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Research Article

Association of Lean Body Mass Index and Peritoneal Protein Clearance in Peritoneal Dialysis Patients

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Key Words
Peritoneal dialysis • Lean body mass index • Bioelectrical impedance analysis • Peritoneal protein clearance • Peritoneal protein loss

Abstract:
Background/Aims: The relationship between peritoneal protein clearance (PPCl) and nutritional status in peritoneal dialysis (PD) population have not been clarified. This study aims to investigate the relationship between PPCl and nutritional status in PD population. ***Methods:*** Prevalent PD patients were enrolled in the cross-sectional survey in a single center from April to November 2013. The total amount of protein loss in the dialysate was calculated. PPCl reflects the individual differences of peritoneal protein loss, and is calculated by the formula, that PPCl (ml/day)=24-h dialysate protein loss / (albumin/0.4783). Nutritional status measured by lean body mass index（LBMI）was assessed by multi-frequency bioelectrical impedance analysis (BIA). ***Results:*** Totally 351 PD patients (55% male, 17.1% with diabetes, mean age 47.7±14.3 years) were included. The median PPCl was 58 ml/day. Patients were divided into four groups for comparison according to the PPCl quartiles. Compared with lower PPCl quartiles, patients with higher PPCl had higher body mass index (BMI) (P<0.001), body surface area (BSA) (P<0.001), LBMI (P<0.001), 4-hour D/P creatinine ratio (P<0.001), and lower residual renal CCl (P<0.001). Compared with conventional body index (BMI and BSA) in ROC analysis, LBMI (area under curve: 0.71, 95% confidence interval [CI]: 0.66-0.77) had better performance in predicting higher PPCl. After adjustment in logistic regression models, each 1 kg/m^2 increase of LBMI (odd ratio[OR] =1.37； 95% CI:1.17-1.60), each 0.1 increase of 4-hour D/P creatinine ratio (OR =1.47； 95% CI:1.11-1.93), and every 1 L/week/1.73m^2 decrease of residual renal CCl (OR =0.98; 95% CI: 0.96-0.99) were independently associated with higher PPCl (>58 ml/day). ***Conclusion:*** Higher LBMI was independently associated with higher PPCl, indicating that better nutritional status dominates peritoneal protein metabolism in PD patients.

J. Fan and H. Ye contributed equally to this work.

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Introduction

Peritoneal dialysis (PD) is one of the important renal replacement treatment for end stage renal disease (ESRD), and has been increasingly received by ESRD patients worldwide [1]. Remarkably, one important defect of PD is the peritoneal protein loss (PPL) during dialysis, which has been reported to be roughly 5-15 g per day and may cause hypoalbuminemia and malnutrition [2]. Peritoneal protein clearance (PPCl), calculated by the formula of daily PPL/(serum albumin/0.4783), was considered as a better index reflecting the individual differences of peritoneal protein loss and the membrane function of of both small pores and large pores [3].

Higher peritoneal PPCl has been reported to be associated with higher incidence of cardiovascular disease (CVD)[4, 5] and higher overall mortality in PD patients [6, 7]. However, newly studies failed to draw similar conclusions [4, 8-10]. These conflicting results arouse new insights on the peritoneal protein metabolism during PD treatment, especially the relationship between PPCl and nutritional status has been questioned [11]. However, few studies have reassessed their relationship using more precise methods.

Multifrequency bioelectrical impedance analysis (BIA), which was verified as a promising method for evaluating the nutritional status in PD patients, has been widely used in this population [12-15]. Lean body mass index (LBMI) measured by BIA and corrected for body height square has been used as a useful marker of nutritional status [16]. Therefore, we conducted this cross-section study in a large cohort of PD patients to explore the associated factors of PPCl, as well as the relationship between PPCl and LBMI.

Materials and Methods

Patient Selection

This is a single center, cross-sectional survey study. Prevalent PD patients from the PD center of The First Affiliated Hospital of Sun Yat-sen University were included from April to November 2013. All the patients had received PD treatment for more than 3 month, and were regularly followed up. All patients were dialyzed with the standard dextrose peritoneal dialysate (1.5%, 2.5%, or 4.25% dextrose, lactate-based, produced by Baxter, Guangzhou). Exclusion criteria included unwilling or unable to receive the examinations of PPCl or BIA, previously received hemodialysis or renal transplantation, currently prescribed any immunosuppressive therapy, active infection, liver cirrhosis, active hepatitis, malignant tumor, or experienced an episode of peritonitis within 3 months. The study protocol was conducted in compliance with the ethical principles of the Helsinki Declaration, and approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University. Written informed consents were obtained from all participants.

Clinical Information, biochemical data and adequacy of PD

Demographic and clinical characteristics including age, gender, primary renal diseases, body mass index (BMI), body surface area (BSA), comorbidity conditions, PD duration, daily dose of PD, and urine volume were recorded. All biochemical tests were determined by automatic chemistry analyzer (Hitachi 7180 or Abbott Aeroset). Urea clearance index (Kt/V urea) was derived from the collection of the 24-h PD effluent and 24-h urine. Weekly total creatinine clearance (CCl) were determined by using standard methods, and total CCl was divided into residual renal CCl and peritoneal CCl [17]. Residual glomerular filtration rate (GFR) was calculated as the average of 24-hour urinary urea and creatinine clearance, as described [18]. Daily protein intake (DPI) was calculated using the modified Bergstrom formula, and normalized by ideal body weight [19]. A standard peritoneal equilibration test (PET) was usually performed at a month after the initiation of PD therapy, classified the patients into four groups: low (L), low average (LA), high average (HA), and high (H) transport type according to the related criteria [20].

Evaluation of peritoneal protein clearance and nutritional status assessment

Peritoneal dialysate protein loss (PPL) was calculated from the collection of 24-h peritoneal dialysate effluent by the Biuret method. Daily peritoneal protein clearance (PPCl) was considered as a better index reflecting the individual differences of peritoneal protein loss, and was calculated according to the recommended formula in previous studies, that is PPCl (ml/day)=24h dialysate protein loss/(albumin/0.4783)[6]. PPCl was expressed as ml of plasma cleared per day. Higher PPCl was defined as the PPCl level higher than its median (>58 ml/day). Lean body mass (LBM) was measured by multi-frequency bioelectric impedance analysis (BIA) (In Body 720, Biospace, Seoul, Korea). Lean body mass index (LBMI) was calculated by LBM correcting for body height square, LBMI (kg/m^2) = LBM/body height square [16].

Statistical Analysis

Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation (SD) for continuous variables, and median (interquartile rang) for skewed distributions. Patients with measured PPCl values were classified into quartiles (Qs): Q1: ≤45ml/day; Q2: 46–58ml/day; Q3: 59–74ml/day; Q4: ＞74ml/day. For comparisons among these groups, chi-square tests and one-way ANOVA tests or Kruskal–Wallis tests were used to evaluate categorical variables and continuous variables, respectively.

The bivariate correlation test was performed to examine the association between body index and PPCl. Multivariate binary logistic regression and multilinear regression models were used for exploring the associated factors of higher PPCl and continuous PPCl, respectively. The area under the ROC curve (AUC) was used for evaluating the performance of different body index in predicting higher PPCl. All calculations were performed with SPSS, version 19.0 (SPSS Inc, and IBM Inc.). P value of less than 0.05 was considered to be significant.

Results

Demographic and Clinical Characteristics

During the study period, 601 patients met the inclusion criteria were screened in the study. According to the exclusion criteria, 250 patients were excluded. Therefore, a total of 351 patients were included in the analysis in the present study (Fig. 1). Among them, 193 (55%) patients were males. The mean age of the population was 47.7±14.3 years, and the median PD duration at enrollment was 29.1 (14.4-45.6) months. The leading cause of ESRD was glomerulonephritis (59.3%), followed by diabetes mellitus (17.1%). The median peritoneal protein loss was 4.6 (3.7-5.6) g/day, and the median PPCl was 58 (45-74) ml/day. Normality testing of the distribution of PPCl in the overall study population indicated non-normal distribution (P < 0.001, Fig. 2).

Comparisons of clinical characteristics stratified according to quartiles of PPCl

According to the PPCl quartiles, patients were divided into four groups. Compared with ones in lower PPCl quartiles, patients with higher PPCl had a higher proportion of males (*P* =0.015) and diabetes mellitus (*P* =0.006); received higher dose of PD treatment (*P*<0.001); had higher

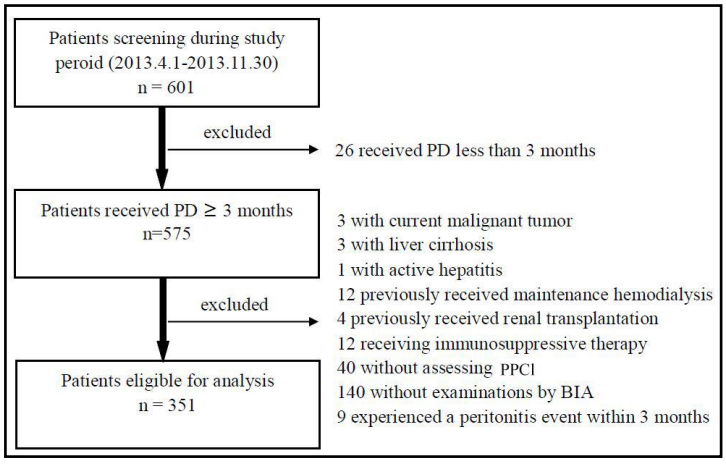


Fig. 1. Flow chart of the patient enrollment.

BMI (*P*<0.001), BSA (*P*<0.001), LBMI (*P*<0.001), peritoneal protein loss (*P*<0.001), and peritoneal albumin loss (*P*<0.001); and lower urine volume (*P*<0.001), serum total protein (*P*<0.001), albumin (*P*<0.001), and daily protein intake (*P*< 0.001). PPCl was also related to the peritoneal dialysis adequacy and peritoneal transport type. Patients with higher PPCl had lower total Kt/v (*P*<0.001), total CCl (*P*=0.004) and residual renal CCl (*P*<0.001), while higher peritoneal CCl (*P*<0.001) and 4-hour D/P creatinine ratio (*P*<0.001). Patients with higher PPCl had a significantly higher proportion of high and high average peritoneal transport type (*P*=0.001) (Table 1).

Close correlation between LBMI and PPCl

The bivariate correlation analysis indicated that PPCl were significantly positively associated with the body indexes: BMI (r=0.242, P<0.01), BSA (r=0.295, P<0.01), and LBMI (r=0.404, P<0.01). Meanwhile, we divided patients into four groups according to the quartiles of LBMI, and PPCl was incrementally significantly higher in patients with higher LBMI quartiles (*P*＜0.001)(Fig. 3).

The ROC analysis was used for evaluating the performance of different body index in predicting higher PPCl(> 58.0 ml/day). As shown in Fig. 4, LBMI has a best discrimination and calibration for predicting higher PPCl compared with BMI and BSA, with a higher area under curve (AUC) of 0.71 (95% confidence interval [CI]: 0.66-0.77).

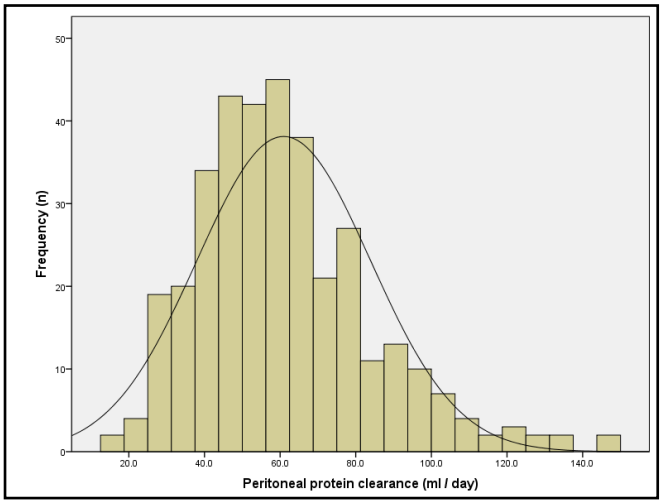


Fig. 2. The distribution of PPCl in the population (P for normality test < 0.001).

Table 1. Comparison of demographic data and biochemical parameters grouped by the quartiles of PPCl. NOTE. Values expressed as mean ± SD, median (quartile) or number of patients (percent). PET, peritoneal equilibration test; CCL, weekly creatinine clearance;BMI , body mass index ; BSA , body surface area; NS, not significant

Variables	PPCl (ml/day)				
	≤ 45 (n=94)	46-58 (n=80)	59-74 (n=88)	>74 (n=89)	P value
Male gender (n,%)	40 (42.6%)	42 (52.5%)	54 (61.4%)	57 (64.0%)	0.015
Age (years)	46.1±14.0	46.8±13.8	48.0±14.2	49.9±15.2	0.316
BMI (kg/m^2)	22.3±3.5	23.4±3.0	23.1±3.2	24.3±3.3	<0.001
BSA (m^2)	1.58±0.18	1.63±0.14	1.66±0.18	1.71±0.16	<0.001
LBMI (kg/m^2)	17.3±2.2	18.2±1.8	18.8±2.3	19.9±2.3	<0.001
Diabetes (n,%)	8 (8.5%)	13 (16.3%)	14 (15.9%)	25 (28.1%)	0.006
Duration of dialysis (months)	27.6 (10.5-43.9)	29.9 (12.7-45.3)	29.1 (15.8-45.9)	30.7 (16.9-50.8)	0.402
Dose of PD (L/day)	8 (6-8)	8 (8-8)	8(8-8)	8(8-10)	<0.001
Urine volume (ml/day)	620 (300-1212)	300 (100-788)	400 (74-888)	100 (15-440)	<0.001
DPI (g/kg/day)	0.97±0.22	0.89±0.18	0.93±0.19	0.86±0.20	<0.001
Total protein (g/L)	71.1±7.1	70.0±5.3	66.3±5.1	65.0±6.0	<0.001
Albumin (g/L)	40.9±3.7	39.5±3.4	37.6±2.9	35.2±3.7	<0.001
Globulin (g/L)	30.4±4.9	30.5±4.6	28.7±4.5	29.8±5.4	0.063
Urine protein loss (g/day)	0.37 (0.15-0.65)	0.26 (0.06-0.53)	0.23 (0.05-0.72)	0.12 (0.01-0.58)	0.026
Peritoneal protein loss (g/day)	3.1±0.6	4.3±0.44	5.1±0.5	6.8±1.3	<0.001
Peritoneal albumin loss (g/day)	2.1±0.5	2.9±0.4	3.4±0.5	4.4±1.0	<0.001
Total protein loss (g/day)	3.7±0.9	4.6±0.7	5.5±0.9	7.3±1.9	<0.001
Total Kt/v	2.6±1.0	2.3±0.5	2.3±0.6	2.1±0.5	<0.001
Total CCL (L/week/1.73m2)	69.5 (54.1-101.0)	60.1 (51.3-71.6)	60.1 (51.3-74.9)	58.7 (50.6-69.3)	0.004
Residual CCL (L/week/1.73m2)	28.3 (9.6-63.7)	9.2 (1.6-23.9)	11.2 (1.5-26.8)	3.2 (0.3-16.9)	<0.001
Peritoneal CCL (L/week/1.73m2)	41.0 (33.5-46.9)	47.5 (42.6-52.4)	46.7 (41.0-52.5)	50.2 (43.7-55.5)	<0.001
D/P cr	0.65±0.11	0.67±0.08	0.69±0.11	0.73±0.09	<0.001
PET					0.001
Low	6 (6.7%)	1 (1.4%)	1(1.3%)	1(1.1%)	
Low Average	38 (42.2%)	27 (37.0%)	31(39.2%)	17(19.5%)	
High Average	41 (45.6%)	40 (54.8%)	35(44.3%)	50(57.5%)	
High	5 (5.6%)	5 (6.8%)	12(15.2%)	19(21.8%)	

Independent factors associated with higher PPCl and continuous PPCl

Multivariate logistic regression model was performed to explore the independent factors associated with higher PPCl (>58 ml/day). After adjustment for age, sex, body surface area, diabetes, the dose of peritoneal dialysis, daily protein intake (DPI), and peritoneal CCl, we found that every 1 L/week/1.73m^2 decrease of residual renal CCl (odd ratio [OR]=0.98; 95% CI: 0.96-0.99; *P*=0.001), each 0.1 increase of 4-hour D/P creatinine ratio (OR=1.47; 95%CI:1.11-1.93; *P*=0.007), and each 1 kg/m^2 increase of LBMI (OR=1.37; 95%CI:1.17-1.60; *P*<0.001) were independently associated with higher PPCl. We also examined the relationship between LBMI and peritoneal protein loss, and the results were similar (Table 2).

Multilinear regression model was conducted to explore the factors influencing continuous PPCl. Results showed that diabetes (β=0.15, *P*=0.003), peritoneal CCl (β=0.13, *P*=0.037), D/P creatinine ratio (β=0.19, *P*<0.001), and LBMI (β=0.31, *P*<0.001) were independently positively linearly associated with continuous PPCl, while residual renal CCL(β=-0.18, *P*=0.006) was negatively linearly associated with continuous PPCl. It seems that LBMI has a highest strength of linear effect with continuous PPCl (standard β coefficient=0.31, $p \leq 0.001$) (Table 3).

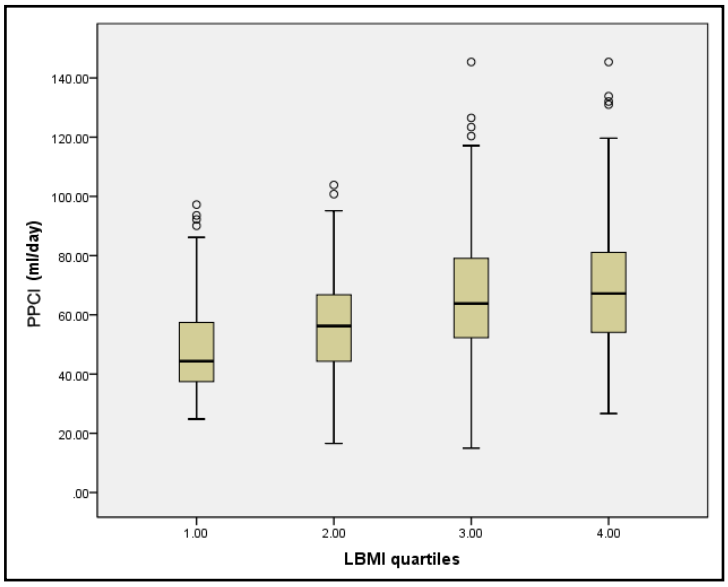
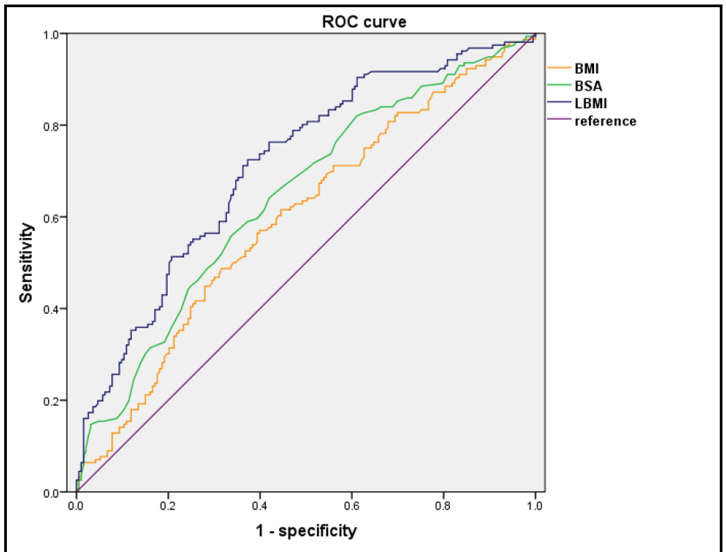


Fig. 3. Comparison of the PPCl levels by the LBMI quartiles (P<0.001).



Performance of different body index in predicting higher PPCl (> 58.0 ml/day) in the ROC analysis

Variables	AUC	SE	P value	95% CI
BMI (kg/m2)	0.60	0.030	0.002	0.54-0.66
BSA (m2)	0.64	0.030	< 0.001	0.59-0.70
LBMI (kg/m2)	0.71	0.028	< 0.001	0.66-0.77

Fig. 4. Performance of different body index in predicting higher PPCl (> 58.0 ml/day) in the ROC analysis. BMI, body mass index; BSA, body surface area; LBMI, lean body mass index.

Discussion

In this cross-section study included 351 PD patients in Southern China, the median PPL was 4.6 (IQR: 3.7-5.6) g/day, and the median PPCl was 58 (IQR: 45-745) ml/day in PD patients. After adjusted for underlying confounders, we found that higher LBMI, higher D/P creatinine ratio, and lower residual renal creatinine clearance were independently associated with higher PPCl. Compared with conventional body index (BMI or BSA), LBMI had better performance in predicting higher PPCl.

As a better index reflecting the individual differences of peritoneal protein loss and the membrane function of both small pores and large pores [3, 6], higher peritoneal PPCl has been remarked as an useful predictor of CVD and mortality in PD patients [5, 7, 9, 10, 21]. However, such conclusions have been queried by many other studies [4, 8]. A longitudinal study included 540 PD patients found that higher PPCl was associated with higher risk of overall mortality in the univariate model, however, while this effect attenuated to a non-statistical significance when adjusting for confounders [4]. Though there are no consensuses on such conflicting results, a concern that higher PPCl may be a mediator rather than an independent risk factor of poor outcomes arouses. And exploring the important determinants of PPCl may be helpful for understanding their relationship.

Indeed, early studies had found many factors are affecting PPL or PPCl, including the frequency and duration of PD, solutions, BSA, serum protein levels, clinical status (such as diabetes), peritoneal transport type, and inflammatory factors [2, 22-24]. However, limited sample size and few associated factors considered in those studies might limit the implications. As proved in the current study with larger sample size, diabetes, higher D/P creatinine ratio, and lower residual renal creatinine clearance were independently associated with higher PPCl, which were consistent with some recent studies [4, 6, 8, 25-27]. These factors have been demonstrated as risk factors of increased mortality in PD population [28-31], which may partially explain the negative effects of higher PPCl on patients outcomes.

Table 2. Associated factors of higher PPCl(> 58.o ml/day) in multivariate logistic regression model. NOTE. Analysis was performed to explore the independent factors associated with higher PPCl and PPL. PPCl, peritoneal protein clearance; PPL, peritoneal protein loss; BSA, body surface area; DPI, daily protein intake; CCl, creatinine clearance; LBMI, lean body mass index

Variables	Higher PPCl (> 58 ml/day)		Higher PPl (>4.6 g/day)	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (years)	1.01 (0.99-1.03)	0.495	1.01 (0.99-1.02)	0.526
Sex (M/F)	1.30 (0.42-1.45)	0.430	1.17 (0.63-2.20)	0.622
BSA (per 0.1 m^2 increase)	1.18 (0.93-1.50)	0.164	1.22 (0.97-1.54)	0.095
Diabetes	1.15 (0.58-2.31)	0.685	0.94 (0.47-1.86)	0.853
Dose of PD (L/day)	0.82 (0.61-1.10)	0.187	0.96 (0.71-1.28)	0.760
DPI (per 0.1 g/kg/day increase)	1.00 (0.86-1.16)	0.979	1.04 (0.90-1.20)	0.605
Residual renal CCl (L/week/1.73m^2)	0.98 (0.96-0.99)	0.001	0.99 (0.97-0.99)	0.016
Peritoneal CCl (L/week/1.73m^2)	1.01 (0.98-1.05)	0.448	1.03(0.99-1.07)	0.164
D/P creatinine ratio (per 0.1 increase)	1.47 (1.11-1.93)	0.007	1.29 (0.99-1.67)	0.062
LBMI (kg/m^2)	1.37 (1.17-1.60)	<0.001	1.22 (1.05-1.42)	0.007

However, few studies have pay enough attention on the relationship between PPL/PPCl and nutritional status. In this study, nutritional status was measured by multifrequency bioelectrical impedance analysis (BIA), and LBM was used as a marker of nutritional state, which with higher level was usually associated with better survival [32]. It was reported that LBM measured by BIA was highly correlated with good method

Table 3. Associated factors of peritoneal protein clearance in multilinear regression model. F=16.27, P<0.001, R^2=0.297. NOTE. Analysis was performed to explore the factors linearly associated with peritoneal protein clearance in multilinear regression model. BSA, body surface area; DPI, daily protein intake; CCl, creatinine clearance; LBMI, lean body mass index

Variables	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Standard Error			
Age (years)	0.08	0.08	0.05	0.99	0.325
Sex (M/F)	3.90	2.89	0.08	1.35	0.178
BSA (m^2)	1.32	1.01	0.10	1.31	0.191
Diabetes	9.07	3.06	0.15	2.96	0.003
Dose of PD (L/day)	-0.18	1.15	-0.01	-0.16	0.876
DPI (0.1 g/kg/day)	-0.16	0.635	-0.01	-0.25	0.800
Residual renal CCL (L/week/1.73m^2)	-0.12	0.04	-0.18	-2.78	0.006
Peritoneal CCL (L/week/1.73m^2)	0.22	0.11	0.13	2.09	0.037
D/P creatinine ratio (per 0.1 increase)	4.01	1.10	0.19	3.66	<0.001
LBMI (kg/m^2)	3.05	0.66	0.31	4.63	<0.001

agreement using dual-energy X-ray absorptiometry (DEXA) as the reference test (r = 0.95) [14]. As shown in this study, LBMI had better performance in predicting higher PPCl when compared with conventional body index (BMI and BSA) in the ROC analysis. BSA mainly reflects the basal metabolic rate of individual, BMI contains the effect of fat on body composition, while LBM more likely is a reflection of patients' global health, uremic control, endogenous testosterone level, lack of inflammation, etc. All these factors resulting in higher skeletal muscle mass. Therefore, it is not surprising that LBMI would be more closely corelated with the body protein metabolism.

An important finding of this study is that higher LBMI was independently associated with higher PPCl, and positively linearly associated with continuous PPCl (overall R^2 for the model=0.297). As mentioned above, higher LBMI is a marker of better nutritional state. Interestingly, this results seems to reverse the conventional viewpoint that higher peritoneal protein loss/PPCl may cause hypoalbuminemia and malnutrition [2]. It should be noted that such previous view was mainly based on the relationship between increased peritoneal protein loss and decreased serum albumin. However, hypoalbuminemia in patients with peritoneal dialysis is not equivalent to malnutrition, because the cause of hypoalbuminemia in PD patients is multifaceted [33, 34]. An observational study by Ates K et al. also suggested that peritoneal protein loss in peritoneal dialysis has no significant effect on the patient's nutritional status [11]. The reason why higher LBMI is associated with higher PPCl is not clarified yet. However, it is not difficult to understand that patients have better nutritional state may have more sufficient protein reserves, as well as more active protein metabolism in the peritoneal cavity and lead to more protein loss. Another hypothesis is that during PD albumin losses may established an effective removal of certain protein-bound uremic toxins [35]. Such process may potentially explain our results that higher lean body mass in those with larger protein losses. Importantly, our results may also partially explain the conflicting results on the impact of higher PPCl on mortality in previous studies [4-10]. Because such key factors affecting higher PPCl include both good (higher LBMI) and bad contents (higher D/P creatinine ratio, diabetes, and lower residual renal creatinine clearance) for patient prognosis. We can infer that the adverse effect of higher PPCl on mortality may be neutralized by the favorable effect of better nutritional status in those patients with higher PPCl. As it has been recognized that better nutritional status in dialysis patients is a very important issue to patients survival [13, 32, 36, 37].

The strengths of this study include its relative large sample size and more precise and comprehensive methodology in assessment of patients. However, our study has several limitations. First, the patients enrolled were from a single PD center and our study did not include the entire population of PD patients, which may introduce selection bias. Second, for the complex assessment procedures and specimens collection in the study, a large proportion of patients were excluded in the enrollment; therefore, selection bias is more difficult to control. Finally, the cross-sectional study did not involve clinical outcomes that we still cannot conclude the exact relationship between PPCl and clinical outcomes, which needs further study in the future.

Conclusion

The median PPCl was 58.0 ml/day in PD patients in Southern China. Higher LBMI, was independently associated with higher PPCl, indicating that better nutritional status dominates peritoneal protein metabolism in PD patients. Prospective studies including more associated factors in evaluating the relationship between PPCl and clinical outcomes are still needed in the future.

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Disclosure Statement

The authors declare that they do not have anything to disclose regarding Disclosure Statement with respect to this manuscript.

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