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Clinical Study

Low-Protein Diet Supplemented with Keto Acids Is Associated with Suppression of Small-Solute Peritoneal Transport Rate in Peritoneal Dialysis Patients

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Objective. We investigate whether low-protein diet would show benefits in suppressing peritoneal transport rate in peritoneal dialysis (PD) patients. *Methods.* This is a supplemented analysis of our previously published trial, which randomized 60 PD patients to receive low- (LP: dietary protein intake of 0.6–0.8 g/kg/d), keto-acid-supplemented low- (sLP: 0.6–0.8 g/kg/d with 0.12 g/kg/d of keto acids), or high- (HP: 1.0–1.2 g/kg/d) protein diet and lasted for one year. In this study, the variations of peritoneal transport rate were assessed. *Results.* While baseline D/P_{cr} (dialysate-to-plasma concentration ratio for creatinine at 4 hour) and $D/D0_{glu}$ (dialysate glucose at 4 hour to baseline dialysate glucose concentration ratio) were similar, D/P_{cr} in group sLP was lower, and $D/D0_{glu}$ was higher than those in the other two groups ($P < 0.05$) at 12th month. $D/D0_{glu}$ increased ($P < 0.05$), and D/P_{cr} tended to decrease, ($P = 0.071$) in group sLP. *Conclusions*. Low-protein diet with keto acids may benefit PD patients by maintaining peritoneum at a lower transport rate.

1. Introduction

Since peritoneal equilibration test (PET) was introduced in 1987 [1], high transporters have been reported to show poor clinical outcomes [2, 3], which are due to fluid overload [4], inflammation [5], or malnutrition [6], and so forth. Peritoneal characteristics were determined by several factors including genetic factors, peritoneal membrane anatomy, effective surface area, age, and uremia, which contribute to the heterogeneity of peritoneal membrane function at the onset of PD [7–10]. Except those inherited high transporters, it was observed that peritoneal transport rate increased with the time of treatment on PD [7]. During the PD process, repeatedly exposure to inflammatory stimuli such as glucose-based solutions and peritonitis episodes may lead to persistent increase of peritoneal transport rate [11].

Many studies explored methods to prevent patient from to be high transporters, thus preserve peritoneal function. Recently, an interesting study found that a strict low-protein diet (0.37 ± 0.05 g/kg/d) during the predialysis period may suppress peritoneal transport rate at induction of PD [12]. However, it is unknown whether low-protein intake during PD would show benefits on peritoneal transport rate maintenance. Since the current PD guidelines recommend high-protein intake of no less than 1.2 g/kg ideal body weight (IBW)/day [13], very few clinical practice could answer this question. Based on what we have found in our recent published paper [14, 15], DPI of 0.6–0.8 g/kg/d resulted in neutral nitrogen balance, maintained good nutritional status, and improved plasma amino acids pattern in PD patients if together with keto acid during 12 months of followup. We, therefore, further assessed the effect of dietary intervention

on peritoneal transport rate by analyzing PET results at baseline and 12th month in the original PD cohort.

2. Methods

2.1. Study Design. The study population and methodology have been previously described in detail [14, 15]. Briefly, 60 PD patients with residual renal function (urine output ≥800 ml/d or eGFR ≥2 ml/min/1.73 m^2) who fitted the inclusion criteria were enrolled and randomized to low- (LP: DPI of 0.6–0.8 g/kg IBW/d), keto-acid-supplemented low- (sLP: DPI of 0.6–0.8 g/kg IBW/d with keto acids of 0.12 g/kg IBW/d, Ketosteril; Fresenius Kabi Co., Ltd., Beijing, China), or high- (HP: DPI of 1.0–1.2 g/kg IBW/d) protein group in the original study. The total energy intake (TEI), including both from diets and PD glucose [16], was prescribed as 35 kcal/kg IBW for patients below 60 years of age and 30 kcal/kg IBW for the rest.

During the 12 months of followup, 7 patients dropped out, thus, 53 patients finished the study (18 in group LP, 18 in group sLP, and 17 in group HP) and were analyzed in the present study. PET was performed at baseline and 12th month as described by Twardowski et al. [1] using 2 liters of 2.5% dextrose solution for a 4-hour dwell. The dialysate-to-plasma concentration ratio for creatinine at 4 hours (D/P_{cr}) and dialysate glucose at 4 hours to the baseline dialysate glucose concentration ratio ($D/D0_{glu}$) were calculated. D/P_{cr} was used to classify the patients as high, high average, low average, or low transporters [1]. The estimated peritoneal glucose exposure was calculated from the dialysis prescription as described by Davies et al. [17]. For example, for a patient dialyzed by 4∗2 L exchanges (2∗1.5%, 1∗2.5%, and 1∗4.25%), daily peritoneal glucose exposure would be 2∗30 + 1∗50 + 1∗85 = 195 g.

During followup, angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) were applied to all the patients to control hypertension. Amino acids and other nutritional supplements were avoided, and aminoglycosides were forbidden for patients with residual renal function when infection occurred during followup.

2.2. Statistical Analysis. Results are presented as mean ± SD or median (interquartile range). Differences across groups were assessed by ANOVA or Kruskal-Wallis test as appropriate. Post hoc analysis was done using methods of Student-Newman-Keuls (S-N-K) for ANOVA or Dunnett's T3 for Kruskal-Wallis test. Comparisons between time periods were performed using paired t-test or Wilcoxon's paired test. Comparisons of numeration data were performed using the Chi-square test. A P value <0.05 was considered statistically significant. All analyses were carried out with SPSS 11.0 for windows statistical software (SPSS Inc., Chicago, Ill, USA).

3. Results

3.1. Baseline Data. Baseline data of the 53 patients were shown in Table 1. Briefly, there were no significant differences in any of the assessed parameters between the groups, except that C-reactive protein (CRP) level was slightly higher in group sLP than group LP (7.8 [3.0–15.0] versus 3.0 [1.0–4.2] mg/l, $P < 0.05$).

3.2. Dietary Compliance and Comorbidities. As we previously reported [14], 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 in months 6 and 10. TEI was similar among the three groups during the study ($P > 0.05$).

During the study, 8 peritonitis episodes occurred in the 53 patients (2 in group LP, 4 in group sLP, and 2 in group HP, $P = ns$). While CRP level at baseline was slight higher in group sLP than group LP, it was similar among the three groups at 12th month (LP: 3.1 [3.0–3.2] mg/l, sLP: 3.1 [3.1–3.9] mg/l, and HP: 3.2 [3.1–6.4] mg/l, $P = ns$).

3.3. Peritoneal Transport Rate. Figure 1 shows data of D/P_{cr} and $D/D0_{glu}$ in the three groups at baseline and 12th month. While baseline D/P_{cr} and $D/D0_{glu}$ were similar among the three groups, at 12th month in group sLP, D/P_{cr} was significantly lower (sLP: 0.59 ± 0.09, LP: 0.70 ± 0.09, and HP: 0.66 ± 0.12, $P < 0.05$) and $D/D0_{glu}$ was higher (sLP: 0.49 ± 0.08, LP: 0.42 ± 0.06, and HP: 0.43 ± 0.11, $P < 0.05$) than the other two groups.

During 12 month followup, $D/D0_{glu}$ increased ($P < 0.05$), and D/P_{cr} intended to decrease ($P = 0.071$) in group sLP. Changes of both D/P_{cr} and $D/D0_{glu}$ in group sLP were more noticeable than the other two groups during followup ($\Delta D/P_{cr}$: sLP: −0.04 [−0.13, 0.05], LP: 0.04 [−0.06, 0.14], and HP: 0.03 [−0.02, 0.12], $P < 0.05$; $\Delta D/D0_{glu}$: sLP: 0.05 [0.01, 0.10], LP: −0.03 [−0.11, 0.06], and HP: −0.04 [−0.10, 0.05], $P < 0.05$).

Table 2 shows distribution of peritoneal transport rate classified by D/P_{cr} among the three groups. At baseline, all of three groups showed similar peritoneal transport rate distribution ($P = 0.559$). At 12th month ($P = 0.175$), the peritoneal transport rate distribution in group sLP showed a borderline difference from group LP ($P = 0.060$), and HP ($P = 0.088$), which indicated that fewer patients in group sLP, had higher peritoneal transport rate after 12 months followup.

3.4. Dialysis Dose and Glucose Exposure. As shown in Table 3, baseline PD dosage and PD glucose exposure were equal among the three groups. During followup, patients in both groups LP and HP tended to increase their PD dosage, while those in group sLP kept stable. PD glucose exposure in both group LP and HP increased significantly (LP: 100 ± 31 to 114 ± 27 g/d; HP: 110 ± 25 to 129 ± 37 g/d, $P < 0.05$ for both), while in group sLP it kept stable (sLP: 107 ± 18 to 109 ± 22 g/d, $P > 0.05$), which in turn leads to markedly lower glucose exposure in group HP than group sLP at 12th month ($P < 0.05$).

4. Discussion

In this supplemented analysis of a prospective randomized trial, we found that in stable PD patients, low-protein diet

Table 1: Baseline data of the 53 PD patients, grouped according to the diet that they asre randomized to.

	Group LP ($n = 18$)	Group sLP ($n = 18$)	Group HP ($n = 17$)
Age (year)	52.5 ± 13.7	56.3 ± 11.5	50.4 ± 12.3
Gender (male : female)	6 : 12	9 : 9	10 : 7
Diabetic nephropathy (yes/no)	1/17	1/17	1/16
BMI (kg/m^2)	21.1 ± 2.1	22.3 ± 3.0	22.2 ± 3.3
Height (cm)	161.8 ± 8.1	163.7 ± 7.7	164.2 ± 6.1
Kt/V_{total}	2.4 ± 0.6	2.2 ± 0.3	2.4 ± 0.4
PD duration (month)	5.6 (1.3–14.2)	11.8 (3.8–20.9)	5.5 (1.3–14.2)
Urine protein (g/d)	0.7 (0.4–1.5)	0.7 (0.5–1.3)	1.0 (0.4–1.4)
Urine volume (ml/d)	1444 ± 460	1153 ± 409	1208 ± 378
e-GFR (ml/min/1.73 m^2)	4.3 ± 2.4	3.7 ± 2.2	4.5 ± 2.4
Ultrafiltrational volume (mL/d)	0 (−240, 200)	130 (70, 610)	300 (−150, 425)
Serum CRP (mg/l)	3.0 (1.0–4.2)	7.8 (3.0–15.0)*	3.1 (2.8–6.4)
Serum albumin (g/l)	36.1 ± 3.2	37.4 ± 4.2	38.3 ± 2.8

Note: *$P < 0.05$, compared with group LP. PD: peritoneal dialysis; BMI: body mass index; e-GFR: estimated glomerular filtration rate, calculated as an average of the creatinine and urea clearances by 24-hour urine; CRP: C-reactive protein.

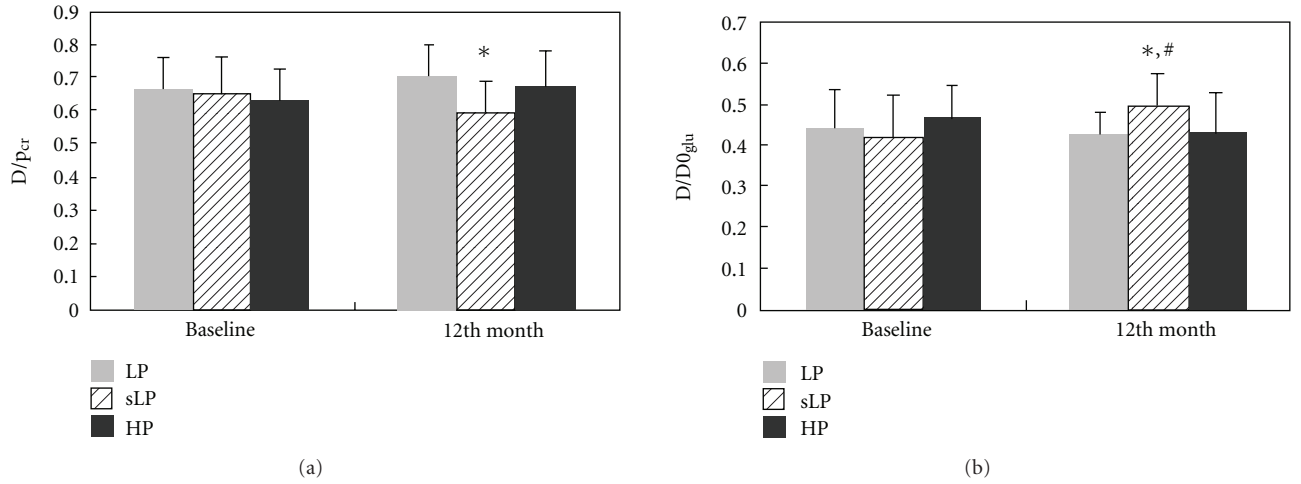

Figure 1: Peritoneal equilibration test (PET) results in the 53 PD patients, grouped according to the diet that they are randomized to during 12 month followup. (a) shows D/P_{cr} (dialysate-to-plasma concentration ratio for creatinine at 4 hours). (b) shows $D/D0_{glu}$ (dialysate glucose at 4 hours to baseline dialysate glucose concentration ratio). *$P < 0.05$, compared with the other two groups. #$P < 0.05$, compared with baseline.

supplemented with keto acids seemed to impact peritoneal characteristics. Indeed, after 12 months of followup, patients on supplemented low-protein diet showed declined D/P_{cr} and elevated $D/D0_{glu}$ compared with patients on either high-protein diet or low-protein diet alone.

As peritoneal membrane function of solute clearance and water removal is the basic rationale of PD therapy, preservation of peritoneal function is critically important. It is generally accepted that avoidance of repeated peritonitis and control of inflammation are favorable to peritoneal transport rate maintenance [5, 18]. Blockades of the rennin-angiotensin-aldosterone system could mitigate peritoneal inflammation and fibrosis, thus preserve peritoneum function [19]. Some studies also found that residual renal function could contribute to peritoneal function maintenance [5]. However, there are certain amount of publications reporting the elevated transport rate with the time on PD [7]. According to recent reports, the increasing use of automated PD [20] and icodextrin-based PD solutions [21] could partly overcome problems caused by fluid overload and improve the clinical outcome among high transporters. Continuous ambulatory peritoneal dialysis (CAPD) by dextrose solutions is, however, the most widely used PD form in developing countries such as China. Thus, studies on suppressing peritoneal transport rate are still highly warranted.

Low-protein diet has been advised for predialysis patients as it shows effects in controlling uremic symptoms, retarding renal function loss [22, 23], and postponing the initiation of dialysis [24] by lowering the requirements for renal nitrogen clearance and/or reducing proteinuria [25, 26]. Low-protein diet among predialysis patients may suppress peritoneal transport rate at induction of PD which was

Table 2: Comparison of peritoneal transport rate distribution classified by D/P_{cr} among the 3 groups at baseline and 12th month.

	Group LP ($n = 18$)		Group sLP ($n = 18$)		Group HP ($n = 17$)	
	Baseline	*12th month*	*Baseline*	*12th month*	*Baseline*	*12th month*
H	1	4	2	0	0	1
HA	9	7	7	6	8	9
LA	8	7	9	9	7	6
L	0	0	0	3	2	1

Table 3: Changes of PD dose and PD glucose exposure in the 53 PD patients, grouped according to the diet which they are randomized to during 12 month followup.

		Group LP ($n = 18$)	Group sLP ($n = 18$)	Group HP ($n = 17$)
PD dose (L/d)	*Baseline*	6.0 ± 1.5	6.7 ± 1.2	6.8 ± 1.2
	12th month	6.4 ± 1.1	6.7 ± 1.2	7.2 ± 1.0
PD glucose exposure (g/d)	*Baseline*	100 ± 31	107 ± 18	110 ± 25
	12th month	$\mathbf{114 \pm 27}^{\#}$	$\mathbf{109 \pm 22}$	$\mathbf{129 \pm 37}^{*,\#}$

Note: $^{*}P < 0.05$, compared with group sLP. $^{\#}P < 0.05$, compared with baseline.

recently reported by Hasegawa et al. [12]. In the present study, we further confirm that low-protein diet during PD therapy benefits patients regarding peritoneum preservation. The exact mechanisms to explain this phenomenon are not clear. One possible explanation is that low-protein diet is associated with decreased expression of fibrotic factors such as transforming growth factor-beta (TGF-β) [27]. In fact, we found that compared with the patients in group sLP, those in the other two groups increased their PD dose and exposed to more hypertonic solutions during 1 year of followup. The increment use of bio-incompatible solution was reported to stimulate the releasing of fibrotic or inflammatory factors [28] and resulted in increased peritoneal transport rate [29]. Secondly, uremia itself may also impact peritoneal transport rate [30]. Low-protein diet reduces uremic wastes such as urea, phosphate, and so forth, in either predialysis patients [24] or PD patients [14], and, in turn, protects peritoneal membrane. On the other hand, the beneficial effects of residual renal function on peritoneal function maintenance have been reported by different studies [5, 31]; therefore, better preservation of residual renal function in group sLP [14] seems to be another explanation supporting current results.

In addition, there are several other factors which may be also involved in. It is well known that peritonitis episodes [18] and inflammation [5] play an important role in the increment of peritoneal permeability. Interestingly, patients in group sLP maintained peritoneal membrane function better during 12 months of followup in our study, even though their baseline CRP level was significantly higher than others. The potential role of keto acids in peritoneum preservation cannot be completely excluded in group sLP. Furthermore, high transporters usually have greater albumin loss through peritoneal cavity [32], which is conceptually analogous to microalbuminuria in diabetic patients [33]. Though the present study did not investigate peritoneal protein loss; however, we observed the decrement of urine protein output in patients receiving keto-acid-supplemented low-protein diet. The prescription of sLP may also suppress peritoneal protein leakage in these patients.

There are several limitations in the present study that need to be discussed. Firstly, the sample size of the study was relatively small, and data of peritoneal transport rate as only available on two time points, lack of data on protein loss and TGF-β levels in dialysate, as it is only a supplemented analysis for our previous study. Secondly, the patients in group LP did not manage their DPI consistently to the prescribed range. Thus, we cannot differentiate in current study whether beneficial effect on peritoneal function comes from low-protein diet or the use of keto acid. Nevertheless, our data provides a new clue for peritoneum preservation among PD patients.

In summary, our results showed that low-protein diet (DPI of 0.6–0.8 g/IBW kg/d) supplemented with keto acids may benefit PD patients by maintaining peritoneum at a lower transport rate.

Conflict of Interests

Qiang Yao is now employed by Baxter Healthcare.

Acknowledgments

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