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Original Article

Better preservation of residual renal function in peritoneal dialysis patients treated with a low-protein diet supplemented with keto acids: a prospective, randomized trial

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Abstract

Background. While a low-protein diet may preserve residual renal function (RRF) in chronic kidney disease (CKD) patients before the start of dialysis, a high-protein intake is usually recommended in dialysis patients to prevent protein-energy wasting. Keto acids, which were often recommended to pre-dialysis CKD patients treated with a low-protein diet, had also been reported to be associated with both RRF and nutrition maintenance. We conducted a randomized trial to test whether a low-protein diet with or without keto acids would be safe and associated with a preserved RRF during peritoneal dialysis (PD).

Methods. To assess the safety of low protein, we first conducted a nitrogen balance study in 34 incident PD patients randomized to receive in-centre diets containing 1.2, 0.9 or 0.6 g of protein/kg ideal body weight (IBW)/day for 10 days. Second, 60 stable PD patients [RRF 4.04 ± 2.30 ml/min/1.73 m^2, urine output 1226 ± 449 ml/day, aged 53.6 ± 12.8 years, PD duration 8.8 (1.5–17.8) months] were randomized to receive either a low- (LP: 0.6–0.8 g/kg IBW/day), keto acid-supplemented low- (sLP: 0.6–0.8 g/kg IBW/day with 0.12 g/kg IBW/day of keto acids) or high-protein (HP: 1.0–1.2 g/kg IBW/day) diet. The groups were followed for 1 year and RRF as well as nutritional status was evaluated serially.

Results. A neutral or positive nitrogen balance was achieved in all three groups. RRF remained stable in group sLP (3.84 ± 2.17 to 3.39 ± 3.23 ml/min/1.73 m^2, P = ns) while it decreased in group LP (4.02 ± 2.49 to 2.29 ± 1.72 ml/min/1.73 m^2, $P < 0.05$) and HP (4.25 ± 2.34 to 2.55 ± 2.29 ml/min/1.73 m^2, $P < 0.05$). There was no change from baseline on nutritional status in any of the groups during follow-up.

Conclusions. A diet containing 0.6–0.8 g of protein/kg IBW/day is safe and, when combined with keto acids, is associated with an improved preservation of RRF in relatively new PD patients without significant malnutrition or inflammation.

Keywords: chronic kidney disease; diet; glomerular filtration rate; malnutrition; nitrogen balance

Introduction

Residual renal function (RRF) is important in patients with chronic kidney disease (CKD), with benefits that go beyond contributing to the achievement of adequacy targets. Recent studies have found that RRF, rather than the overall clearance adequacy (RRF plus dialysis), is an essential predictor of patient survival in dialysis patients [1,2] and technique survival in chronic peritoneal dialysis (PD) patients [1,3]. In dialysis patients, besides dialysis adequacy, RRF plays a major role in inhibiting inflammation [4], maintaining nutritional status [5], preventing left ventricular hypertrophy [6], keeping the balance between serum phosphate and calcium [7], and even decreasing peritonitis rates [1,3]. The understanding that dialysis could not completely replace the function of the kidney highlights the importance of protecting RRF in CKD patients, even after starting dialysis.

Dietary protein intake (DPI) is the major determinant of the amount of nitrogen excreted as urea by the kidney [8,9], and a decreased protein intake has been associated with a retardation of kidney function loss in pre-dialysis CKD patients [10–13], an effect presumably mediated by lowering the requirement for renal nitrogen clearance [10,12,14,15] and/or a reduction in proteinuria [11,16,17], as well as other factors [15]. While a low-protein diet is recommended to CKD patients before the start of dialysis to preserve RRF [18,19], current therapy recommendations in PD patients are for a DPI of no less than 1.2 g of protein/kg ideal body

weight (IBW)/day [18] to prevent protein-energy wasting (PEW) [20]. Keto acids were often supplied to low-protein diets in pre-dialysis CKD patients not only for nutrition safety but also because of their independent impact on RRF maintenance [21,22]. There are no previous randomized prospective studies evaluating the impact of a low-protein diet whether with or without keto acids on nutritional status and RRF, respectively, in PD patients.

We hypothesized that a low-protein intake would be safe, i.e. result in neutral or positive nitrogen balance, and also able to slow the loss of RRF in PD patients. To test these hypotheses, we conducted two prospective, randomized trials involving a total of 94 PD patients: a short-term nitrogen balance study where patients ($n = 34$) were randomized to receive in-centre diets containing 1.2, 0.9 or 0.6 g of protein/kg IBW/day for 10 days, and a 12-month study where the patients ($n = 60$) were randomized to receive either a low- (LP: 0.6–0.8 g/kg IBW/day), keto acid-supplemented low- (sLP: 0.6–0.8 g/kg IBW/day with 0.12 g/kg IBW/day of keto acids) or high-protein (HP: 1.0–1.2 g/kg IBW/day) diet.

Subjects and methods

To test the safety of a low-protein intake in PD patients, we first conducted an in-centre 10-day nitrogen balance study of three diets containing different amounts of protein. Based upon the results from this study, we next randomized stable PD patients to three groups with different diets and followed them prospectively for 12 months. The protocol was approved by the Ethical Committee of Shanghai Jiaotong University School of Medicine and registered in ClinicalTrials.gov (ClinicalTrials.gov number: NCT00633646).

Nitrogen balance study

Stable PD patients with vintage >1 month met the recruitment criteria. We excluded patients with evidence of infection or inflammation (C-reactive protein, CRP > 10 mg/l [4]); persistent anorexia, vomiting or diarrhoea; concurrent wasting disease, i.e. cancer or tuberculosis. The patients could withdraw from the study at any stage as per their own will. PD was performed using a 1.5% or 2.5% dextrose solution (Dianeal®; Baxter China Ltd, Guangzhou, China) with Twin Bag system (UltraBag®; Baxter China Ltd). The patients were hospitalized and randomized to receive in-centre meals containing a net DPI of 1.2, 0.9 or 0.6 g/kg IBW. Approximately half of this protein was from animal products. In accordance with current therapy guidelines, the total energy intake (TEI), including both from diets and PD glucose [23], was 35 kcal/kg IBW for patients below 60 years of age, and 30 kcal/kg IBW for the rest. Based upon actual food consumption, DPI and TEI was calculated (Keto Acids Diet Calculator 2.0; Fresenius-Kabi Co., Ltd, Beijing, China).

After a 3-day wash-in period, baseline data were collected and patients were then followed for 10 days. Nitrogen balance, nutritional markers and blood biochemistry were assessed at baseline and after 7 and 10 days. All the laboratory measurements were performed using routine methods. A simplified nitrogen balance was calculated as described by Rao *et al.* [24]. Briefly, nitrogen (N) input was calculated from DPI. N output included estimated values of dialytic and urinary nitrogen losses based on measured urea losses (urea nitrogen, UN). Non-urea nitrogen (NUN) losses in urine and dialysate (contained in creatinine and uric acid) were assumed to contribute only a small fraction to the N output [25]. The sum of faecal losses and other nitrogen losses (through skin, sweat and breath) that we assumed did not change significantly with a protein intake was estimated using the value 0.031 g/kg/day suggested by Maroni *et al.* for non-dialysed patients [9]. Thus, nitrogen balance (NB) was calculated as NB = Dietary N – (UN + 0.031 g/kg/day) and was normalized to IBW calculated as [height (cm) −105] [26].

RRF study

Stable PD patients with urine output ≥800 ml or eGFR ≥2 ml/min/1.73 m^2 (calculated as an average of the creatinine and urea clearances by 24-h urine) were evaluated. Inclusion criteria were RRF as above, age 18–80 years, stable PD for at least 1 month. Exclusion criteria were a high probability (assessed by the recruiting physician) of receiving a kidney transplant within 1 year; overt infection within the last month; persistent anorexia, vomiting or diarrhoea and the presence of wasting diseases such as cancer or tuberculosis. Conditions requiring withdrawal from the study included severe malnutrition (subjective global assessment of nutrition, SGA [28]), transplantation, transference to haemodialysis, the development of serious medical conditions or the patient's own will to withdraw.

The patients were randomized to either a low- (LP: 0.6–0.8 g/kg IBW/day), keto acid-supplemented low- (sLP: 0.6–0.8 g/kg IBW/day with keto acids of 0.12 g/kg IBW/day, Ketosteril®; Fresenius-Kabi Co.) or high-protein (HP: 1.0–1.2 g/kg IBW/day) diet based on the results of the nitrogen balance study. TEI was prescribed as above. During a 1-month wash-in period after randomization, patients were repeatedly instructed by dietitians on how to prepare their food and record the actually consumed food. Then, baseline data, such as RRF, Kt/V and blood biochemistry, etc, were collected and enrolled patients were assessed serially for 12 months, and diet, RRF, nutritional status, as well as blood chemistry followed.

PD was performed in the same way as the nitrogen balance study. Angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) were given to all the patients during the study to control hypertension. Amino acids and other nutritional supplements were avoided during the study. Aminoglycosides were forbidden for patients with RRF when infection occurred during follow-up.

Dietary protein and energy intake was assessed by 3-day diet diary (Keto Acids Diet Calculator 2.0). This method has previously been validated in PD patients [27]. The protein equivalent of nitrogen contained in keto acids was added to DPI of group sLP. RRF was assessed as above, while dialysis adequacy was assessed using Kt/V and creatinine clearance. SGA was performed using conventional methods [28]. LBM was estimated using creatinine kinetics [29]. All the other parameters were measured using routine procedures.

Statistical analysis

The results are presented as mean ± SD or median (interquartile range). A P-value <0.05 was considered statistically significant. Differences across groups were assessed by ANOVA or the Kruskal–Wallis test as appropriate. *Post hoc* analysis was done using methods of Student–Newman–Keuls (S-N-K) for ANOVA and Dunnett T3 for the Kruskal–Wallis test. Repeated measures ANOVA was used to assess changes over time. All analyses were carried out with the SPSS 11.0 for Windows statistical software (SPSS, Inc., Chicago, IL, USA).

Results

Nitrogen balance study

Thirty-four incident PD patients were recruited after informed consent and 10 were randomized to receive 1.2 g (group A), 13 to receive 0.9 g (group B) and 11 to receive 0.6 g (group C) of protein/kg IBW/day (Figure 1A). Four patients dropped out, of their own will (1 in group A, 1 in group B and 2 in group C), and 30 patients who completed the study are presented in the following data. Baseline characteristics were similar in all three groups (Table 1). DPI was significantly different (Figure 2A) while TEI (including energy uptake from both diet and PD solutions) was similar among the three groups (Figure 2B).

A positive nitrogen balance was found in group A and neutral nitrogen balance was found in groups B and C on both the 7th and 10th days of the study (Figure 3). Nitrogen balance in group C showed a small increase on the 10th day compared with baseline, but not significant. Blood

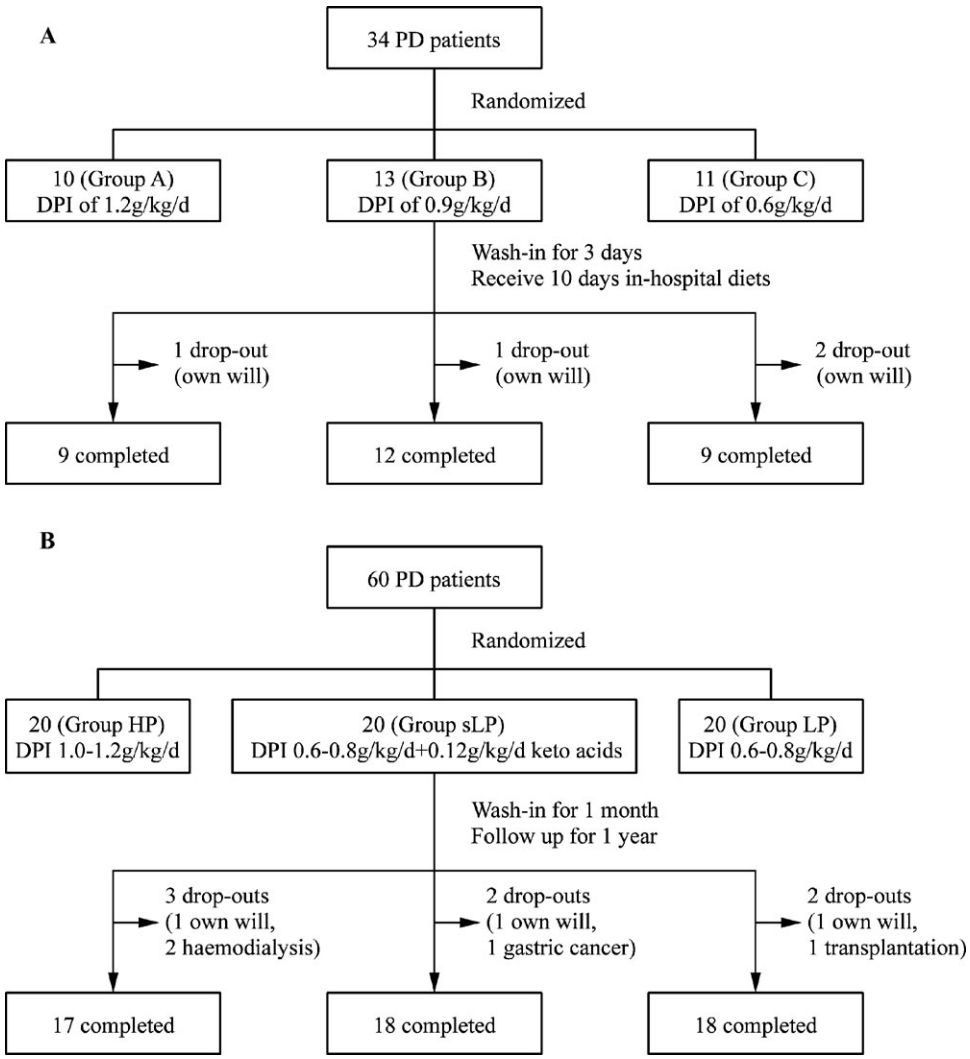

Fig. 1. Flow diagrams of the randomized prospective study design and the flow of participants through the stages of the study. Panel **A** shows the nitrogen balance study. Panel **B** shows the residual renal function study.

biochemistry, including albumin, pre-albumin, etc., was stable in all the groups throughout the study (detailed data not shown).

RRF study

Sixty stable PD patients were recruited after informed consent. Baseline characteristics of the patients randomized to receive LP, sLP or HP are presented in Table 2. During follow-up, 7 patients dropped out (2 in group LP, 2 in group sLP, 3 in group HP, Figure 1B) due to their own will ($n = 3$, 1 in each group), transfer to HD ($n = 2$, group HP), transplantation ($n = 1$, group LP) and comorbidity ($n = 1$, gastric cancer, group sLP). During the study, 16 hospitalizations occurred, mainly due to lung infection or peritonitis (4 in group LP, 5 in group sLP, 7 in group HP, $P =$ ns). As shown in Figure 4A, DPI differed significantly during the whole period between group sLP and the others ($P < 0.05$). Group LP achieved a significantly lower protein intake than group HP only in Months 6 and 10. TEI was similar among the three groups during the study (Figure 4B).

Figure 5 shows data on RRF. Briefly, the patients in group sLP maintained a stable estimated glomerular filtration rate (eGFR) and urine output throughout the study, while both indices declined significantly in the other two groups ($P < 0.05$). Declines of Kt/V_{renal} and Ccr_{renal} were also different among the three groups. Urine protein secretion started to decline significantly from the 4th month in group sLP (1.09 ± 0.87 g/day at baseline, 0.76 ± 0.43 g/day at the 4th month, 0.59 ± 0.29 g/day at the 12th month, $P < 0.05$), while it was stable in the other two groups during the study (LP: 1.03 ± 0.77 to 0.91 ± 0.54, $P =$ ns; HP: 0.94 ± 0.58 to 0.92 ± 0.60 g/d, $P =$ ns). The mean Kt/V_{total} was above 1.7/week at each visit in each of the groups. While stable in group sLP (2.21 ± 0.31 to 2.20 ± 0.48, $P =$ ns), Kt/V_{total} declined significantly from the 4th month in group LP (2.35 ± 0.61 at baseline, 2.20 ± 0.52 at the 4th month, 2.12 ± 0.49 at the 12th month, $P < 0.05$) and from the 6th month in group HP (2.45 ± 0.41 at baseline, 2.16 ± 0.31 at the 6th month, 2.03 ± 0.48 at the 12th month, $P < 0.01$), concurrently with the drop of RRF. The net peritoneal ultrafiltration was similar at each visit among

Table 1. Baseline characteristics of 30 PD patients randomized to group A (DPI 1.2 g/kg IBW/day), group B (DPI 0.9 g/kg/day) or group C (DPI 0.6 g/kg/day) who completed nitrogen balance study

	Group A ($n = 9$)	Group B ($n = 12$)	Group C ($n = 9$)
Age (years)	47.6 ± 22.4	50.8 ± 18.5	53.2 ± 12.0
Gender (male:female)	4:5	5:7	3:6
BMI (kg/m^2)	22.1 ± 4.1	21.6 ± 3.8	22.5 ± 3.3
Diabetes (%)	22.0	0	0
Dialysis duration (day)	43 (38–60)	42 (35–49)	45 (44–60)
Dialysis dose (l/24 h)	6.7 ± 1.0	7.0 ± 1.0	7.1 ± 1.1
Serum albumin (g/l)	34.9 ± 3.8	34.5 ± 4.8	33.9 ± 4.0
Kt/V_{total}	2.3 ± 0.4	2.7 ± 0.4	2.7 ± 0.7
Kt/V_{renal}	0.8 ± 0.4	1.2 ± 0.3*	1.0 ± 0.5
D/P_{Cr}	0.61 ± 0.13	0.60 ± 0.12	0.58 ± 0.17
Ultrafiltration volume (ml/day)	363.3 ± 885.2	300.0 ± 517.3	220.0 ± 509.6
Serum bicarbonate (mmol/l)	29.5 ± 3.9	30.5 ± 3.2#	26.9 ± 4.2

BMI, body mass index; D/P_{cr}, 4-h dialysate to plasma ratio of creatinine.
*$P < 0.05$ compared with group A, #$P < 0.05$ compared with group C.

Table 2. Baseline characteristics of 60 PD patients randomized to group LP (DPI 0.6–0.8 g/kg/day), sLP (DPI 0.6–0.8 g/kg/day + 0.12 g/kg/day keto acids) or HP (DPI 1.0–1.2 g/kg/day) who underwent residual renal function study

	Group LP ($n = 20$)	Group sLP ($n = 20$)	Group HP ($n = 20$)
Age (years)	51.4 ± 13.8	56.3 ± 11.6	53.0 ± 13.2
Gender (male:female)	7:13	11:9	12:8
Diabetes *n* (%)	1 (5%)	1 (5%)	1 (5%)
BMI (kg/m^2)	21.0 ± 2.0	22.4 ± 3.0	22.1 ± 3.0
Height (cm)	162.4 ± 8.0	164.8 ± 7.9	163.9 ± 6.1
Kt/V_{total}	2.4 ± 0.6	2.2 ± 0.3	2.5 ± 0.4
PD duration (months)	6.0 (1.4–14.8)	10.6 (3.2–20.4)	10.0 (1.4–16.2)
PD dose (l/day)	6.0 ± 1.5*	6.8 ± 1.2	7.0 ± 1.2
PD glucose load (g/day)	101 ± 29	109 ± 19	114 ± 28
Urine volume (ml/day)	1360 ± 532	1123 ± 406	1197 ± 383
eGFR[a] (ml/min/1.73 m^2)	4.0 ± 2.5	3.8 ± 2.2	4.3 ± 2.3
Urine protein (g/day)	1.0 ± 0.8	1.1 ± 0.9	0.9 ± 0.6
Serum glucose (mmol/l)	6.3 ± 2.9	6.2 ± 1.3	6.4 ± 4.5
Serum prealbumin (mg/l)	359.6 ± 77.7	381.8 ± 95.4	344.7 ± 83.8
Serum cholesterol (mmol/l)	5.5 ± 1.0	5.5 ± 1.0	5.5 ± 0.9
Serum triglyceride (mmol/l)	1.7 ± 0.8	2.1 ± 1.5	1.8 ± 1.0
Serum LDL-C (mmol/l)	3.3 ± 0.8	3.4 ± 0.8	3.2 ± 0.6
Serum HDL-C (mmol/l)	1.6 ± 0.4*	1.4 ± 0.3	1.2 ± 0.3

PD, peritoneal dialysis; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol, HDL-C, high density lipoprotein cholesterol.
[a]Calculated as an average of the creatinine and urea clearances by 24-h urine.
*$P < 0.05$, compared with group HP.

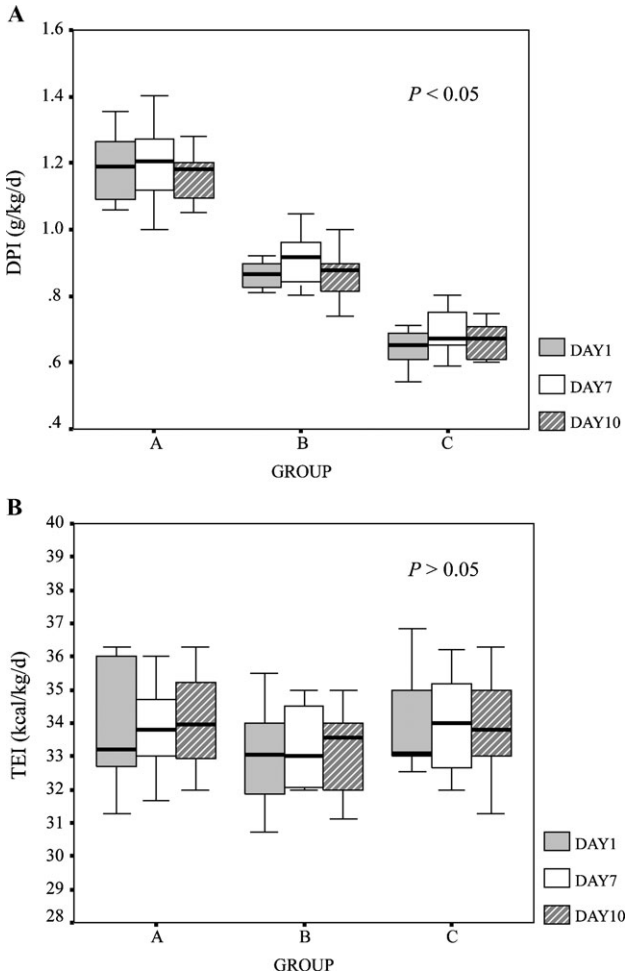

Fig. 2. Panel **A** shows the estimated dietary protein intake (DPI, g/kg IBW/day) of the three groups during the 10 days in-hospital follow-up. At all the visits, DPI of the three groups was significantly different from each other ($P < 0.05$). Panel **B** shows total energy intake (TEI, kcal/kg/day) calculated from both diets and PD solutions of the three groups. TEI was similar among the three groups during the study ($P > 0.05$).

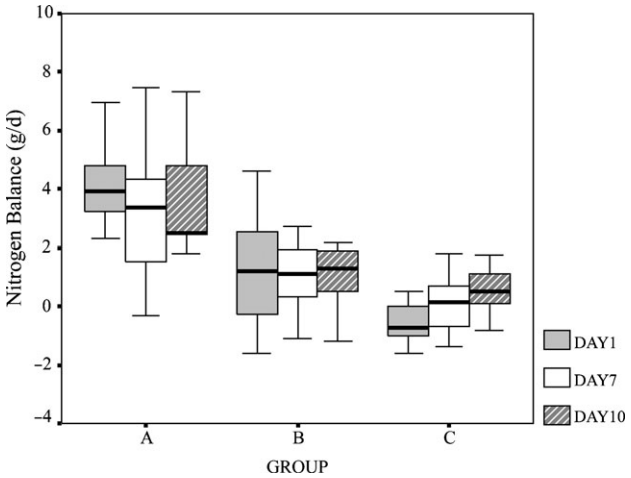

Fig. 3. Nitrogen balance of the three groups during the 10-day in-hospital follow-up. Positive nitrogen balance was found in group A, and neutral nitrogen balance was found in group B and C on both the 7th and 10th days of the study.

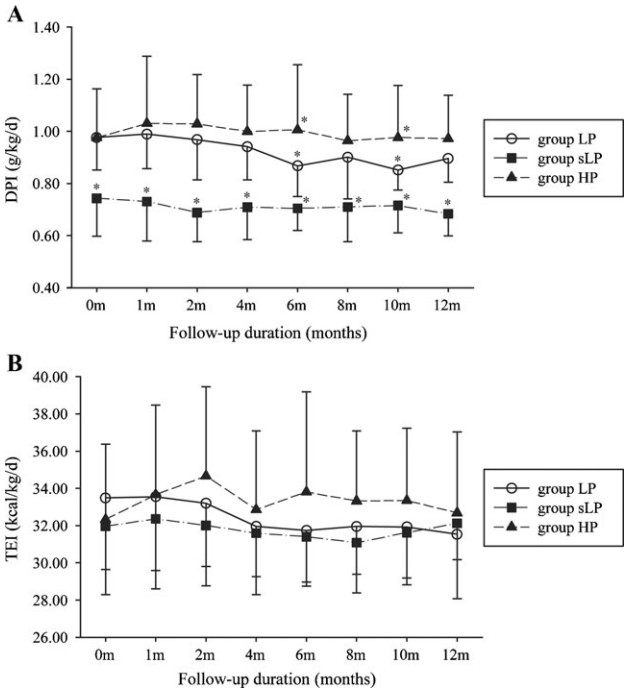

Fig. 4. Panel **A** shows the estimated dietary protein intake (DPI, g/kg IBW/day) of the three groups during 1 year of follow-up in the interventional study. Difference in DPI between groups sLP and HP was achieved in the 1st month and remained constant throughout the follow-up. DPI between groups LP and HP was different in the 6th and 10th month. $^{*}P < 0.05$, compared with the other two groups. Panel **B** shows total energy intake (TEI, kcal/kg/day) calculated from both diets and PD solutions of the three groups. TEI was similar among the three groups during the study ($P > 0.05$).

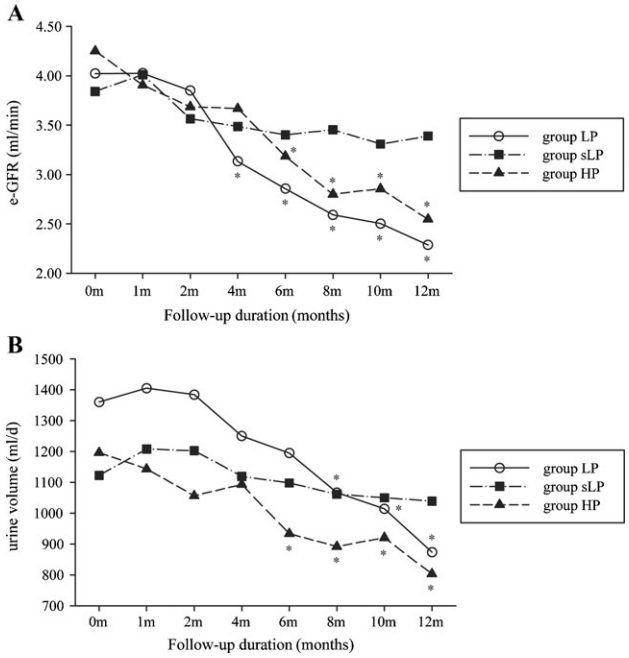

Fig. 5. Changes of renal function during the 12 months of the study in the three groups, LP (0.6–0.8 g/kg/day), sLP (0.6–0.8 g/kg/day + tx) and HP (1.0–1.2 g/kg/day). Panel **A** shows eGFR (estimated glomerular filtration rate, calculated as an average of the creatinine and urea clearances by 24-h urine). Panel **B** shows daily urine volume. Using repeated measures ANOVA, there was significant time effect for group LP and HP ($P < 0.01$ for both eGFR and urine volume), but no significant group effect ($P > 0.05$ for both eGFR and urine volume). $^{*}P < 0.05$, compared with 0 month.

the groups and did not change during the study [sLP: 130 (−60, 610) to 410 (50, 580) ml/day, $P =$ ns; HP: 200 (−150, 420) to 250 (−30, 650) ml/day, $P =$ ns], except in group LP where it increased significantly from the 6th month [0 (−240, 200) ml/day at baseline, 100 (0, 620) ml/day at the 6th month, 350 (150, 725) ml/day at the 12th month, $P < 0.05$], concurrently with the decline of urine output from the 4th month.

As shown in Table 3, SGA, LBM and body mass index (BMI) were similar among the groups and remained stable during follow-up. So were the blood albumin and other nutritional indices. ACEIs and/or ARBs were given to all the patients, and mean artery pressure (MAP) showed no difference among the three groups during the study (Table 3). Though a higher CRP was present in group sLP at baseline, there was no difference among the three groups at any time during follow-up. This and other biochemical data are presented in Table 3.

Discussion

To our knowledge, this is the first prospective and randomized trial of low-protein diets in PD patients. We report that a DPI of 0.6–0.8 g/kg/day, nearly half the currently recommended level [18], is associated with a neutral nitrogen balance in PD patients without significant malnutrition or inflammation, and a better preservation of RRF when in combination with keto acid supplementation.

Several previous studies have looked at protein consumption in dialysis patients [30–32]; for example, a trial from Rao *et al*. [24] found that DPI of 0.6 g/kg/day resulted in a negative nitrogen balance in 12 haemodialysis patients studied in an outpatient setting. Our nitrogen balance study was conducted in-hospital by a randomized study design, and suggests that at least in Chinese PD patients, a DPI of 0.6 g/kg/day is associated with a short-term neutral nitrogen balance that is necessary for the maintenance of nutritional status. The large Modification of Diet in Renal Disease (MDRD) study [33,34] of CKD patients demonstrated the safety of a DPI as low as 0.58 g/kg/day over periods of 2–3 years. However, in that study a small but significant decline of nutritional status was reported, suggesting that this amount may have been too low in this highly uraemic, pre-dialysis population. Of note, we did not exclude the amount of nitrogen contained in the protein which lost from dialysate and urine when assessing nitrogen balance, thus may over estimate the result of nitrogen balance; this amount should be considered. This is also the reason for us to increase the protein intake (0.6–0.8 g/kg IBW/day) slightly for the long-term RRF study. The low-protein diet did not result in malnutrition during the long-term study period according to both SGA and biochemical indices. Moreover, LBM increased during the study period even in patients with the lowest DPI, which is perhaps as a result of ameliorated wasting following the initiation of PD therapy (median PD vintage was only 8.8 months at baseline) [35].

Table 3. Temporal changes of selected parameters of the 60 PD patients randomized to group LP (0.6–0.8 g/kg IBW/day), sLP (0.6–0.8 g/kg IBW/day) or HP (1.0–1.2 g/kg IBW/day), respectively, who underwent residual renal function study

		Follow-up duration (months)			
		0 month ($n = 60$)	4 months ($n = 55$)	8 months ($n = 54$)	12 months ($n = 53$)
SGA[a] (%)	LP	10.0	21.0	27.8	11.8
	sLP	15.0	11.1	16.7	0.0
	HP	10.0	26.3	16.7	20.0
BMI (kg/m^2)	LP	21.0 ± 2.0	21.4 ± 1.9	21.3 ± 2.1	21.7 ± 2.2
	sLP	22.4 ± 3.0	22.6 ± 3.2	22.3 ± 3.1	23.1 ± 3.7
	HP	22.1 ± 3.0	22.3 ± 2.9	22.6 ± 2.3	22.7 ± 3.3
LBM (kg)	LP	23.5 ± 5.3	24.9 ± 5.8	28.0 ± 7.4*	29.0 ± 6.2*
	sLP	25.4 ± 4.8	26.3 ± 6.7	27.6 ± 6.5*	29.8 ± 6.6*
	HP	25.1 ± 5.4	26.7 ± 6.9	28.2 ± 8.4*	30.3 ± 8.7*
Albumin (g/l)	LP	35.9 ± 3.3	35.3 ± 4.2	36.2 ± 3.0	36.9 ± 3.5
	sLP	37.4 ± 4.4	36.5 ± 3.8	37.1 ± 4.6	38.9 ± 4.4
	HP	38.1 ± 2.8	35.8 ± 3.6*	37.9 ± 3.4	39.2 ± 4.0
MAP (mmHg)	LP	101 ± 16	103 ± 11	101 ± 21	106 ± 11
	sLP	101 ± 11	101 ± 10	98 ± 13	105 ± 16
	HP	105 ± 14	106 ± 16	105 ± 14	108 ± 16
CRP (mg/l)	LP	2.97 (1.00–3.92)	3.12 (2.97–5.08)	3.00 (1.56–3.24)	3.12 (3.00–3.17)
	sLP	7.77 (3.00–13.90)#	3.00 (1.00–5.29)	3.12 (2.99–4.09)	3.12 (3.09–3.89)
	HP	3.17 (2.78–6.03)	2.97 (1.00–4.60)	3.12 (2.98–4.44)	3.16 (3.06–6.35)
Calcium (mmol/l)	LP	2.46 ± 0.17	2.38 ± 0.18	2.36 ± 0.17*	2.30 ± 0.16*
	sLP	2.46 ± 0.28	2.54 ± 0.24#	2.40 ± 0.15##	2.46 ± 0.28
	HP	2.33 ± 0.18	2.36 ± 0.16	2.27 ± 0.15*	2.35 ± 0.26
Phosphorus (mmol/l)	LP	1.46 ± 0.35	1.59 ± 0.44	1.70 ± 0.38*	1.54 ± 0.30
	sLP	1.48 ± 0.36	1.42 ± 0.23	1.42 ± 0.26	1.49 ± 0.21
	HP	1.28 ± 0.32	1.59 ± 0.39*	1.61 ± 0.41*	1.71 ± 0.50*
iPTH (pg/ml)	LP	133.5 (76.7–406.2)	215.5 (117.2–275.0)	219.5 (106.6–305.0)	232.0 (100.5–284.2)
	sLP	149.0 (36.7–411.0)	125.0 (34.8–229.5)	67.3 (36.4–207.5)##	64.4 (35.6–234.2)##
	HP	203.5 (115.5–609.6)	197.5 (84.8–324.5)	256.0 (70.8–472.8)	215.0 (131.8–444.2)

SGA, subjective global assessment of nutrition; BMI, body mass index; MAP, mean artery pressure; iPTH, intact parathyroid hormone.
[a]Percentage with malnutrition.
*$P < 0.05$, compared with 0 month, #$P < 0.05$, compared with the other two groups, ##$P < 0.05$, compared with group HP.

Our results also showed a better preservation of RRF, lower serum phosphorus level, as well as lower intact parathyroid hormone (iPTH) level over 12 months in patients prescribed a low-protein diet supplemented with keto acids, but not in those patients prescribed a low-protein diet alone. No definite conclusion should be drawn from this, however, as the patients in the LP group did not manage to reduce their protein intake to the desired levels. Although some studies [21,22] suggest that keto acids may be nephroprotective *per se*, an alternative explanation could be that the low DPI in the patients of group sLP contributed to the observed maintenance of RRF. Indeed, in most previously published studies, lowering of DPI has been shown to preserve renal function, which may be mediated by lowering the requirement for renal nitrogen clearance [10,12,14,15] and/or a reduction in proteinuria [11,16,17], as well as other factors [15]. A reduction in proteinuria was also observed in our PD patients with a low-protein diet supplemented with keto acids, which also may be due to the lower DPI in these patients [17]. In view of the better dietary compliance in group sLP, it is of interest to note that in one study in haemodialysis patients, keto acid supplementation was thought to have contributed to lowering of the protein intake through unknown mechanisms [36], and it is possible that a similar effect was seen in our patients.

Inflammation (assessed by CRP) was slightly more prevalent in group sLP at baseline, but the temporary high level of CRP did not seem to have a negative impact on signs of PEW or rate of decline of RRF among the patients in group sLP, although inflammation in CKD is known to have a negative impact on both PEW [37] and RRF decline [38]. Serum calcium levels were higher and iPTH levels were lower in group sLP during follow-up, as the keto acid tablets contain 50 mg of calcium each, giving a total daily supplementation of 0.01 g/kg IBW, which may indicate an iatrogenic effect [39]. Keto acid treatment had been reported to have a direct suppressive effect on PTH secretion [40]. Though researches focusing on the possible risk for adynamic bone disease in PD patients treated with keto acids are limited now, caution is needed. Low calcium PD solutions were effective to normalize hypoparathyroidism in PD patients with low bone turnover [41,42]; and thus should be recommended to the patients prescribed with keto acids. In our study, in order to exclude the impact of dialysis solutions, we have not proactively treated patients using low calcium PD solutions.

Some limitations of the present study should also be discussed. First, the sample size in both trials was small with relatively short follow-up time, which likely limited the power of the study and may explain the non-significant difference in the protein intake between group LP and HP. Secondly, DPI was assessed using a 3-day food diary, and while this method has been shown to correlate with other markers of protein intake in both renal [27] and non-renal [43] populations, we cannot exclude the possibility that a few patients misstated their intake. Our patients had been

educated repeatedly to manage their diet within the prescribed ranges; nevertheless, the difference of DPI between group LP and HP was only reached on the 6th and 10th months. We cannot exclude that better maintenance of RRF would be seen also in group LP if DPI had been the same as in group sLP.

In summary, we report the results of a prospective and randomized trial of a low-protein diet in PD patients, adding to the small body of evidence available to support the view that the use of low-protein diets in this patient group may both be safe from a nutritional point of view and also lead to better preservation of RRF. It is possible that complications such as hyperphosphataemia are also less likely to occur in patients with a low-protein intake. Our patients were relatively new PD patients representing a selected group with little comorbidity (e.g. malnutrition, inflammation), a low-degree of proteinuria and a rather high total Kt/V. Thus, caution is needed when applying the findings to the clinic especially to those with incident malnutrition or inflammation. As today a large proportion of patients in developing countries ingest a low-protein diet and receive a low dose of PD, further studies are needed to assess the impact of a low-protein diet in patients receiving a low dose of PD.

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