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Original Article

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Effect of prescribing a high protein diet and increasing the dose of dialysis on nutrition in stable chronic haemodialysis patients: a randomized, controlled trial

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Abstract

Background. Protein requirements in stable, adequately dialysed haemodialysis patients are not known and recommendations vary. It is not known whether increasing the dialysis dose above the accepted adequate level has a favourable effect on nutrition. The aim of this study was to determine whether prescribing a high protein diet and increasing the dose of dialysis would have a favourable effect on dietary protein intake and nutritional status in stable, adequately dialysed haemodialysis patients. Effects on hyperphosphataemia and acidosis were also studied.

Methods. Patients were randomized to a high dialysis dose (HDD) group (target Kt/V_{eq} of 1.4) or a regular dialysis dose (RDD) group (target Kt/V_{eq} of 1.0). All patients were prescribed a high protein (HP) diet [1.3 g/kg of ideal body weight (IBW)/day] and a regular protein (RP) diet (0.9 g/kg/day), each during 40 weeks in a crossover design. In 50 patients, 23 in the HDD and 27 in the RDD group follow-up was $\geq$10 weeks. These patients, aged 56 ± 15 years, were included in the analysis. Nutritional status was assessed by anthropometry, plasma albumin and a nutritional index.

Results. Delivered Kt/V_{eq} in the HDD group (1.26 ± 0.14) was significantly higher than in the RDD group (1.02 ± 0.08). Protein intake estimated from total nitrogen appearance (PNA) measurements and food records (DPI) was significantly higher during the HP diet (PNA_{IBW}, 1.01 ± 0.18 g/kg/day; DPI_{IBW}, 1.15 ± 0.18 g/kg/day) than during the RP diet (PNA_{IBW}, 0.90 ± 0.14 g/kg/day; DPI_{IBW}, 0.94 ± 0.11 g/kg/day). Increasing the dialysis dose did not increase protein intake either during the HP or RP diet. Plasma albumin (41.9 ± 3.0 g/l) lean body mass (107 ± 15% of normal values) and the nutritional index did not differ between the dialysis dose groups or protein diets and remained stable overtime. Dry body weight (97 ± 14%) and total fat mass increased over time in the HDD group, but remained stable in the RDD group suggesting an effect of dialysis dose on energy balance. There was no effect of the protein diets on dry body weight or total fat mass. Plasma phosphate levels and oral bicarbonate supplements were lower in the HDD group, but were comparable between the protein diets.

Conclusions. Prescribing a HP diet resulted in a modest increase in actual protein intake, but increasing dialysis dose did not have a contributing effect. A HP diet or increasing the dialysis dose did not have a favourable effect on the nutritional status. A dietary protein intake of at least 0.9 g/kg IBW/day appears to be sufficient for adequately dialysed haemodialysis patients without overt malnutrition.

Keywords: dialysis dose; dietary protein intake; haemodialysis; Kt/V; nutritional status; protein diet; protein equivalent of total nitrogen appearance; prospective randomized study

Introduction

Protein intake and nutritional status are associated with morbidity and mortality in chronic haemodialysis patients, independent of the dose of dialysis [1,2]. Poor nutrient intake is probably an important factor in the development of malnutrition, which is frequently observed in the dialysis population [3,4].

Protein requirements in present-day adequately dialysed haemodialysis patients are not known. The National Kidney Foundation-Dialysis Outcomes Quality Inititiative (NKF-DOQI) nutritional guidelines recommend a minimum protein intake of at least

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1.2 g/kg/day for stable maintenance haemodialysis patients, which is considerably more than the estimated protein intake in Dutch haemodialysis patients [5]. The recommended protein intake is based on short-term nitrogen balance studies in small numbers of patients, some performed before the introduction of modern dialysis techniques [6,7]. A deliberate increase in dietary protein intake might have a negative effect on the health of dialysis patients, since dietary protein is a significant source of uraemic toxins, phosphate and hydrogen. Possibly, a concomitant increase in dialysis dose is necessary to prevent a further increase in uraemic toxicity, hyperphosphataemia and metabolic acidosis.

Poor dietary protein intake may be caused by an insufficient dose of dialysis. Several studies have shown a link between single-pool Kt/V and protein intake that was estimated from the protein catabolic rate, which has more recently been described as protein equivalent of total nitrogen appearance (PNA) [8–10]. It has been suggested that the relationship between Kt/V and PNA is an artefact due to mathematical coupling [11]. Based on available evidence about the urea clearance and mortality, the NKF-DOQI guidelines propose a minimum delivered equilibrated double-pool Kt/V_{eq} of 1.0 in thrice weekly haemodialysis patients [12]. The impact of the dialysis dose on nutrition remains controversial and studies have shown conflicting results [1–4,9]. It is not known whether a further increase in the dose of dialysis would have a favourable effect on nutrition.

In this prospective, randomized study we questioned whether a high protein (HP) diet would have a favourable effect on dietary protein intake and nutritional status over time compared with a regular protein (RP) diet in clinically stable, chronic, adequately dialysed haemodialysis patients. Secondly, we questioned whether increasing the dialysis dose above the minimum accepted level would have a favourable effect on protein intake and nutritional status. Finally, we evaluated the effect of the prescribed protein diets and dialysis dose on the control of hyperphosphataemia and metabolic acidosis.

Subjects and Methods

Demographics and clinical characteristics of the study population

Patients were recruited from six dialysis centres in The Netherlands (Dialysis Centre Groningen and University Hospital Groningen, Dianet and University Medical Centre Utrecht, Martini Hospital Groningen and Scheper Hospital Emmen). Patients had to be treated by haemodialysis three times weekly for at least 3 months using low-flux (ultrafiltration coefficient < 10 ml/mmHg/h) dialysers with low complement activation and dialysate containing 32 mmol/l of bicarbonate. Patients with a Kt/V between 0.8 and 1.2 per session, a residual renal function < 3 ml/min, a stable clinical condition without hospitalization during ≥ 3 months were eligible for the study. Patients with overt oedema, inflammatory diseases, diabetes mellitus, active systemic diseases or known malignancies were excluded. Nutritional status was not a selection criterion. All included patients gave informed consent. The study was approved by the Medical Ethical Committee of the participating centres.

The patients were dialysed for 3–4.5 h/dialysis session and blood flow was set individually at a constant rate of 200–300 ml/min. Angioaccess in the majority of the patients was a Cimino AV-fistula in the forearm. The medical records of the patients were reviewed for co-morbid conditions and patients were assigned a low, medium or high survival risk index based on co-morbidity and age [13]. The Karnofsky Index was used to describe the functional status of the patients.

Study design

The study was a prospective, non-blinded, randomized crossover study with four regimens for dialysis dose and protein diet (Figure 1) After a 10-week baseline period patients were allocated to a high dialysis dose (HDD) group with a target Kt/V_{eq} of 1.4 or a regular dialysis dose (RDD) group with a target Kt/V_{eq} of 1.0. During the 80-week study period, a HP diet containing 1.3 g protein/kg/day and a RP diet containing 0.9 g protein/kg/day diet were prescribed to both groups during 2×40 weeks in a crossover design. Patients started on the HP diet or RP diet in random order. Randomization was performed using concealed minimization in order to maximize the probability that important prognostic variables would be evenly distributed between treatment groups, taking into account the variables gender, age (≤ 60 and > 60 years), baseline Kt/V (≤ 1.0 and > 1.0) and baseline plasma albumin (≤ 40 and > 40 g/l) [14].

Incrementing the dialysis dose to the target Kt/V_{eq} of 1.4 in the HDD group was achieved by increasing blood flow rate, increasing dialyser surface area and extending dialysis time, in that order. In the RDD group, the target Kt/V_{eq} of 1.0 was to be maintained within ± 0.1 by adjusting blood flow rate. Attempts were being made to reach the target dialysis dose within the first 5 weeks of the study. During this period urea kinetics were performed every week and thereafter every 5 weeks. The dialysis prescription was adjusted empirically to meet the target dose of dialysis.

Dietary protein and energy prescription was based on the patient's ideal body weight (IBW) adjusted for sex, frame size and height described in the Metropolitan weight tables [15]. Each patient was prescribed a HP diet containing 1.3–1.4 g/kg/day and a RP diet containing 0.9–1.0 g/kg/day of mainly high-biological-value protein. Protein supplements (Fortimel®, Fortifresh®, Protifar®, Nutricia Nederland B.V., Zoetermeer, The Netherlands) were added if protein requirements were not met with regular food. The minimal energetic value of the diets was defined as 1.27 times the basal metabolic rate based on the IBW, which is assumed to be the minimal energy requirement to maintain body weight [16]. Attempts were being made to prescribe two protein diets with comparable energetic values. Dietary sodium, potassium and fluid intake were restricted, according to Dutch dietary guidelines. All diets were composed by qualified dieticians with a long experience in the dialysis field. The dieticians encouraged the patients to comply with the prescribed diet on a regular basis. They counselled the patients at least once every 5 weeks during dialysis sessions and the diet prescription was modified if necessary.

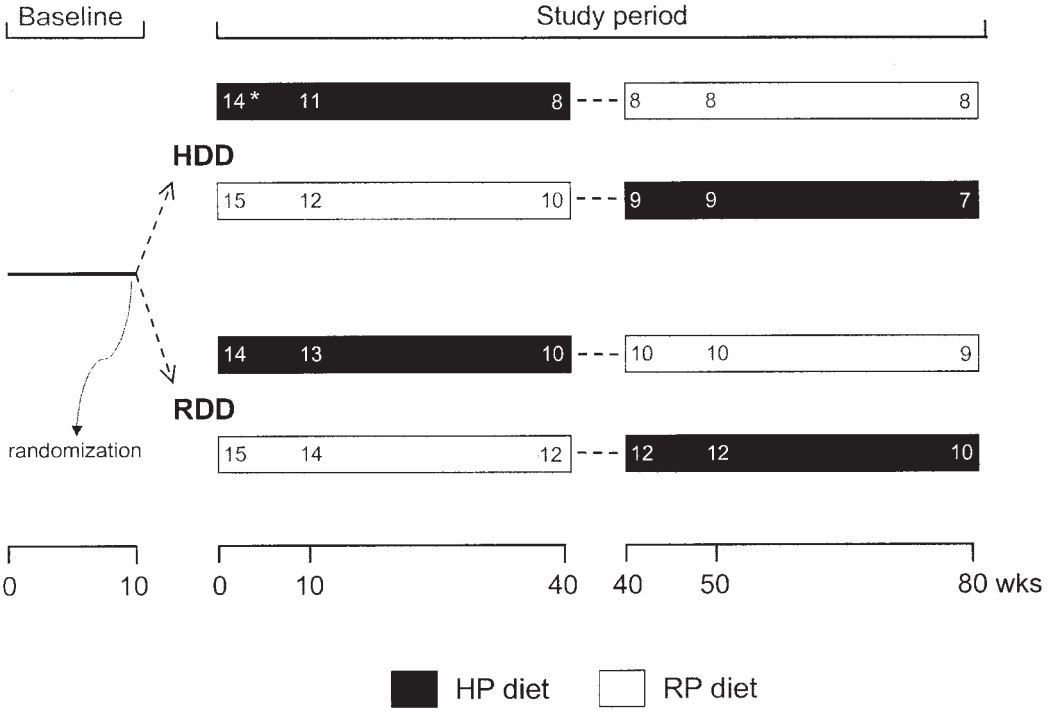

Fig. 1. Study design. See 'Subject and methods' section for detailed description. HDD, high dialysis dose group with target Kt/V_{eq} of 1.4; RDD, regular dialysis dose group with target Kt/V_{eq} of 1.0. HP diet, high protein diet containing 1.3 g protein/kg IBW/day; RP diet, regular protein diet containing 0.9 g protein/kg IBW/day. *Number of patients.

No guidelines for long-term patient management were made, besides the dialysis dose and the prescribed diet. Hyperphosphataemia and acidosis were corrected using the appropriate drugs and not by restriction of protein intake.

The study was ended by: (i) completion of the 80-week study period, (ii) death, (iii) transplantation, (iv) withdrawal of consent, (v) withdrawal because of medical reasons.

Urea kinetics

Urea kinetics, including Kt/V_{eq} and PNA, were performed during midweek dialysis sessions every 5 weeks, at baseline as well as during the study period. Mathematical details of the urea kinetic parameters are given in the Appendix. Delivered Kt/V_{eq} was calculated using pre- and 15-min post-dialysis urea concentrations according to the second-generation logarithmic Daugirdas equation [17].

PNA (g/day) was calculated according to the equation originally proposed by Borah *et al.* [7]. However, PNA calculated by the Borah equation does not include a value for unmeasured nitrogen losses in breath, hair, sweat and skin. Consequently, PNA almost always underestimates dietary protein intake (DPI). We, therefore, corrected PNA by adding 45 mg protein/kg actual body weight/day to approximate usual unmeasured nitrogen losses as has been proposed by Kopple *et al.* [18].

The urea distribution volume (UDV) that was used in the PNA calculations was determined thrice by direct dialysate quantification using continuous partial dialysate sampling at baseline [19]. The average of the three available UDV measurements at baseline was used in all subsequent PNA calculations.

Residual renal urea clearance (CL_U) and proteinuria were determined if urine production was >200 ml/24 h. Renal urea clearance was calculated from 24-h urinary urea output on the day after the modelled dialysis session and the time-averaged urea concentration.

All urea kinetic calculations were performed using plasma water urea concentrations by dividing the plasma urea concentrations values by 0.93.

Dietary protein and energy intake measurements

DPI and energy intake (DEI) were assessed by self-recording of food intake during 7 consecutive days, starting on the day before the modelled dialysis session, once at baseline and subsequently every 10 weeks during the study period. The patients were carefully instructed by a trained dietician to record their total oral intake in a dietary diary using household measures. The recorded intake was analysed using a nutritional database (BECEL-EXTRA, version 5, 1995, Unilever Research Laboratorium, Vlaardingen, The Netherlands). Values of DPI and DEI were normalized by IBW.

Nutritional status assessment

The nutritional status was assessed by anthropometry and plasma albumin levels. Anthropometry was performed once at baseline and at 40 and 80 weeks during the study period. Predialysis plasma albumin levels were assessed every 5 weeks at baseline and at 30, 35, 40, 70, 75 and 80 weeks during the study period. The averaged value of the plasma albumin concentrations at baseline and during the last 10 weeks of each protein

diet was used as a measure of the visceral protein status. The anthropometric measurements were performed after the dialysis session by a single observer (W.D.K.). Total fat mass and lean body mass were calculated according to Durnin and Womersley [20]. Percentage of IBW was calculated by dividing actual post-dialysis body weight by the patient's IBW. Relative body weight was calculated by dividing post-dialysis body weight by the patient's normal body weight, expressed as a percentage. Normal body weight represents the median body weight of normal Americans adjusted for sex, frame size, height and age, described in the National Health and Nutrition Examination Surveys (NHANES) I and II [21]. Relative fat mass and relative lean body mass were calculated using normal fat and lean body mass values, that were calculated from the median body weight and median triceps skinfold thickness of the NHANES reference population. The degree of nutrition was determined by a modified version of the nutritional index described by Harty *et al*. [22]. The index was derived from four subscores based on the values of relative body weight, triceps skinfold thickness, arm muscle area and albumin concentration. A value of 3, 2, 1 or 0 was obtained for each anthropometric parameter ($\geq$15th, 10–15th, 5–10th or $<$5th percentile of the reference population, respectively) and for the albumin concentration ($\geq$40, 35–40, 30–35 or $<$30 g/l, respectively). Summation of the four subscores resulted in an index of nutrition ranging from a maximum of 12 to a minimum of 0. In addition, the nutritional parameters in the haemodialysis patients were compared with a control group of 51 age-matched healthy Dutch subjects.

Laboratory analysis of blood, urine and dialysate

Haemoglobin, plasma total CO_2 and phosphate concentrations were determined every 5 weeks at baseline and during the study period. Laboratory analysis of blood, urine and dialysate samples were analysed using routine laboratory methods. Plasma albumin concentration was measured by the bromcresol-green method using an autoanalyser (Kodak Ektachem, Rochester NY, USA). Pre-dialysis and post-dialysis blood samples were analysed in one run.

Medications and morbidity

All prescribed medications, and the number of hospital admissions as well as the number of hospital days were recorded every 10 weeks.

Statistical analysis

The minimum sample size required was based on the assumption that a mean minimal difference in plasma albumin of 2.5 g/l between the HDD and RDD treatment groups is clinically relevant. The plasma albumin in our study group was assumed to range from 35 to 45 g/l with an overall standard variation of 2.5 g/l. The required sample size to detect this difference with a two-sided significance level of 5% and with a 80% power would be 17 subjects in each treatment group and thus 34 in total. Based on an expected drop-out rate of 20% per 40 weeks, 54 patients would have to be randomized.

Data were analysed using a per-protocol analysis. Only patients with a follow-up of $\geq$10 weeks were included in the analysis.

Averaged values of the outcome measures in the treatment groups over time were calculated as follows: at first all measurements available in an individual patient were averaged for the baseline period and for each protein diet. Then, the single values per patient were averaged across the treatment group.

Data were analysed in three different ways. First, the effect of the four combinations of dialysis dose and protein diet on the outcome measurements were analysed. Secondly, the effect of the dialysis dose was analysed by comparing the effects of the HDD and RDD treatment regimens regardless of the protein diet. Thirdly, effects of the protein diet were analysed by comparing the outcome measurements obtained during the HP and RP diets regardless of the dialysis dose.

Within-patient comparisons were performed using Wilcoxon signed rank tests and between-patient comparisons using Mann–Whitney U tests. Discrete data was analysed using Pearson's χ^2 tests. Change in nutritional status over time was analysed by Friedman test for $\geq$2 related variables.

Spearman correlation analysis, stepwise multiple regression analysis or forward logistic regression analysis was used to analyse the association between patient characteristics at baseline and the delivered dose of dialysis, actual protein intake and nutritional status during the study period. The F-statistic, with $P < 0.05$ for entry and $P > 0.1$ for exclusion, was used in the multivariate analyses.

Data are presented as mean $\pm$ SD or as mean with 95% confidence intervals (95% CI) unless stated otherwise. A two-sided P-value < 0.05 was considered statistically significant. All statistical calculations were performed using the SPSS for Windows statistical software package, release 10.0 (SPSS inc, Chicago, IL, USA).

Results

Patient number and follow-up

Sixty-three patients out of 119 eligible patients agreed to participate in the study and entered the baseline study period. Fifty-eight patients completed the baseline period successfully and could be randomized (four patients withdrew consent and one patient was transferred to another dialysis facility). In 50 patients the follow-up was $\geq$10 weeks. Data of 45 patients could be analysed on the HP diet and of 44 patients on the RP diet. Thirty-four patients completed the total study period of 80 weeks (see Figure 1).

After randomization, 24 patients dropped out, 14 patients in the HDD group (death, $n = 3$; transplantation, $n = 5$; withdrawal of consent, $n = 5$; other, $n = 1$) and 10 patients in the RDD group (death, $n = 3$; transplantation, $n = 4$; withdrawal of consent, $n = 2$; other, $n = 1$).

Follow-up in the HDD group on the HP diet was at 35 ± 10 weeks and on the RP diet 37 ± 9 weeks. In the RDD group follow-up was at 37 ± 8 weeks and 37 ± 10 weeks, respectively. Follow-up did not differ between the groups. Total follow-up in the HDD group was at

62 ± 28 weeks and in the RDD group at 67 ± 23 weeks. Total follow-up on the HP diet was at 36 ± 9 weeks and on the RP diet at 37 ± 8 weeks.

Patient characteristics, dialysis adequacy and outcome measurements at baseline

Table 1 presents the baseline characteristics, dialysis adequacy and nutritional status of the 50 randomized haemodialysis patients with a follow-up of ≥10 weeks that were included in the analysis and the nutritional status of the 51 Dutch healthy controls. Fat mass, plasma albumin and the index of nutrition in the dialysis patients were significantly lower than that in the Dutch controls. In addition, body weight and total fat mass were significantly below the normal values of the NHANES reference population. Body weight, total fat mass and lean body mass were < 90% of normal values in 32, 60 and 8% of the patients, respectively. Plasma albumin was > 35 g/l in all patients but one and > 40 g/l in the majority of the patients. The baseline values were comparable between the HDD and RDD groups.

Delivered dose of dialysis during the study period

Delivered Kt/V_{eq} in the HDD group (1.26 ± 0.14) was significantly higher than that in the RDD group (1.02 ± 0.08) as a result of the higher blood flow rate, dialysis time and dialyser surface area (Table 2 and Figure 2). In the HDD group a Kt/V_{eq} of ≥1.4 was achieved in five of the 23 patients. In the RDD group Kt/V_{eq} was > 1.10 in three (11%) and < 0.90 in one (4%) of the 27 patients. The Kt/V values were maintained during the total study period.

PNA and dietary intake during the study period

Complete food records during the study period were obtained in 43 of the 50 patients. Protein intake derived from both PNA and DPI values during the HP diet were higher than that during the RP diet (Table 2 and Figure 2). DPI values were significantly higher than the PNA values, the difference being largest during the HP diet. DPI values correlated significantly with PNA values ($R = 0.53$, $P < 0.001$). During the HP diet protein supplements were prescribed to 67% of the patients and during the RP diet to 2% of the patients.

Values of DEI were highest during the HP diet both in the HDD and RDD group (Table 2 and Figure 2). Averaged DEI_{IBW} was comparable between the HDD (29 ± 5 kcal/kg/day) and RDD groups (28 ± 5 kcal/kg/day). In the total study group actual DEI_{IBW} (29 ± 5 kcal/kg/day) did not differ significantly from the estimated minimum energy requirements (29 ± 2 kcal/kg/day).

Phosphorus intake was highest during the HP diet. Dietary phosphorus intake correlated with PNA ($R = 0.41$, $P < 0.01$) and with DPI ($R = 0.93$, $P < 0.001$).

Table 1. Demographics, clinical status, dialysis adequacy and nutritional status at baseline in randomized patients with ≥10 weeks follow-up and a group of Dutch healthy controls

	Patients	Controls
Number	50	51
Demographics		
Age (years)	56 ± 15	57 ± 17
Male:female	36:14	38:13
Time on dialysis (months)	48 ± 52	–
Clinical status		
Co-morbidity-age index		
Low	58%	–
Medium	28%	–
High	14%	–
Karnofsky index	87 ± 8	–
Dialysis dose and protein intake		
Kt/V_{eq}	1.00 ± 0.13	–
PNA (g/day)	63 ± 13	–
PNA_{IBW} (g/kg/day)	0.92 ± 0.16	–
DPI_{IBW} (g/kg/day)	0.93 ± 0.16	–
Nutritional status		
Body weight (kg)	72.4 ± 9.8	74.8 ± 10.8
Body mass index (kg/m^2)	24.0 ± 3.8	24.5 ± 2.7
Percentage IBW (%)	107 ± 15	109 ± 12
Relative body weight (%)	97 ± 14[b]	99 ± 12
Lean body mass (kg)	52.5 ± 7.7	52.8 ± 8.9
Relative lean body mass (%)	101 ± 11	99 ± 9
Total fat mass (kg)	19.2 ± 6.5[a]	22.0 ± 6.2
Relative total fat mass (%)	84 ± 26[a,b]	98 ± 26
Albumin (g/l)	41.9 ± 3.0[a]	47.7 ± 3.1
Index of nutrition	10.4 ± 2.1[a]	11.2 ± 1.5

Values are mean ± SD.
[a] $P < 0.05$ *vs* controls.
[b] $P < 0.05$ *vs* NHANES reference population.

Table 2. Haemodialysis technique, adequacy and dietary intake during the treatment regimens

Dose of dialysis	HDD		RDD	
Protein diet	HP	RP	HP	RP
Number of patients	20	20	25	24
Haemodialysis adequacy				
Blood flow rate (ml/min)	310 ± 48[a]	316 ± 39[a]	236 ± 40	239 ± 38
Dialysis time (min)	246 ± 15[a]	242 ± 22[a]	227 ± 28	225 ± 28
Dialyser surface area (m^2)	1.64 ± 0.25[a]	1.67 ± 0.13[a]	1.46 ± 0.28	1.46 ± 0.24
Kt/V_{eq}	1.25 ± 0.12[a]	1.29 ± 0.14[a]	1.00 ± 0.09	1.01 ± 0.08
PNA (g/day)	68 ± 9[b]	60 ± 8	68 ± 16[b]	61 ± 14
PNA_{IBW} (g/kg/day)	1.01 ± 0.14[b]	0.90 ± 0.07	1.00 ± 0.2[b]	0.90 ± 0.17
Dietary intake				
DPI (g/day)	79 ± 14[b]	63 ± 9	76 ± 15[b]	63 ± 10
DPI_{IBW} (g/kg/day)	1.18 ± 0.17[b]	0.94 ± 0.10	1.13 ± 0.18[b]	0.94 ± 0.11
DEI (kcal/day)	2044 ± 406[c]	1889 ± 361	1918 ± 398[d]	1842 ± 331
DEI_{IBW} (kcal/kg/day)	30 ± 4[c]	28 ± 4	29 ± 6[d]	28 ± 5
Phosphorus (mg/day)	1370 ± 210[b]	1129 ± 162	1298 ± 297[d]	1095 ± 221

Values are mean ± SD.
[a] $P < 0.05$ *vs* RDD/HP and RDD/RP.
[b] $P < 0.05$ *vs* HDD/RP and RDD/RP.
[c] $P < 0.05$ *vs* HDD/RP.
[d] $P < 0.05$ *vs* RDD/RP.

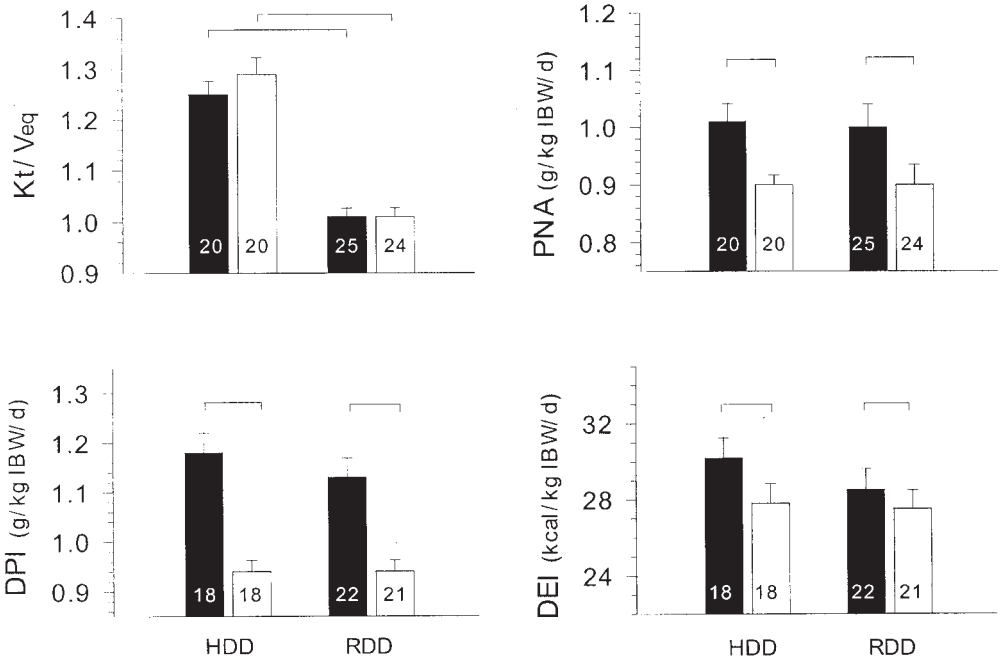

Fig. 2. Dose of dialysis, PNA and dietary protein (DPI) and energy intake (DEI) during the treatment regimens. ■, High protein diet; □, Regular protein diet. The number in the bars indicates the number of patients, $P < 0.05$.

Effect of the dialysis dose and prescribed protein diet on actual protein intake

Averaged PNA_{IBW} during the HP diet (1.01 ± 0.18 g/kg/day) was significantly higher than during the RP diet (0.90 ± 0.014 g/kg/day), indicating that an increase in prescribed dietary protein results in an increase in actual protein intake. However, actual protein intake assessed by both PNA and DPI during the HP diet was comparable between the HDD and RDD groups, while actual protein intake was still significantly lower than prescribed ($P < 0.001$) (Table 2 and Figure 2). This suggests that the dialysis dose did not have any contributing effect on protein intake. PNA_{IBW} values during the HP diet correlated negatively with the co-morbidity-age index ($R = -0.33$, $P < 0.05$), and positively with baseline plasma albumin ($R = 0.31$, $P < 0.05$), and cholesterol levels ($R = 0.31$, $P < 0.05$). No correlation was found between PNA and

Kt/V_{eq}. Multiple regression analysis revealed that only baseline plasma albumin was independently associated with PNA_{IBW} values during the HP diet.

Effect of the dialysis dose and prescribed protein diets on nutritional status

The measures of nutritional status did not differ between the treatment regimens (Table 3). In addition, the nutritional measures did not change significantly over time during the treatment regimens, except for actual body weight in the HDD group on the RP diet, which increased by 1.9% (95% CI: 0.5–3.4%). Analysis of the separate effects of the HP and RP diets regardless of the dialysis dose revealed no differences in nutritional status. In contrast, analysis of the effect of dialysis dose regardless of the protein diet revealed that actual body weight increased over time in the HDD group by 2.3% (95% CI: 1.1–3.6%). Body weight did not change significantly in the RDD group, 1.2% (95% CI: –0.6–3.0%). Total fat mass increased by 9.0% (95% CI: 1.2–16.8%) in the HDD group as well, while fat mass did not change in the RDD group, 2.8% (95% CI: –3.4–9.0%). Lean body mass, plasma albumin and the index of nutrition remained stable over time. The change in body weight, lean body mass and fat mass of the 34 patients who completed the 80-week study period is presented in Figure 3. Bivariate correlation analysis, including case-mix variables, nutritional status and quality of life at baseline as well as morbidity, delivered dose of dialysis and actual dietary intake during the study period of these 34 patients, revealed that an increase in body weight was associated with the HDD group ($R = 0.36$, $P < 0.05$), a higher Karnofsky Index ($R = 0.48$, $P < 0.01$), fewer months on dialysis ($R = –0.38$, $P < 0.05$), and a lower relative body weight ($R = –0.44$, $P < 0.05$) and relative lean body mass ($R = –0.48$, $P < 0.01$) at baseline. Logistic regression analysis revealed that only a higher Karnofsky Index was independently associated with an increase in body weight.

Effect of the prescribed protein diets and dialysis dose on hyperphosphataemia and metabolic acidosis

During the HP diet, plasma phosphate was significantly lower in the HDD group than in the RDD group (Table 4). Aluminium OH and elemental calcium intake did not differ among the treatment regimens. Averaged over the 80-week study period, plasma phosphate in the HDD group (1.77 ± 0.30 mmol/l) was significantly lower than in the RDD group (2.01 ± 0.41 mmol/l), while the intake of dietary phosphorus (Table 2) and phosphate-binding drugs did not differ between either group. Plasma phosphate was comparable between the HP (1.89 ± 0.39 mmol/l) and RP diet (1.88 ± 0.40 mmol/l).

The degree of acidosis and sodium bicarbonate intake did not differ among the treatment regimens. However, averaged over the 80-week study period sodium bicarbonate intake in the HDD group (103 ± 334 mg/day) was significantly lower than in the RDD group (419 ± 684 mg/day) ($P < 0.05$), while the degree of acidosis was comparable. Only three out of the 23 HDD patients used sodium bicarbonate *vs* 10 of the 27 RDD patients ($P = 0.054$). Metabolic acidosis and sodium bicarbonate intake did not differ between the HP and RP diet.

Effect of the dialysis dose and protein diet on morbidity and mortality

Our study was not designed to detect differences in morbididy and mortality. Nevertheless, it appeared interesting to look at possible trends. The number of hospitalized patients was somewhat lower in the HDD (four out of 23) than in RDD group (10 out of 27), but the difference did not reach the level of significance ($P = 0.123$). The number of hospital days did not differ between the HDD (4 ± 12) and RDD groups (7 ± 18). Morbidity did not differ between the HP diet and RP diet. In the HDD group, one out of 23 patients died and in the RDD group three out of 27 died.

Table 3. Nutritional status at the end of the treatment regimens

Dose of dialysis	HDD		RDD	
Protein diet	HP	RP	HP	RP
Number of patients	15	18	20	21
Body weight (kg)	72.1 ± 8.7	72.8 ± 9.2	74.0 ± 11.2	72.0 ± 10.3
Δ *body weight (%)*	*1.3 ± 3.0*	*1.9 ± 2.9*[a]	*0.9 ± 3.0*	*0.3 ± 3.5*
Lean body mass (kg)	*50.1 ± 7.2*	52.0 ± 7.2	51.9 ± 8.9	52.1 ± 8.9
Δ *Lean body mass (%)*	*–0.6 ± 2.2*	*0.9 ± 2.5*	*–0.1 ± 2.9*	*0.1 ± 3.6*
Total fat mass (kg)	19.2 ± 8.4	19.1 ± 6.6	18.9 ± 6.5	19.0 ± 5.9
Δ *Total fat mass (%)*	*6.9 ± 16.1*	*3.6 ± 11.3*	*4.4 ± 13.9*	*–0.90 ± 8.5*
Albumin (g/l)	41.5 ± 3.3	42.1 ± 3.4	41.7 ± 2.6	41.7 ± 2.8
Δ *Albumin (%)*	*–0.8 ± 5.1*	*1.4 ± 5.3*	*–0.1 ± 6.0*	*–1.3 ± 5.0*
Index of nutrition	10.1 ± 2.5	10.3 ± 2.5	10.0 ± 2.1	10.1 ± 2.2
Δ *Index of nutrition (%)*	*3.2 ± 16.2*	*3.4 ± 10.6*	*–0.6 ± 9.8*	*–1.5 ± 12.6*

Values are mean ± SD. Shown are the absolute values at the end of each treatment regimen and the percentage change (Δ).
[a] $P < 0.05$ *vs* zero change.

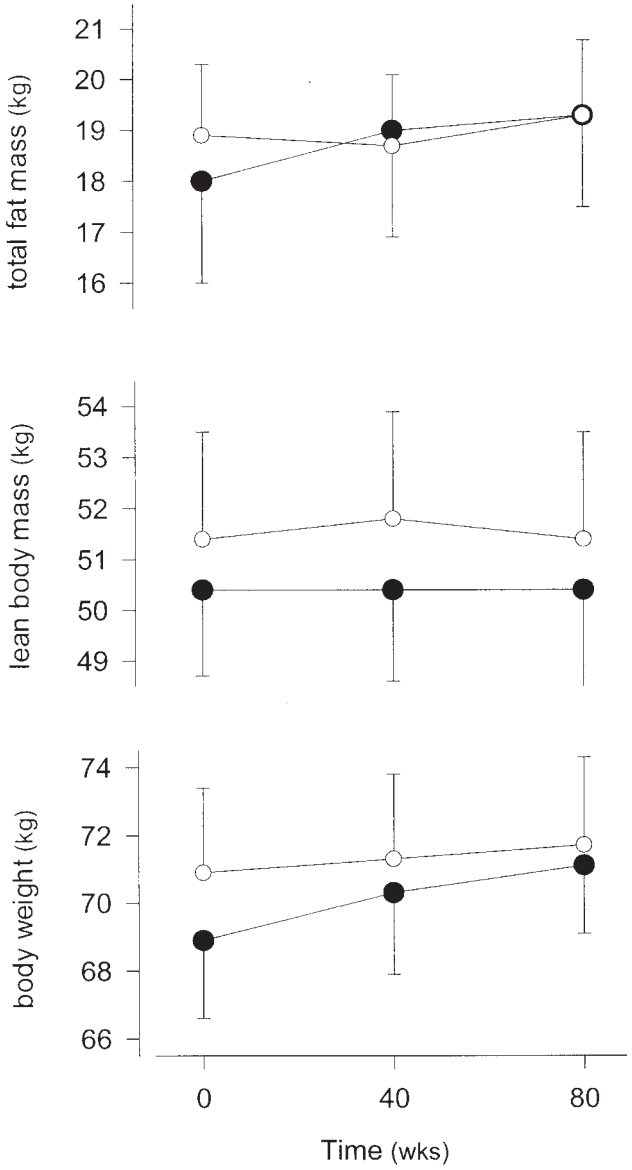

Fig. 3. Change in actual body weight, lean body mass and total fat mass of the 34 patients that completed the total study period. Values shown are mean ± SEM. In the HDD group body weight ($P < 0.001$) and total fat mass ($P < 0.05$) increased over time during the 80-week study period (Friedman non-parametrical test). ● High dialysis dose group; ○ Regular dialysis dose group.

Discussion

The main findings of our study are that prescribing a HP diet to stable haemodialysis patients resulted in only a small increase in actual protein intake and had no beneficial effect on the nutritional status. Increasing the dialysis dose above adequate levels did not have a favourable effect on protein intake or on the nutritional status, but improved the control of hyperphosphataemia and metabolic acidosis. The nutritional status did not deteriorate over time, despite a dietary protein and energy intake below recommended values. The results of our study suggest that recommended dietary protein requirements are higher than necessary. A protein intake of at least 0.9 g/kg IBW/day appears to be sufficient in stable adequately dialysed haemodialysis patients without overt malnutrition.

The difference in actual protein intake was small between the HP and RP diet, despite the use of protein supplements and intensive dietary counselling. The study shows that patients were not able to comply fully with the HP diet that was significanly higher than their habitual protein intake. Possibly, the patients even overestimated their actual protein intake, as self-recorded protein intake was higher than the PNA values, particularly during the HP diet. A lower DPI than the prescribed diet has also been observed in other studies [3,23]. In our study, the dieticians were often not able to compose a balanced HP diet using regular food products, because of restricted fluid intake. Consequently, protein supplements had to be prescribed and the patients disliked these products after a while. The elderly and more inactive patients in particular felt that the amount of food they had to consume during the HP diet was more than they needed. The observation that a high co-morbidity–age index was related to a lower PNA_{IBW} during the HP diet also indicates that older patients and patients with more co-morbid conditions had a lower protein intake. Interestingly, patients with the highest plasma albumin levels at baseline were able to comply best with the HP diet, confirming the association between albumin and normalized PNA found in cross-sectional studies [4]. These findings support the idea that other factors such as co-morbid condition or inflammation could largely explain the positive correlation between protein intake and plasma albumin in haemodialysis patients [24]. Unfortunately, we did not assess C-reactive protein as a measure of inflammation.

We did not find an effect of increasing delivered Kt/V_{eq} above 1.0 during the HP diet on PNA or DPI. The target Kt/V_{eq} of 1.4 was not reached in all HDD patients, because patients showed a great reluctance to have their dialysis time increased. The limited increase in Kt/V_{eq} could have flawed the effect of increasing the dialysis dose on nutrition in our study, but even a positive trend was absent. The results of our study suggest that the protein intake in stable haemodialysis patients does not depend on the dialysis dose provided that the dose of dialysis is adequate. Several prospective studies have shown an association between Kt/V and PNA, but these studies included patients with a Kt/V_{eq} well below 0.9 [8]. It is very conceivable that protein intake will decrease if Kt/V falls below 0.9 due to deterioration of the uraemic state. In another prospective study Marcus *et al.* did show a relationship between a Kt/V above adequate levels and PNA, but this study was not randomized and single-pool urea kinetics were used [10]. The use of single-pool urea kinetic models will introduce calculation bias, which can result in an artificial relationship between Kt/V and PNA. Observational studies are not suitable for exploring

Table 4. Laboratory variables and medication during the treatment regimens

Dose of dialysis	HDD		RDD	
Protein diet	HP	RP	HP	RP
Number of patients	20	20	25	24
Laboratory variables				
Haemoglobin (g/l)	113 ± 13	110 ± 11	108 ± 10	108 ± 11
Urea (mmol/l)	28.5 ± 4.8[a]	25.1 ± 3.5[c]	31.7 ± 6.2[b]	28.0 ± 5.1
Phosphate (mmol/l)	1.73 ± 0.30[d]	1.79 ± 0.35	2.03 ± 0.40	1.95 ± 0.44
Total CO_2 (mmol/l)	22.7 ± 3.9	22.2 ± 4.0	22.1 ± 2.6	22.3 ± 2.7
Medication				
Aluminium OH (% of pts)	80%	70%	60%	67%
Elemental calcium (g/day)	2.4 ± 1.5	2.5 ± 1.9	2.3 ± 1.7	2.1 ± 1.3
Sodium bicarbonate (mg/day)	113 ± 349	125 ± 393	330 ± 694	411 ± 691

Values are mean ± SD.
[a] $P < 0.05$ *vs* HDD/RP.
[b] $P < 0.05$ *vs* RDD/RP.
[c] $P < 0.05$ *vs* RDD/HP and RDD/RP.
[d] $P < 0.05$ *vs* RDD/HP.

the Kt/V–PNA relationship because of error coupling and confounding [11]. We cannot exclude an effect of the dialysis dose on protein intake if the haemodialysis treatment is intensified by increasing the dialysis frequency combined with a substantial lengthening of the dialysis duration. A change from conventional to nocturnal haemodialysis was associated with a significant increase in spontaneous protein intake, which may be explained by a more liberal diet and an increased clearance of middle molecule-sized uraemic toxins [25].

Although the development of malnutrition is multifactorial, insufficient nutrient intake is probably an important factor. The fact that body protein stores in our patient group did not deteriorate over time despite a DPI well below the protein requirement of at least 1.2 g/kg/day recommended in the NKF-DOQI nutritional guidelines, suggests that the recommended protein intake may be too high in stable haemodialysis patients who are in a relatively good clinical condition. The DPI recommended by NKF-DOQI is primarily based on short-term nitrogen balance studies in small numbers of haemodialysis patients [6,7]. The patients included in these studies were generally stable without overt malnutrition and thus reasonably comparable with our study population. The interpretation of these studies varies and Lim *et al*. argued that a protein intake of 0.9–1.0 g/kg/day should be appropriate for stable chronic haemodialysis patients after reviewing the results of these studies [26].

It is important to emphasize that protein requirements are dependent on the concomitant energy intake [6]. Because the studied patients augmented energy stores over time, the energy intake was probably sufficient, despite an apparent energy intake that was on average well below recommended values of 30–35 kcal/kg/day [5]. This could indicate that the recommended energy requirements are too high for stable haemodialysis patients. However, underreporting of energy intake by the patients cannot be excluded.

Increasing the dose of dialysis above the adequate level did not have a favourable effect on body protein stores, including plasma albumin, confirming the results of cross-sectional studies [1,2,4]. In contrast, non-randomized observational studies observed an increase in PNA and serum albumin while Kt/V increased over a period of several years [9]. However, the haemodialysis modality and prescribed protein diet may have been changed over time. Interestingly, in our study the increase in body weight and fat mass during the 80-week follow-up was significant only in the HDD group. However, a correlation analysis did not show an association between the actual dialysis dose delivered during the study period and the increase in the body mass measurements. The apparent association between the dialysis dose and change in body mass is difficult to interpret. It might suggest that increasing the dialysis dose has a favourable effect on energy balance, but this interpretation requires confirmation in future studies.

One of the reasons why we did not find an effect of a high prescribed protein diet combined with a HDD on the nutritional status, could be the inclusion of relatively well-nourished patients, although the nutritional status was not as good as that in the Dutch controls. It should be stressed that nutritional status as such was not a selection criterion in our study. A further improvement in nutritional status in these patients is more difficult to obtain. Whether an increase in DPI would have a beneficial effect on the nutritional status in selected malnourished haemodialysis patients cannot be answered from our study. As far as we know, no studies on the effect of a HP diet have been performed in malnourished patients. However, an elegant, controlled randomized study in hypoalbuminaemic haemodialysis patients on the effect of essential amino acids supplementation has shown a small significant increase in plasma albumin in supplemented patients [27].

Potential carry-over effects could also have flawed the effect of prescribing a HP or RP diet on nutrition in

our study. The major outcome data were, therefore, analysed at the end of each protein diet. The long follow-up period on both protein diets probably minimizes the risk of carry-over effects, but does not eliminate this risk.

The PNA was used to assess protein intake in our study. A reliable estimate of the UDV is required to assess PNA. The UDV was determined by direct dialysate quantification, which is a cumbersome procedure, prone to measurement errors. Averaging the multiple UDV measurements at baseline and using the averaged UDV value in all subsequent PNA calculations was perfomed in order to prevent measurement errors in UDV would affect the reliability of the PNA values. The drawback of this method is that true changes in UDV over time were not accounted for in the PNA calculations. However, we do not think that this approach affected the results of the study. Changes in UDV were probably small, because changes in lean body mass, which is the main determinant of UDV, observed in individual patients were small. In addition, lean body mass remained stable over time in all treatment groups.

Prescribing a HP diet did not lead to a deterioration of hyperphosphataemia, possibly due to the relative small increase in actual protein intake. A higher dialysis dose appeared to prevent hyperphosphataemia, as the plasma phosphate level was lowest in the HDD patients, while no more phosphate-binding drugs were used. This suggests increased phosphate removal in the HDD patients, probably as a result of longer dialysis time. Aggravation of metabolic acidosis during the HP diet did not occur. Notably, increasing the dose of dialysis appeared to have a beneficial effect on acid–base balance as sodium bicarbonate intake was lowest in the HDD patients, while the degree of acidosis was similar to that in the RDD patients.

In conclusion, prescribing a HP diet to clinically stable haemodialysis patients who are dialysed three times weekly resulted in a modest increase in actual protein intake, but a concomitant increase in Kt/V_{eq} above 1.0 did not have a contributing effect on Dietary Protein Intake. A high-prescribed protein diet combined with an increase in Kt/V_{eq} above the adequate level did not have a favourable effect on the nutritional status. A Dietary Protein Intake of at least 0.9 g/kg IBW/day might be sufficient for stable haemodialysis patients without overt malnutrition. Increasing the dialysis dose appeared to improve the control of hyperphosphataemia and metabolic acidosis.

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Conflict of interest statement. None declared.

Appendix

Calculation of the urea kinetic parameters

List of abbreviations

U_1, U_2, U_3, plasma water urea concentration before (1) and 15-min after (2) the modelled dialysis and before (3) the next dialysis (mmol/l).

W_1, W_2, W_3, body weight before (1) and after (2) the modelled dialysis and before (3) the next dialysis (kg).

T_D, T_{ID}, duration of dialysis and interdialytic interval (min).

V_D, U_D, total volume of dialysate (l) and dialysate urea concentration (mmol/l).

V_U, U_U, total 24-h volume of urine (l) and urinary urea concentration (mmol/l).

UDV, urea distribution volume (l).

TAC_U, time-averaged concentration of urea (mmol/l).

CL_U, residual renal clearance of urea (ml/min).

UNA, urea nitrogen appearance (g N/day).

UA, urea appearance (mmol/min).

PNA, protein equivalent of total nitrogen appearance (g/day).

The Kt/V_{eq} was calculated according to the second generation logarithmic Daugirdas equation [17]:

$$Kt/V = -\ln\left(\frac{U_2}{U_1} - 0.008 \times (T_D/60)\right) + \left(4 - 3.5 \times \frac{U_2}{U_1}\right) \times \frac{(W_1 - W_2)}{W_2} \quad (1)$$

Residual renal urea clearance (CL_U) and proteinuria were determined in patients if urine production was > 200 ml/24 h. CL_U was calculated from 24-h urinary urea output on the day after the modelled dialysis session and the TAC_U according to:

$$TAC_U = \frac{T_D \times (U_1 + U_2) + T_{ID} \times (U_2 + U_3)}{2 \times (T_D + T_{ID})} \quad (2)$$

$$CL_U = \frac{(V_U \times U_U)}{TAC_U} \times 0.6944 \quad (3)$$

The UDV was determined kinetically by direct dialysis quantification. UDV was corrected for urea appearance, residual renal urea clearance and ultrafiltration during the modelled dialysis session, according to the equation described by Stegeman *et al*. [19]:

$$UDV = \Big\{(V_D + W_1 - W_2) \times U_D - \frac{T_D \times (W_3 - W_2) \times U_3}{T_{ID}} - \frac{T_D \times \left(V_{ID_U} \times U_{ID_U}\right)}{T_{ID}} - (W_1 - W_2) \times U_1\Big\} \Big/ \{(U_1 - U_2) + T_D \times ((U_3 - U_2)/T_{ID})\} \quad (4)$$

where V_{ID_U} is the volume (l) and U_{ID_U} is the urea concentration (mmol/l) of all the urine that is collected during the total interdialytic interval. In the present study, the urinary urea output during the total interdialytic interval was estimated from the residual urea clearance (CL_U) and the average interdialytic plasma urea concentration according to:

$$V_{ID_U} \times U_{ID_U} \approx \frac{CL_U}{1000} \times \frac{(U_2 + U_3)}{2} \times T_{ID} \quad (5)$$

Now, by substituting equation 5 in equation 4, $V_{ID_U} \times U_{ID_U}$ can be eliminated, resulting in equation 6, which was actually used to calculate UDV:

$$\begin{aligned} UDV = \{&(V_D + W_1 - W_2) \times U_D \\ &- \frac{T_D \times (W_3 - W_2) \times U_3}{T_{ID}} \\ &- T_D \times \left(\frac{CL_U}{1000} \times \frac{(U_2 + U_3)}{2}\right) \\ &- (W_1 - W_2) \times U_1\} / \\ &\left\{(U_1 - U_2) + T_D \times \frac{(U_3 - U_2)}{T_{ID}}\right\} \end{aligned} \quad (6)$$

The protein equivalent of PNA was calculated from UNA during the interdialytic interval using the equation originally described by by Borah *et al*. [7]:

$$PNA = 6.49 \times UNA + 11.04 \quad (7)$$

The second term on the right-hand side in equation 7 represents the average value for non-urea nitrogen losses. Equation 7 was later modified by dividing the constant term by the average value of the patients' UDV, namely 38 l, resulting in equation 8:

$$PNA = 6.49 \times UNA + 0.294 \times UDV \quad (8)$$

Instead of measuring urea nitrogen, expressed in g N/l, we measured urea concentration, expressed in mmol/l. In addition, the interdialytic interval in the present study was expressed in minutes, instead of days. Because 1 mmol of urea contains 0.028 g N and 1 day contains 1440 min, the UNA term in equation 8 can be rearranged to UA, expressed in mmol/min, resulting in equation 9:

$$PNA = 6.49 \times 0.028 \times 1440 \times UA + 0.294 \times UDV \quad (9)$$

Urea appearance was estimated from the interdialytic increase in plasma urea, estimated urinary urea output, UDV and interdialytic weight gain according to:

$$\begin{aligned} UA = &\frac{CL_U}{1000} \times \frac{(U_2 + U_3)}{2} + U_3 \times \frac{(W_3 - W_2)}{T_{ID}} \\ &+ UDV \times \frac{(U_3 - U_2)}{T_{ID}} \end{aligned} \quad (10)$$

Finally, PNA was corrected for unmeasured nitrogen losses, which was not accounted for in the original Borah equation (equation 7), by adding 0.045 g protein/kg actual dry body weight/day as has been proposed by Kopple *et al*. [18] and urinary protein losses (g/day). PNA in the present study was then calculated according to equation 11:

$$\begin{aligned} PNA = &261.7 \times UA + 0.294 \times UDV + 0.045 \\ &\times W_2 + \text{urinary protein loss.} \end{aligned} \quad (11)$$

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