearance (ml/min). The daily Kt/V_{urea} varied between 0.21 and 0.41 and the daily Kt/V_{Cr} varied between 0.18 and 0.45. There was no significant difference in urea and creatinine clearances (total, dialysate and renal) and Kt/V_{urea} between the early and late studies, but Kt/V_{Cr} tended to be lower ($P = 0.057$) during the late studies (1.52 ± 0.28) than during the early studies (1.91 ± 0.61). The NB studies were carried out at the Renal Clinic, St. Erik's Hospital and then at the Renal Clinic, Huddinge University Hospital. The study protocol was approved by the Ethics Committee of Karolinska Institute.

Dialysis technique

CAPD was performed with four to five, usually four, daily exchanges of 2 liters of dialysis fluid (Dianeal^R, Baxter Travenol, Deerfield, Illinois, USA or Halden, Norway), using different concentrations of glucose, as required, to remove excess fluid. During each NB study the number of daily exchanges and the glucose concentrations were identical to those used during the period preceding the NB study.

Dietary intakes and nitrogen balance

When starting CAPD the patients were prescribed a dietary protein intake (DPI) of 1.2 g/kg body wt/day, mainly of high biological value, and a dietary energy intake (DEI) of 35 kcal/kg body wt/day. However, repeated nutritional assessments during the treatment showed that their actual intakes deviated considerably from these recommendations. Before each nitrogen balance (NB) study the dietary habits and nutritional intake of the patients were carefully evaluated by a skilled dietitian, who examined the diaries kept concerning diets and made recall interviews. On the basis of the nutritional assessments, individualized balance diets were prepared for each study aimed at providing the patients' usual dietary intake of protein and energy during the weeks before the study. Three different menus were prepared and deep-frozen in batches for each study. These were alternated during the study period. The nitrogen content of the diets was checked by the Kjeldahl method and the contents of carbohydrate and fat were calculated from food tables. Energy derived from glucose absorption was calculated for each exchange as the difference between the amount of glucose in the fresh dialysis fluid and the amount in

Table 1. Sex, age, duration of CAPD, body weight, serum chemistries, clearances and Kt/V_s after 3.4 ± 1.2 months (early studies) and after 13.5 ± 4.3 months (late studies) on CAPD

						Serum				Clearance *ml/min*						Kt/V (per day)	
										Urea			Creatinine				
Patient	Sex	Age *years*	Duration of CAPD *months*	Body weight *kg*	Body mass index	Albumin *g/l*	Bicarbonate *mmol/liter*	Creatinine *mmol/liter*	Urea *mmol/liter*	Renal	Dialysis	Total	Renal	Dialysis	Total	Urea	Creatinine
(A) Early studies																	
1	M	58	2	70.7	22.6	26	24.0	0.91	13.3	0.2	6.6	6.7	0.4	5.1	5.5	0.23	0.19
2	M	60	3	58.2	17.6	32	24.0	0.58	21.8	3.7	6.2	10.0	5.8	5.1	10.9	0.41	0.45
3	M	62	6	66.9	21.1	35	23.0	0.85	22.8	1.0	6.5	7.5	1.6	5.3	6.9	0.27	0.25
4	M	57	4	57.0	17.3	31	26.0	0.63	25.7	0.7	5.8	6.5	0.9	6.3	7.2	0.28	0.30
5	M	57	3	70.9	22.4	37	23.5	1.24	31.1	0.5	7.0	7.4	0.6	4.2	4.8	0.25	0.16
6	F	37	3	60.2	24.1	36	26.0	0.69	27.0	1.4	6.0	7.4	1.9	6.2	8.1	0.29	0.32
7	M	27	2	66.0	20.0	41	25.0	1.08	17.7	1.4	6.8	8.2	2.3	3.9	6.3	0.30	0.23
8	M	37	4	65.1	21.3	38	23.5	0.93	25.8	0.0	6.7	6.7	0.0	6.4	6.4	0.25	0.24
9	M	54	2	57.8	20.3	41	21.0	0.70	17.2	1.2	6.5	7.7	2.9	4.8	7.7	0.32	0.32
10	F	59	5	69.6	23.2	36	20.0	0.88	14.3	0.3	6.3	6.7	0.7	6.1	6.8	0.23	0.23
11	M	59	3	62.8	19.3	39	22.5	0.91	30.0	0.5	6.3	6.9	0.6	5.9	6.5	0.26	0.25
12	M	52	4	81.1	27.5	43	24.0	1.09	23.6	2.5	6.5	9.0	4.8	4.7	9.4	0.27	0.28
(B) Late studies																	
1			10	74.2	23.6	30	23.0	0.85	8.4	0.5	5.9	6.4	1.2	5.5	6.7	0.21	0.22
1			16	70.4	22.4	24	25.5	0.80	7.3	0.3	6.3	6.6	0.3	5.9	6.2	0.22	0.21
2			11	62.5	18.8	28	22.0	0.76	21.6	1.7	6.3	7.9	2.8	4.8	7.6	0.30	0.29
3			14	70.0	22.0	32	23.5	0.75	22.8	1.7	6.4	8.1	2.6	5.3	7.9	0.28	0.27
3			24	67.6	21.4	38	22.0	0.77	22.3	1.6	6.5	8.0	2.8	6.1	8.9	0.29	0.32
4			11	59.1	18.0	36	24.0	0.75	23.2	0.3	6.0	6.3	0.3	5.3	5.6	0.26	0.23
5			10	72.0	22.7	43	23.0	1.10	33.2	0.4	7.2	7.5	0.5	5.2	5.8	0.25	0.19
6			17	60.4	24.2	46	22.5	1.16	29.7	0.0	8.3	8.3	0.0	4.8	4.8	0.33	0.19
7			9	70.9	21.3	42	23.0	1.21	22.2	0.8	6.9	7.7	1.5	4.5	5.9	0.26	0.20
8			14	66.9	21.8	36	18.0	1.21	33.7	0.0	6.9	6.9	0.0	5.1	5.1	0.25	0.18
9			13	65.0	22.7	42	21.0	0.97	21.7	0.2	6.1	6.3	0.4	4.6	5.0	0.23	0.18

the dialysate drained. The protein and energy intakes during each NB study are given in Table 2.

In 20 studies the NB period lasted for seven days, and in three studies the periods were six, nine and ten days, respectively. The balance periods were preceded by an adaptation period of two to seven days (mean 4 days). All feces were collected over 24 hour periods for determinations of total nitrogen and the mean daily fecal loss during the balance periods was calculated. The urine and dialysate samples were collected over 24 hour periods for determinations of total nitrogen, urea, creatinine and total protein. Venous blood samples were obtained at two to three day intervals for the measurements of urea, creatinine, albumin, standard bicarbonate and other blood biochemistries. The samples were refrigerated immediately and kept deep-frozen until analysis.

Nitrogen was determined by a semi-micro Kjeldahl technique, as previously described [22]. Routine methods were used to determine protein, albumin (an immunological method), urea, creatinine, standard bicarbonate and glucose.

Calculations

DPI was determined by multiplying the measured dietary nitrogen intake (DNI) by 6.25 [23]. Daily NB was calculated as the difference between the daily DNI and the daily total nitrogen appearance (TNA), that is, the sum of the nitrogen output in urine, dialysate and feces, adjusted for changes in body urea nitrogen. This was done by calculating the changes in serum urea nitrogen and a distribution volume of urea assumed to be 60% of the body weight, as previously described [22]. No adjustment was made for nitrogen losses that were not measured, such as from skin, respiration, flatus and blood sampling. Non-protein nitrogen appearance (NPNA) was calculated by subtracting the total protein losses (PL)/6.25 from TNA. PNA (the protein equivalent of TNA) was calculated as 6.25 TNA and PNPNA (the protein equivalent of NPNA) as 6.25 NPNA. The urea nitrogen appearance (UNA) was calculated from the sum of urea nitrogen output in urine and dialysate, corrected for changes in total body urea nitrogen. Total non-protein-non-urea nitrogen output was calculated by subtracting protein nitrogen and urea nitrogen output in urine and dialysate from total nitrogen output.

Statistical methods

The Student's *t*-test for paired data and the calculation of the correlation coefficient were used to evaluate the results. Group data are expressed as mean ± standard deviation. In the calculation of correlations, one value from each balance study, representing the daily mean value, was used. Multiple regression analysis was used when appropriate.

Results

Data for protein and energy intakes, losses of protein, nitrogen losses, nitrogen appearances and NB are given in Table 2.

Nutritional intakes

DPI ranged between 0.62 and 2.09 g/kg/day and DEI between 20.7 and 44.6 kcal/kg/day. DEI consisted of carbohydrate 43 ± 7%, fat 39 ± 8% and protein 19 ± 4%, and was about the same in the early and late studies. These intakes resembled the patients' usual intakes before they were admitted to the studies.

Table 2. Protein and energy intakes, protein and nitrogen losses, protein equivalents of nitrogen appearances and nitrogen balance

Patient	Energy intakes *kcal/kg/day* DEI	PEI	TEI	DPI *g/kg/day*	DNI *g/day*	Protein loss *g/day* Urine	Dialysate	Fecal N	TNA	NPNA	Urea N loss *g/day* Urine	Dialysate	UNA	N balance
								g/day					*g/day*	
(A) Early studies														
1	34.0	9.4	43.4	0.76	8.61	0.15	5.19	1.04	6.98	6.13	0.09	3.51	3.61	1.63
2	37.4	5.1	42.5	2.09	19.44	0.97	8.39	1.50	14.09	12.59	3.27	5.48	9.24	5.35
3	32.1	13.4	45.5	1.37	14.66	0.41	8.57	0.73	10.87	9.43	0.94	5.96	7.48	3.79
4	42.4	7.9	50.3	1.81	16.51	0.35	10.45	0.95	11.38	9.65	0.75	6.03	7.14	5.13
5	32.1	4.1	36.2	1.51	17.15	0.32	6.80	2.31	13.45	12.31	0.58	8.73	8.60	3.70
6	35.4	8.0	43.4	1.72	16.52	1.99	8.58	1.69	14.24	12.55	1.57	6.48	7.64	2.28
7	39.4	6.3	45.7	1.39	14.69	0.41	4.04	1.28	11.04	10.33	1.01	4.84	5.26	3.65
8	25.0	7.9	32.9	1.40	14.58	0.00	9.33	2.80	13.16	11.67	0.00	7.92	7.31	1.42
9	33.5	8.4	41.9	1.28	11.85	0.15	5.70	1.35	8.86	7.92	0.83	4.48	4.93	2.99
10	31.5	7.4	38.9	0.76	8.45	0.11	4.13	1.52	7.52	6.84	0.18	3.64	3.95	0.93
11	37.9	6.3	44.2	1.39	13.99	0.35	6.07	1.79	11.92	10.89	0.64	7.67	8.09	2.07
12	22.8	5.4	28.2	1.12	14.50	0.52	5.49	1.96	13.52	12.56	2.35	6.22	8.36	0.98
(B) Late studies														
1	25.9	5.2	31.1	0.64	7.62	0.56	5.80	0.91	5.51	4.49	0.17	2.00	2.16	2.11
1	26.6	7.9	34.5	0.69	7.77	0.22	6.68	0.52	5.50	4.40	0.10	1.85	1.90	2.27
2	24.9	4.5	29.4	1.28	12.75	0.53	7.59	1.10	10.78	9.48	1.45	5.45	6.50	1.97
3	30.4	7.7	38.1	1.32	14.77	0.41	11.70	1.13	12.31	10.37	1.45	5.30	7.14	2.46
3	31.5	11.5	43.0	1.26	13.63	0.60	8.66	0.68	10.92	9.44	1.39	5.84	6.94	2.71
4	44.6	6.3	50.9	1.69	16.09	0.08	8.78	0.92	10.94	9.52	0.07	5.65	5.68	5.15
5	26.4	4.1	30.5	1.40	16.16	0.22	7.41	2.32	16.25	15.03	0.50	9.59	10.22	−0.09
6	28.7	5.0	33.7	1.50	14.51	0.00	6.51	1.43	12.85	11.81	0.00	9.95	9.46	1.66
7	20.7	4.5	25.2	1.03	11.64	0.33	5.14	1.46	10.55	9.67	0.75	6.16	6.02	1.09
8	27.2	5.8	33.0	1.39	14.91	0.00	7.43	2.26	14.57	13.38	0.00	9.34	9.77	0.34
9	29.5	9.5	39.0	1.10	11.42	0.11	3.48	1.46	9.03	8.46	0.15	5.36	5.57	2.39

Abbreviations are: DEI, dietary energy intake; PEI, peritoneal energy intake; TEI, total energy intake; DPI, dietary protein intake; DNI, dietary nitrogen intake; TNA, total nitrogen appearance; PNA, protein equivalent of TNA; NPNA, non-protein nitrogen appearance; PNPNA, protein equivalent of NPNA; UNA, urea nitrogen appearance.

No correlation was found between DPI and DEI (r = 0.23). Additional energy was provided as glucose via the peritoneal route (PEI), and it amounted to 4.1 to 13.4 kcal/kg/day. The serum urea showed only minor changes during the adaptation periods and the NB periods. The urea nitrogen output in the dialysate + urine (6.77 ± 2.30 g/day) did not differ significantly from UNA (6.55 ± 2.26 g/day). This indicated a close agreement between the nitrogen content of the balance diets and that of the patients' usual diets. Patients 1 to 9, in whom the studies were repeated, tended to have higher protein and energy intakes during the early studies than during the late ones, but this was significant only for TEI [early study 2690 ± 326 kcal/day; late (second) study 2286 ± 396 kcal/day; P = 0.030].

DPI (g/day) and DPI (g/kg body wt/day) correlated with Kt/V_{urea} (r = 0.45, P = 0.032, and r = 0.71, P = 0.0001, respectively) and with Kt/V_{Cr} (r = 0.46, P = 0.026, and r = 0.50, P = 0.014), respectively). The relationship between Kt/V and DPI (g/kg body wt/day) is shown in Figure 1. DPI (g/day) correlated with the total (renal + dialysis) urea clearance (r = 0.415, P = 0.049) and with the total creatinine clearance (r = 0.425, P = 0.043). The above-mentioned relationships indicate that the removal of small molecules affects the protein intake in CAPD patients. Multiple regression analysis demonstrates that DPI (g/day) correlated with the renal clearances of urea (r = 0.48, P = 0.029) and creatinine (r = 0.44, P = 0.046), but not with the dialytic clearances of urea (r = 0.04) and creatinine (r = 0.14), indicating that the residual renal function has a greater influence on the protein intake than does the daily dialysis treatment. DPI and DEI were not correlated with PEI, suggesting that variations in glucose absorption had no major influence on the appetite. DEI did not correlate with Kt/V_{urea} and Kt/V_{Cr}, nor with the clearances of urea and creatinine.

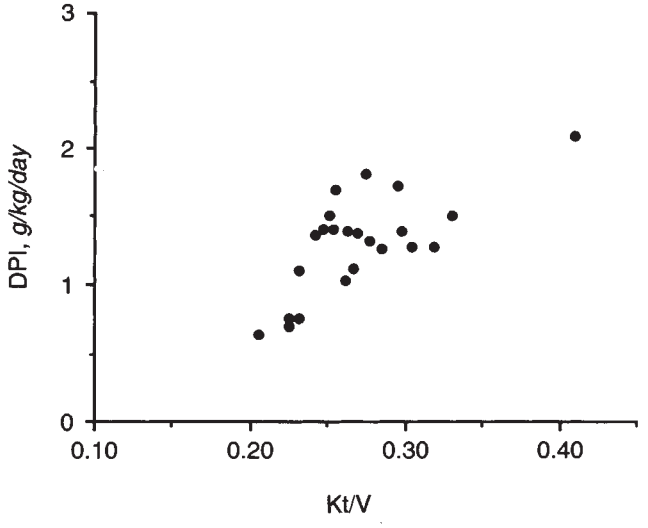

Fig. 1. *Relationship between daily Kt/V_{urea} and dietary protein intake (DPI) at the time of the 23 nitrogen balance studies.* DPI was assessed from diaries kept concerning diets and recall interviews by a dietitian. Kt/V_{urea} and DPI were correlated; r = 0.45, P = 0.032.

Nitrogen balance

NB, not corrected for non-measured nitrogen losses, was within ± 1.0 g N/day in three studies and more positive in 20

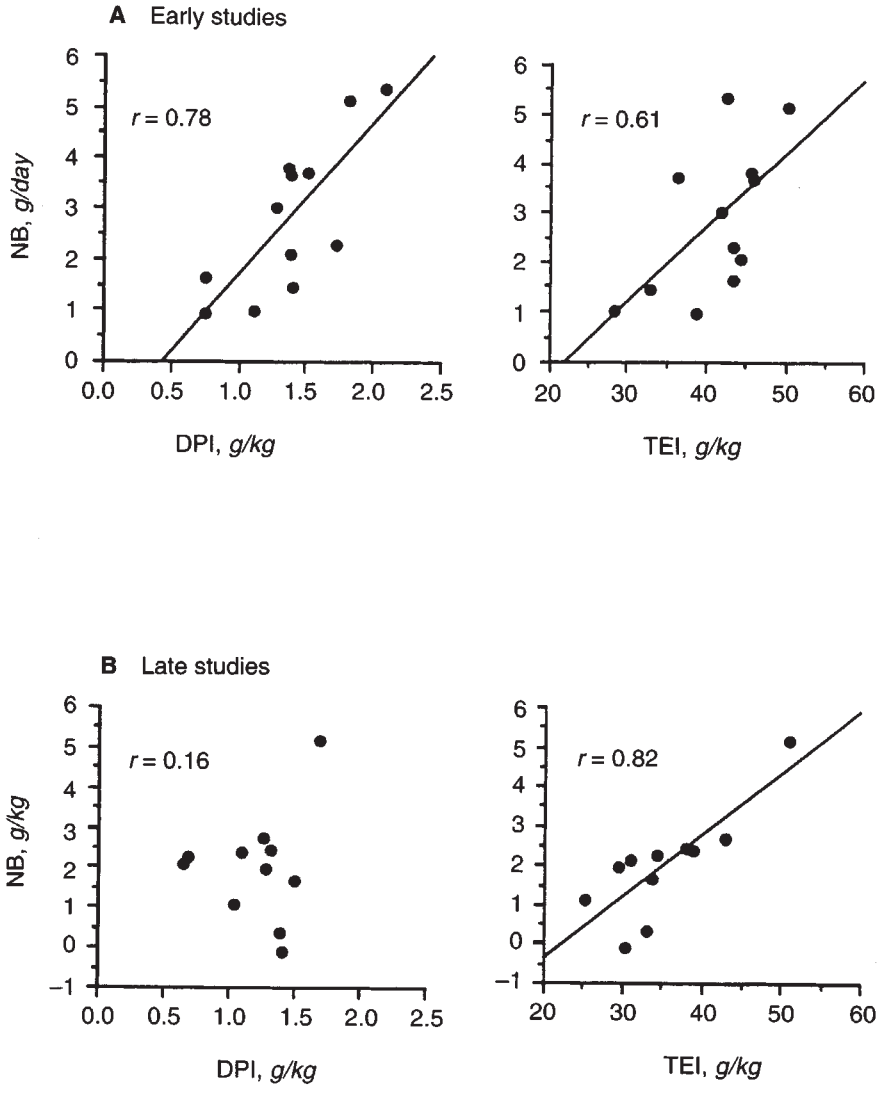

Fig. 2. *Relationships between nitrogen balance (NB) not corrected for "unmeasured" nitrogen losses and dietary protein intake (DPI) and total energy intake (TEI) during the early and late studies.*

studies. In patients 1 to 9, in whom the investigation was repeated, NB was more positive ($P < 0.021$) during the early study (3.33 ± 1.39 g/day) than during the late (second) one (1.90 ± 1.51 g/day). There was a correlation between NB and DPI (g/kg body wt/day) as well as TEI (kcal/kg body wt/day) during the early studies; during the late studies NB correlated with TEI but not with DPI (Fig. 2). Multiple regression analysis performed with NB as the dependent variable and DPI and TEI as the predictors demonstrates that both (DPI, $r = 0.65$, $P = 0.005$; TEI, $r = 0.40$, $P = 0.048$) had an independent effect on NB during the early studies. The following equation is obtained for the combined data from the early studies: NB (g) = −4.79 + 2.54 DPI (g/kg) + 0.10 TEI (kcal/kg) ($r = 0.87$, $P = 0.002$).

Protein and nitrogen losses and nitrogen appearances

The protein losses in the dialysate ranged between 4.0 and 11.7 g/day (mean value in all studies 7.0 ± 2.1 g/day). The urinary protein losses were less than 0.3 g/day during 10 studies, and exceeded 0.6 g/day during two studies. The total protein losses in urine and dialysate (PL) were 7.4 ± 2.2 g/day. The mean loss of nitrogen due to blood sampling was estimated to be 375 mg/day. The total non-protein-non-urea nitrogen losses were 51 ± 15 mg/kg body wt/day, of which 29 mg/kg body wt/day was a dialysate nitrogen loss and 22 ± 1.9 g/kg body wt/day a fecal nitrogen loss. The fecal nitrogen output differed between the various subjects (0.5 to 2.3 g/day), but it tended to be constant in the same subjects during the early and late studies, as demonstrated in Figure 3.

Figure 4 shows that DNI correlated with TNA, and in most cases it was higher than TNA. DPI (DNI) and net protein intake (DPI − PL) correlated with UNA ($r = 0.85$ and $r = 0.87$, respectively). Higher correlations were observed between TNA ($r = 0.96$) and NPNA ($r = 0.95$), respectively, and UNA (Fig. 5). DPI correlated with the total non-protein-non-urea nitrogen output ($r = 0.47$, $P < 0.05$). Multiple regression analysis showed that this was mainly because the fecal nitrogen output tended to vary with DPI ($r = 0.40$, $P = 0.023$), whereas the non-protein-non-urea nitrogen output in the dialysate was not correlated with DPI ($r = 0.29$). When the data were pooled with those of Blumenkrantz et al [15], the correlation between the

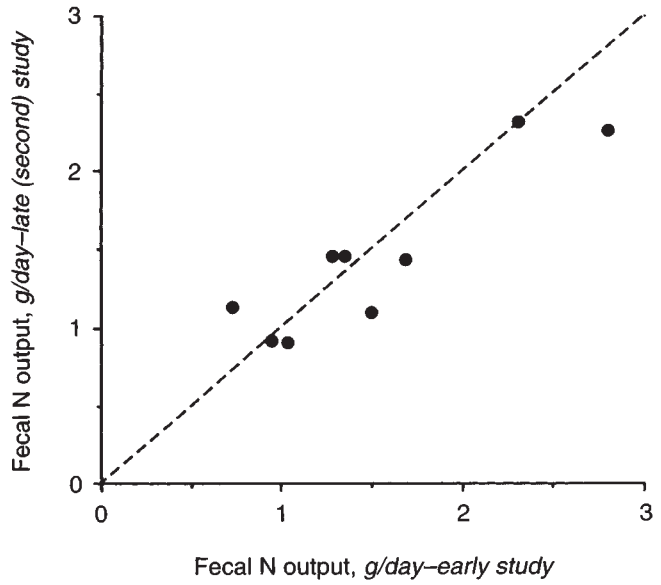

Fig. 3. *The fecal nitrogen output during the early and late studies in 9 patients who were studied twice, at an interval of more than 7 months.* Identity line: - - - - - - - -.

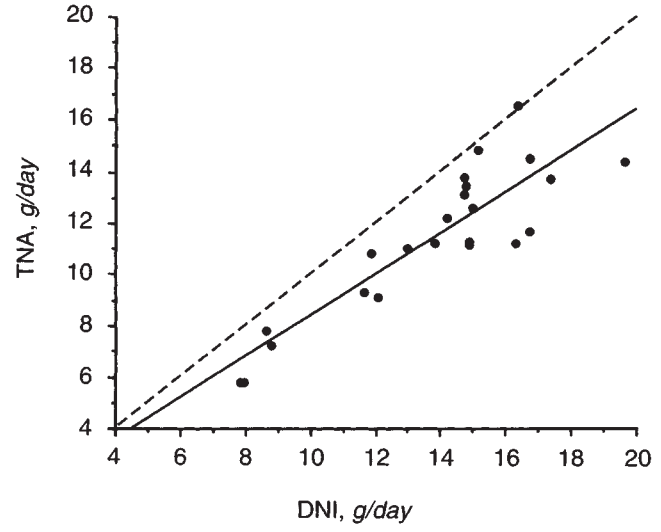

Fig. 4. *Correlation between dietary nitrogen intake (DNI) and total nitrogen appearance (TNA).* TNA was in most cases lower than DNI, reflecting that the measured nitrogen balance was positive. Identity line: - - - - - - - -. TNA = 0.24 + 0.80 DNI; r = 0.88.

fecal nitrogen output and DPI reached higher statistical significance (r = 0.45, P = 0.019, N = 34).

To check the validity of our results regarding the relationship between the nitrogen appearances and UNA, we compared our data with those from 11 N balance studies in seven CAPD patients, as reported by Blumenkrantz et al [15]. Figure 6 shows that the results overlap to such an extent that it is justifiable to treat the two groups as a single group in order to compute more accurately the regression of NPNA and TNA with UNA.

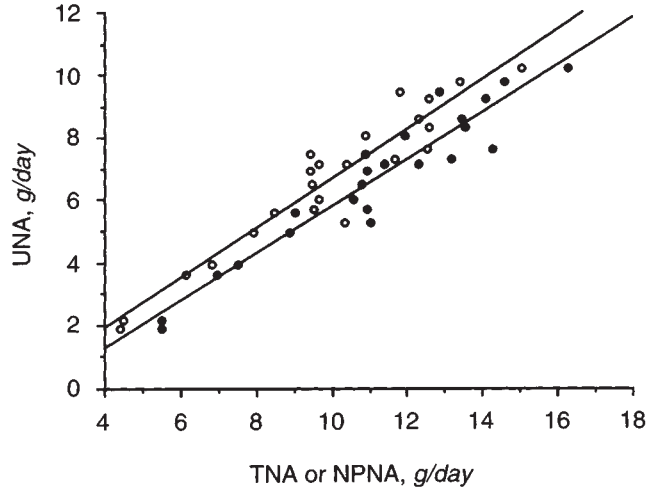

Fig. 5. *Relationship between total nitrogen appearance (TNA) and non-protein nitrogen appearance (NPNA), respectively, and urea nitrogen appearance (UNA) during the 23 nitrogen balance studies.* UNA = −1.30 + 0.80 NPNA; r = 0.95. TNA = −1.83 + 0.76x; r = 0.95.

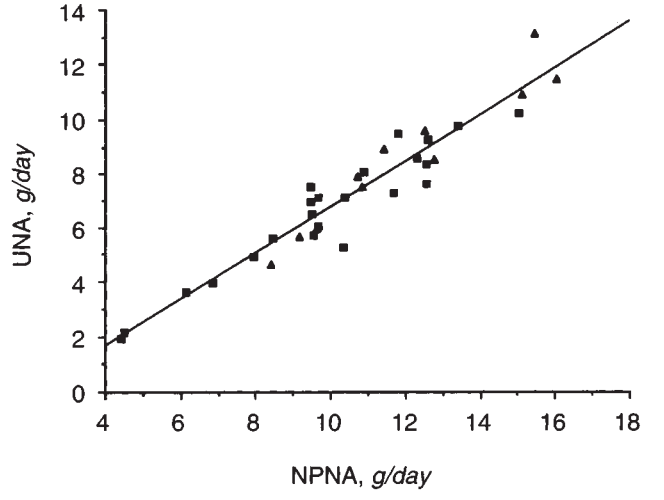

Fig. 6. *The relationship between non-protein-nitrogen appearance (NPNA) and urea nitrogen appearance (UNA) using the pooled data from the present study (■) and the studies of Blumenkrantz et al (▲) [14, 15].* The Blumenkrantz data were obtained from 11 studies; data from one study during which the patient had mild peritonitis were excluded. Urinary protein excretion was not reported by Blumenkrantz et al; the patients were anuric during 7 of the 11 studies and urinary protein excretion was assumed to be quantitatively insignificant in the remaining 4 studies. Total protein output was therefore taken to be equal to dialysate protein loss, when calculating NPNA. There was a high degree of overlap of the data from the two studies as was also the case when total nitrogen appearance (TNA) and UNA were plotted against each other. The regression equations describing the relationship between NPNA and TNA, respectively, and UNA are given in the text (equations 1 and 2).

The following regression equations were obtained by using the combined data from this study and that by Blumenkrantz et al [14].

$$\text{UNA (g/day)} = -1.81 + 0.855 \text{ NPNA (g/day)} \quad (r = 0.96) \qquad (1)$$

$$\text{UNA (g/day)} = -2.50 + 0.819\ \text{TNA (g/day)}\ (r = 0.95) \quad (2)$$

Equation (1) can be rearranged to enable the calculation of PNPNA (that is, the protein equivalent of NPNA) when UNA is known. In stable CAPD patients, PNPNA thus calculated, may be used to estimate the net protein intake: DPI − PL (see **Discussion**). Likewise, equation (2) can be rearranged to enable the calculation of PNA (the protein equivalent of TNA), which reflects DPI in stable CAPD patients without large losses of protein (see **Discussion**).

Discussion

The patients in this study were prescribed a protein intake of 1.2 g/kg body wt/day and a dietary energy intake of 35 kcal/kg body wt/day. However, repeated nutritional assessments during treatment showed that their actual intakes deviated considerably from these recommendations and, in some cases, were lower than prescribed. One factor which may have influenced the dietary intakes is the efficacy of toxin removal by dialysis and residual kidney function. It is a common experience that uremia leads to anorexia, which is generally thought to be due to the accumulation of toxic compounds which inhibit appetite. The observations in this study that the protein intake correlates significantly with the Kt/V_s for urea and creatinine, and also with the clearances of urea and creatinine, are in keeping with the supposition that the low efficacy of removal of small molecules leads to suppression of the appetite for protein, presumably by the inhibition of feedback caused by one or more uremic toxins. A correlation has earlier been observed between PNA (PCR), obtained by measuring UNA, and Kt/V_{urea} in CAPD as well as in HD patients [7, 16–19]. However, it cannot be ruled out that these relationships were more of a mathematical than a biological nature, since common factors were used to calculate Kt/V_{urea} and PNA.

Multiple regression analysis revealed that the renal component of the total clearances of urea or creatinine correlated significantly with DPI, whereas the dialytic clearances, although varying widely, showed no such relationship. This suggests that residual renal function has a greater influence than the dose of peritoneal dialysis on the appetite for protein.

DEI tended to be lower when Kt/V_{urea} or Kt/V_{Cr} was low, but it was not correlated with the Kt/V_s or the clearances of urea and creatinine in the same way as the dietary protein intake. These findings suggest that the uremic feedback inhibition of appetite affects the protein intake more markedly than the energy intake does.

It has been suggested that the appetite of patients undergoing long-term treatment with CAPD may be impaired by the continuous glucose absorption from the dialysis fluid. However, in the present study there was no relationship between the amount of glucose absorbed and the dietary protein or energy intake. This accords with a recent study of CAPD patients by Hylander, Barkeling and Rössner [24], who found no difference in appetite during standardized conditions, whether the abdomen was filled with a dialysis fluid containing glucose or was empty.

In most of the studies NB (not corrected for "unmeasured" nitrogen losses) was positive and significantly more positive during the first months of treatment than after nine months or more. The results agree with two previous reports on NB in CAPD patients undergoing their first 0.5 to six months on CAPD. Giordano et al [25] found a neutral or a positive NB in seven of eight patients following a diet containing 1.2 g protein/kg body wt/day. Blumenkrantz et al [15] reported that the mean NB (not corrected for "unmeasured" N losses) was neutral when the patients were fed a diet which provided 0.98 g/kg body wt/day and was positive by an average of 2.9 g/day when they ingested 1.44 g protein/kg body wt/day. On the basis of these results and on the assumption that the "unmeasured" nitrogen losses are about 0.5 g/day, they concluded that CAPD patients should be advised to ingest at least 1.2 g protein/kg body wt/day. However, the design differs from that of the present study, since Blumenkrantz' patients were given standardized diets with no apparent relation to their usual intakes of protein and energy, whereas our patients during the NB studies followed diets that were individualized and aimed to provide the usual intakes of protein and energy. In our studies the relationship between DPI and NB showed large variations between the patients, individual patients having a positive NB, even when the protein intake was below 1.0 g/kg body wt/day. The relationship between protein intake and NB in our studies performed early after the start of CAPD largely agrees with the findings by Blumenkrantz et al. Altogether, the data from all three studies indicate that in clinically stable CAPD patients, a safe diet should have a protein content of about 1.2 g/kg body wt/day during the initial months of treatment to allow for individual variations in protein requirements. Protein-depleted patients, however, may need considerably more protein. The results of the present study indicate that some patients may benefit by eating 1.4 to 2.1 g protein/kg/day during the initial months of treatment.

After more prolonged CAPD treatment, there were also large variations in DPI and in NB, which were not correlated. This indicates that other factors may have been more important than protein intake for the utilization of dietary protein. TEI was correlated to NB, the lowest NB being observed in three of the six patients with a TEI of less than 35 kcal/kg body wt/day. These results agree with observations in normal subjects, chronic renal failure patients, and HD patients, which shows that the utilization of dietary protein depends largely on the energy supply [24, 26, 27]. The results also suggest that low TEI is not uncommon in CAPD patients, despite the supply of glucose by the peritoneal route, and that this may be no less detrimental than a low protein intake during long-term treatment. Unfortunately, there is no simple, objective method for assessing DEI. Therefore dietary interviews, recall data and clinical observations must be relied on to evaluate whether the patients' energy requirements are met.

Our results demonstrate that UNA in CAPD patients shows a strongly positive correlation with TNA and with NPNA. Blumenkrantz et al [14] compared the relation between UNA and total nitrogen output in CAPD patients with that in normal subjects, in non-dialyzed CRF patients and in maintenance HD patients, derived from studies published earlier. There was a considerable overlap in all patient groups, except the CAPD group, in whom UNA was proportionately lower for each level of total nitrogen output. This difference was larger than could be attributed to the peritoneal loss of protein, which indicated that the loss of non-protein nitrogenous compounds other than urea was also higher in relation to UNA than in the non-CAPD subjects.

In the present study we observed that the non-protein-non-urea nitrogen output was 51 ± 15 mg/kg body wt/day, which is in agreement with the results in CAPD patients reported previously [14]. In the combined group of 44 non-dialyzed CRF patients derived from two studies [9, 10], the non-urea nitrogen output was 30 ± 10 mg/kg body wt/day and the urinary protein nitrogen loss was negligible. The increase in non-protein-non-urea nitrogen output in CAPD, amounting to about 20 mg/kg/day, corresponds to about 9 g protein per/day in a 70 kg man. Blumenkrantz et al [14] observed amino acid nitrogen losses of about 6 mg/kg body wt/day in the dialysate, leaving the largest part of the higher non-protein-non-urea nitrogen losses in CAPD unaccounted for. One explanation may be a continuous loss of non-protein nitrogen compounds of larger molecular size than that of urea through the peritoneum, which is a "leaky" membrane for larger molecules [28].

The correlation between DPI and non-protein-non-urea nitrogen output was significant in our study, mainly because fecal nitrogen excretion varied with the protein intake. A relationship between fecal nitrogen excretion and protein intake has been observed in normal subjects [29], but it was not observed in non-dialyzed patients with CRF [9]. However, the correlation between fecal nitrogen excretion and DPI in such patients is significant ($r = 0.45$, $P < 0.01$, $N = 44$) when the data from the studies by Cottini, Gallina and Dominguez [8] and Maroni, Steinman and Mitch [9] are combined. Hence, some adaptive variation in fecal nitrogen excretion with DPI takes place both in CAPD patients and non-dialyzed CRF patients.

In addition to DPI, other factors, such as dietary roughage and intestinal transit time, may be determinants of fecal nitrogen excretion. In those of our patients who were studied twice, the mean daily fecal nitrogen output in each subject tended to be similar, despite an interval of more than seven months between the two studies, which suggested that the dietary habits (on each occasion the NB diets were individualized according to the patient's dietary habits) and that gut function had not changed appreciably over this period.

A puzzling phenomenon, repeatedly observed, is that the NB measured in adult subjects tends to become more positive with increasing protein intake, without evidence of a corresponding increase in the body protein stores [30]. An explanation may be that there are systematic errors in the NB technique, leading to an overestimation of the nitrogen intake and an underestimation of the nitrogen losses. When PNA is calculated from the nitrogen output in urine, feces and dialysate, as in the present study, "unmeasured" nitrogen losses by other routes, such as respiration, sweat, skin desquamation, nails, hair and ejaculates, are not taken into account. Such losses were observed to be about 0.5 g/day directly measured in normal sedentary adults in a comfortable environment. The finding that dermal losses varied directly with the protein intake was thought to be due to differences in blood urea [31].

In CAPD patients who have increased levels of urea and other nitrogenous metabolites in body fluids, the "unmeasured" nitrogen losses are conceivably much higher. The integumental losses of nitrogen in uremic patients have not been determined, but it is known that uremic patients have increased respiratory losses of volatile nitrogenous compounds [22]. In the NB studies performed after more than nine months on CAPD, the mean NB was +2 g per day. Assuming that, on average, these patients were in a steady state which was neither markedly catabolic nor anabolic, this should approximately equal the "unmeasured" nitrogen losses, of which about 0.4 g per day is due to blood sampling, leaving 1.6 g per day unaccounted for, that is, considerably more than the "unmeasured" nitrogen losses in normal, sedentary adults. Therefore, assuming (in stable CAPD patients) DPI to be equal to PNA (6.25 TNA) or NPI (DPI − PL) to be equal to PNPNA (6.25 NPNA) will lead to an underestimation of the "true" protein intakes by an amount in the order of 9 g protein per day. However, it should be pointed out that this figure is indirectly derived and very approximate, and that the variations between patients may be considerable.

There was a high degree of correlation between UNA and TNA as well as between UNA and TNA in this study and in the study by Blumenkrantz et al [14, 15], with a considerable overlap of the data. The similarity of our data to those of Blumenkrantz et al suggested that there were no large systematic errors in methodology in either of these studies. Accordingly, the two groups were combined in a single group to increase the accuracy of the regression equations describing the relationships between TNA and NPNA, respectively, and UNA.

It should be pointed out that none of the patients included in the combined material had peritonitis or large protein losses. The high correlation between TNA and UNA would presumably have been flawed by the inclusion of patients who had peritonitis with a high loss of protein in the dialysate, since the loss of protein in CAPD represents protein that is not catabolized to generate urea.

It is of interest to compare the relationship between PNA (and PNPNA) and UNA in the combined group of CAPD patients with those in non-dialyzed CRF patients and maintenance HD patients. The regression lines and equations are shown in Figure 6. The equation for non-dialyzed CRF patients was obtained by combining data from the studies by Cottini et al [8] and Maroni et al [9] which overlapped. The equation for HD was taken from the study by Borah et al [10] on the basis of 10 NB studies in five patients. In such an analysis it is appropriate to compare both the PNA and the PNPNA regression lines of the CAPD patients with the regression lines of the non-dialyzed and HD patients, since the CAPD patients invariably have relatively high protein losses, whereas the protein losses in the other groups of end-stage renal failure patients are presumably negligible. The regression lines for CAPD and non-dialyzed CRF patients were strictly parallel, having almost identical regression coefficients, which indicated that UNA increased to the same extent for the same increase in protein intake in both groups, and that the difference in UNA at a given PNA level (in the CAPD patients at a given PNPNA level) between the two groups was constant over a wide range of PNA. UNA also appears to be higher in relation to PNA in HD than in CAPD patients, the difference tending to increase with PNA. However, the regression equation for HD, although widely employed for assessing protein intake, is probably less accurate than the equations for CAPD and non-dialyzed CRF patients, since the HD data stem from only 10 weekly NB studies in five patients performed at a single center, whereas the CAPD and non-dialyzed CRF data were obtained from a greater

number of studies in larger groups of patients at different centers.

The regression lines in Figure 6 demonstrate in patients with CRF that the relationship between UNA and TNA (in CAPD patients, also PNPNA) depends on the type of treatment. The use of an equation for non-dialyzed patients in CAPD patients would underestimate the "net protein intake" by about 9 g/day, thus introducing a systematic error of 12% when the protein intake is 70 g/day and proportionally more if the intake is lower, and to an additional underestimation of about 6 g/day, if the protein losses are not taken into account. The CAPD and HD regression equations are also so different that the same equation should not be employed for both groups.

From our analysis of the relationship between NPNA and UNA in the combined material of 34 CAPD patients (Equation 1), the following equation has been derived for estimating PNPNA from UNA:

$$\text{PNPNA (g/day)} = 13 + 7.31 \text{ UNA (g/day)} \quad (3A)$$

or, using urea appearance (UA) instead of UNA:

$$\text{PNPNA (g/day)} = 13 + 0.261 \text{ UA (mmol/day)} \quad (3B)$$

In stable, adult CAPD patients PNPNA, calculated by these equations, reflects NPI, that is, DPI − PL. To estimate DPI, the 24-hour protein losses in the dialysate (and in the urine, if appreciable) should be directly determined and added to PNPNA.

Equations based on the relationship between UNA and TNA, earlier presented (Equation 2), may be derived for estimating PNA from UNA:

$$\text{PNA (g/day)} = 19 + 7.62 \times \text{UNA (g/day)} \quad (4A)$$

or

$$\text{PNA (g/day)} = 19 + 0.272 \text{ UA (mmol/day)} \quad (4B)$$

A prerequisite for using PNA, thus calculated to estimate DPI in CAPD patients is an absence of excessive protein losses. Such losses may be noted during or after an episode of peritonitis or in patients with severe nephrotic syndrome.

It should again be emphasized that PNA and PNPNA, calculated from UNA (or UA) by the above equations, underestimate the "true" DPI and NPI, respectively, because the "unmeasured" losses of nitrogen, which may be highly variable between the patients, are not taken into consideration. Nevertheless, an estimate of protein intakes based on the determination of UNA has proved to be of great value in stable patients with chronic uremia [9, 32].

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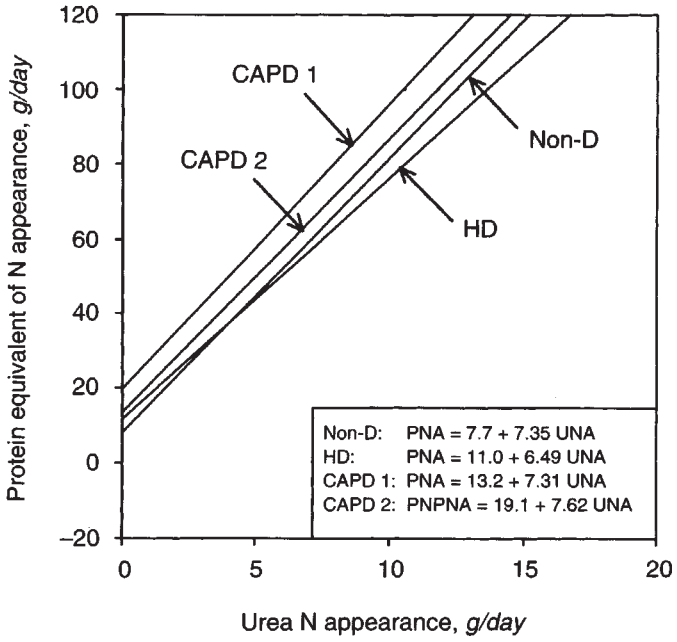

Fig. 7. *Relationship between protein equivalent of nitrogen appearance (PNA) and UNA in CAPD, HD and non-dialyzed (Non-D) patients with chronic renal failure.* The relationship between protein equivalent of non-protein nitrogen appearance (PNPNA) and UNA for the CAPD patients is also presented in the graph. The equations and lines for CAPD were calculated from the combined data in this study and that of Blumenkrantz et al [14]. For HD patients from the data of Borah et al [10] and for non-dialyzed chronic renal failure patients from the combined data of Cottini et al [8] and Maroni et al [9] were used.

Appendix. Abbreviations

BMI	=	Body mass index
CAPD	=	continuous ambulatory peritoneal dialysis
CRF	=	chronic renal failure
DNI	=	dietary nitrogen intake
DPI	=	dietary protein intake
DEI	=	dietary energy intake
HD	=	hemodialysis
N	=	nitrogen
NB	=	nitrogen balance, that is, DNI − TNA
NPI	=	net protein intake, that is, DPI − PL
NPNA	=	non-protein nitrogen appearance, that is, TNA − PL/6.25
PEI	=	peritoneal energy intake
PL	=	protein losses in urine + dialysate
PNA	=	protein equivalent of total nitrogen appearance (an estimation of DPI)
PNPNA	=	protein equivalent of non-protein nitrogen appearance (an estimation of NPI)
TEI	=	total energy intake
TNA	=	total nitrogen appearance
UA	=	urea appearance
UNA	=	urea nitrogen appearance

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