

# The Relationship Between Serum Folate Level and Residual Renal Function in CAPD Patients

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**Objective:** To investigate the relationship between serum folate (FA) levels and residual renal function (RRF) in continuous ambulatory peritoneal dialysis (CAPD) patients.

**Methods:** Clinical data were collected from 180 hospitalized patients who received CAPD regularly. Patients were divided into the FA deficiency group and the FA non-deficiency group according to serum FA level. Data on age, sex, PD vintage, hemoglobin, mean corpuscular volume, serum FA, total Kt/V, residual kidney Kt/V, peritoneum Kt/V, creatinine clearance (Ccr), ultrafiltration volume, cystatin C (cytC), serum creatinine (Scr), urea nitrogen, retinol-binding protein and the primary disease were gathered from 2 groups. Statistical methods were used to analyze the relationship between serum FA level and RRF.

**Results:** Peritoneal Kt/V, cytC, Scr were higher, and residual kidney Kt/V was lower in FA deficiency group than in non-deficiency group. Univariate correlation showed the peritoneal Kt/V, cytC, Scr negatively correlated with serum FA while residual kidney Kt/V positively correlated with serum FA, and there was a simple linear regression relationship between serum FA and residual kidney Kt/V. Differences were statistically significant ( $P < 0.05$ ).

**Conclusion:** There is a relationship between serum FA and RRF in CAPD patients. Prospective studies or trials should be performed to clarify the importance of FA supplementation on RRF during peritoneal dialysis.

**Keywords:** folate, continuous ambulatory peritoneal dialysis, residual renal function

## Introduction

Peritoneal dialysis (PD) is an important renal replacement therapy for patients with end-stage renal disease, however, concurrent cardiovascular disease (CVD) or PD-related peritonitis can not only affect the smoothness of the PD process but also be life-threatening in serious cases. Residual renal function (RRF) plays an important role in the quality of life and prognosis of PD patients. Studies have shown that a 5 L/1.73-m<sup>2</sup> per-week increase in GFR and a 10 L/1.73-m<sup>2</sup> per-week increase in Ccr reduce the mortality risk by 12% and 40%, respectively, in PD patients.<sup>1,2</sup> Simultaneously, preservation of even a small amount of RRF also has significant positive effects during PD treatment.<sup>3</sup> Furthermore, a decline in RRF can lead to malnutrition, infection, CVD and other serious adverse events during dialysis.<sup>4</sup> Therefore, protecting RRF in PD patients as much as possible is important to prolonging the dialysis age and improving quality of life.

Folate (FA), also known as vitamin B<sub>9</sub>, is a water-soluble vitamin that plays important roles in the metabolism of genetic material and proteins, growth, development, and immunity enhancements that maintain normal life activities. FA deficiency can lead to anaemia, infertility and muscle weakness<sup>5-7</sup> and is closely associated with hyperhomocysteinaemia,<sup>8</sup> which correspondingly increases the risk of CVD.<sup>9</sup> Previous research reported that approximately 40–60% of deaths among PD patients are related to CVD,<sup>10</sup> while long-term FA supplementation significantly reduces all-cause mortality and cardiovascular mortality in continuous ambulatory peritoneal dialysis (CAPD) patients.<sup>11</sup> FA cannot be synthesized by the human body, so its physiological level is entirely dependent on exogenous FA intake.<sup>12</sup> The upper small intestine is the main FA absorption

site; patients who have renal function damage up to uraemia often have concomitant gastrointestinal symptoms such as nausea, vomiting and loss of appetite, which decreases FA intake to a certain extent. Decreased of serum FA levels in PD patients have also been reported in the literature,<sup>13</sup> FA supplementation has been shown to reduce Scr and increase GFR in subjects with atherosclerosis hazards.<sup>14</sup> Therefore, we speculated that appropriate FA supplementation may play roles in maintaining RRF in PD patients. Although the relationship between serum FA and PD or serum FA and renal function has been reported in some studies, there are no direct analyses exploring the relationship between serum FA and RRF in PD patients. Therefore, we analysed the relationship between serum FA and RRF in CAPD patients, and preliminarily discuss the mechanism in this context.

## Methods

### Study Participants

Our study used a cross-sectional design. We collected the clinical data of 213 hospitalized patients who received CAPD regularly at Department of Nephrology, Shanghai Changhai Hospital between March 1, 2019, and March 19, 2021. The exclusion criteria were as follows:<sup>1</sup> patients aged <18 years;<sup>2</sup> patients who had acute kidney injury and received emergency haemodialysis;<sup>3</sup> patients with concomitant malignant tumours; or<sup>4</sup> patients who had received FA supplement treatments. Among those excluded, there were 16 patients who had received emergency haemodialysis and 17 patients who had received FA supplementation. Finally, 180 patients were enrolled in the study. The serum FA level was determined by radioimmunoassay, and a level <4 ng/mL was defined as FA deficiency.<sup>15</sup> Then, patients were divided into 2 groups according to FA levels. There were 83 cases in the FA deficiency group and 97 cases in the non-deficiency group. Figure 1 shows the distribution of serum FA levels in this study.

### Data Collection

The information collected consisted of enumeration and measurement data. Enumeration data were collected for the sex and primary disease of the PD patients, which was categorized as male, female, diabetic nephropathy (DN) and non-diabetic nephropathy (NDN). Measurement data were collected for the age, PD vintage, hemoglobin (Hb), mean corpuscular volume (MCV), serum FA, total Kt/V, residual kidney Kt/V, peritoneum Kt/V, creatinine clearance (Ccr), ultrafiltration volume, cystatin C (cytC), serum creatinine (Scr), urea nitrogen (BUN) and retinol-binding protein (RBP).

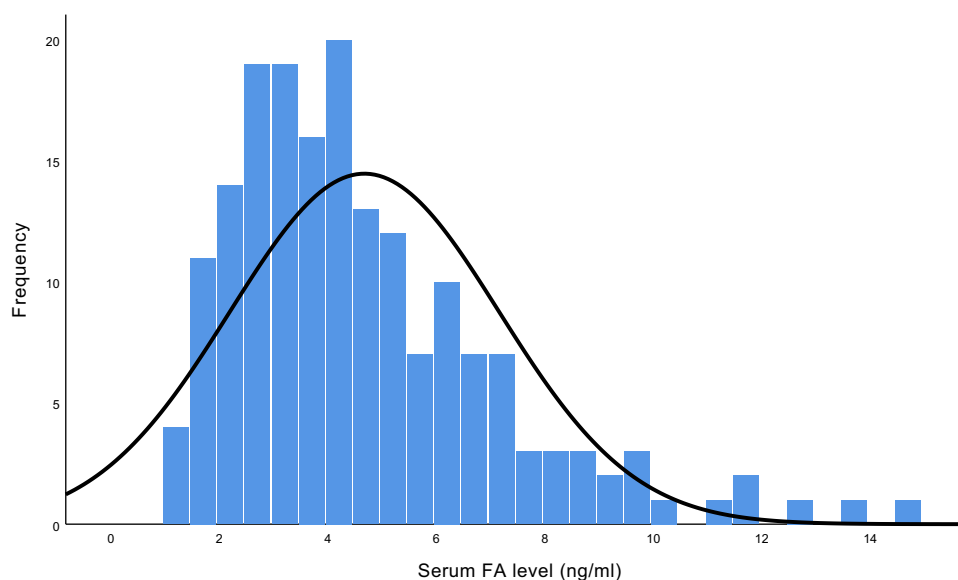


Figure 1 Frequency distribution histogram of serum FA levels.

## Statistical Analyses

Statistical analysis was performed using SPSS, IBM (version 26) software. Measurement data with a normal distribution are shown as means  $\pm$  standard deviations, and differences between 2 groups were evaluated by independent-sample *t*-tests. Measurement data without a normal distribution are expressed as the median (interquartile range) and were analysed by means of the Mann–Whitney *U*-test. Enumeration data are expressed as frequencies (percentages) and were analysed by means of the chi-square test. Spearman correlation analysis was used to determine the correlation between serum FA and all measurement data. Simple linear regression analysis was performed with residual kidney Kt/V and Ccr as the dependent variable and serum FA level as the independent variable. Adjustments were made for the influence of sex, age, brain natriuretic peptide (BNP), and Lipoprotein a (LP(a)) on serum FA in the model.  $P < 0.05$  indicates significant differences. Figure 2 shows the flow chart of this research process.

## Results

### Comparison of Observation Indices Between 2 Groups

Table 1 shows the comparison of all observation indices between the 2 groups. The peritoneal Kt/V, cytC, and Scr in the FA deficiency group were higher than those in the non-deficiency group, and the residual kidney Kt/V was lower in the FA deficiency group than in non-deficiency group; the differences were statistically significant ( $P < 0.05$ ). There were no statistically significant differences in the age, sex, PD vintage, Hb, MCV, primary disease, total Kt/V, Ccr, ultrafiltration volume, BUN or RBP between the 2 groups ( $P \geq 0.05$ ).

### Univariate Correlations Between Serum FA Level and Other Factors

Table 2 shows the univariate correlation between serum FA and all measurement data. Peritoneal Kt/V, cytC, and Scr were negatively correlated with serum FA (peritoneal Kt/V:  $\rho = -0.181$ ;  $P = 0.014$ , cytC:  $\rho = -0.326$ ;  $P = 0.000$ , Scr:  $\rho = -0.287$ ;  $P = 0.000$ ), while residual kidney Kt/V positively correlated with serum FA ( $\rho = 0.251$ ;  $P = 0.001$ ).

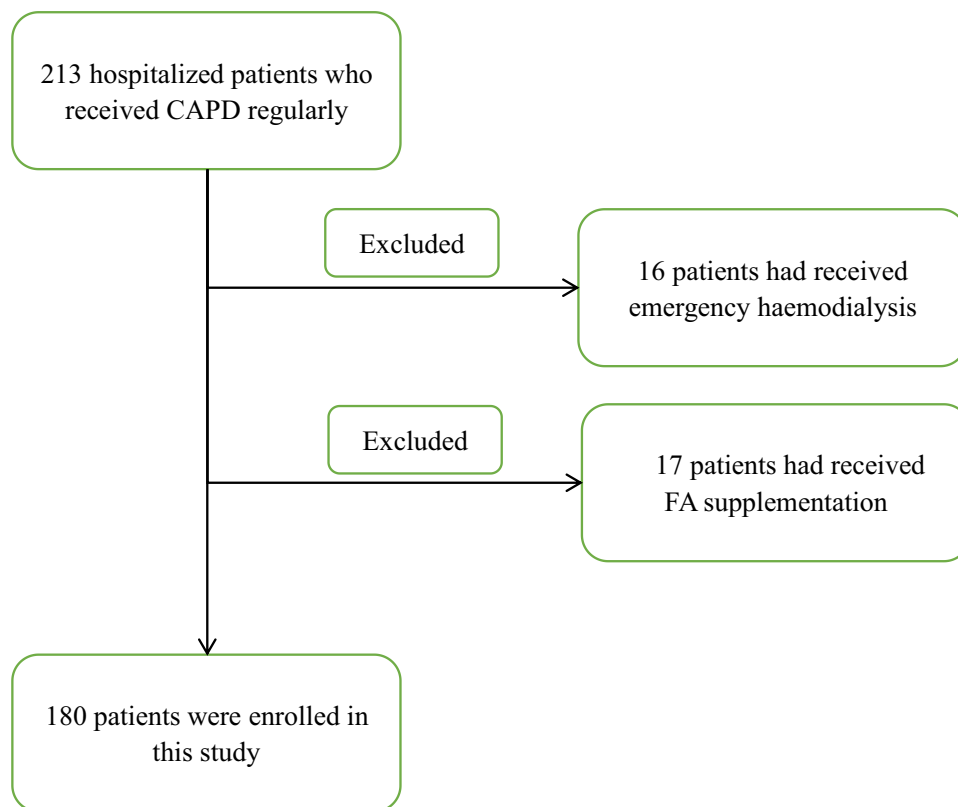


Figure 2 Flowchart of the study.

**Table 1** Comparison of Observation Indices Between the 2 Groups

Factors	All (n=180)	FA Deficiency (n=83)	FA Non-Deficiency (n=97)	Statistical Magnitude	P value #
Age	53±14	52±15	54±13	t= 1.052	0.294
Sex				χ <sup>2</sup> =0.058	0.809
Male	85 (47.2%)	40 (48.2%)	45 (46.4%)		
Female	95 (52.8%)	43 (51.8%)	52 (53.6%)		
PD vintage (month)	18.9 [4.54–48.83]	19.33 [2.77–45.03]	18.2 [4.60–54.29]	Z= -0.452	0.651
Hb (g/L)	97±22	95±22	98±22	t= 0.803	0.423
MCV (fL)	90.7±5.7	91.2±6.0	90.4±5.5	t= -0.896	0.371
Total Kt/V	1.84 [1.66–2.05]	1.84 [1.65–2.04]	1.85 [1.69–2.08]	Z= -0.585	0.558
Residual kidney Kt/V‡	0.37 [0.00–0.78]	0.21 [0.00–0.64]	0.49 [0.08–0.92]	Z= -2.655	0.008
Peritoneal Kt/V†	1.37 [1.01–1.70]	1.48 [1.04–1.78]	1.29 [0.97–1.63]	Z= -2.063	0.039
cytC (mg/L)†	7.0±1.7	7.5±1.6	6.6±1.7	t= -3.482	0.001
Scr (mmol/L)†	847 [661–1105]	928 [726–1163]	794 [633.50–1016.25]	Z= -2.643	0.008
Ultrafiltration volume (mL)	260 [0.00–654.25]	323 [17.5–771]	255 [0.00–528]	Z= -1.284	0.199
RBP (mg/L)	112.0±24.1	112.2±24.3	111.8±24.2	t= -0.110	0.912
BUN (mmol/L)	18 [14.90–22.00]	17.5 [14.8–20.8]	18.5 [15.10–23.45]	Z= -1.288	0.198
Ccr	56.79 [46.49–75.29]	54.71 [43.73–69.62]	58.27 [50.17–79.17]	Z= -1.351	0.177
Primary disease				χ <sup>2</sup> =1.023	0.312
DN	25 (13.9%)	9 (10.8%)	16 (16.5%)		
NDN	155 (86.3%)	74 (89.2%)	84 (86.6%)		

**Notes:** #Compared to the deficiency and non-deficiency groups. †Value is significantly higher than the corresponding value in the non-deficiency group (P < 0.05). ‡Value is significantly lower than the corresponding value in the non-deficiency group (P < 0.05).

**Table 2** Univariate Correlations Between Serum FA Level and Other Factors

Factors	Spearman ρ	P value
Age	0.122	0.103
PD vintage	-0.006	0.935
Hb	0.110	0.145
MCV	-0.009	0.904
Total Kt/V	0.099	0.203
Residual kidney Kt/V **	0.251	0.001
Peritoneum Kt/V *	-0.181	0.014
cytC **	-0.326	0.000
Scr **	-0.287	0.000
Ultrafiltration volume	-0.072	0.379
RBP	-0.076	0.316
BUN	0.104	0.162
Ccr	0.139	0.075

**Notes:** Differences were considered to be statistically significant at \*P<0.05, \*\* P<0.01.

### Linear Regression Analysis Between Residual Kidney Kt/V, Ccr and Serum FA

Simple linear regression analysis was performed with serum FA as an independent variable and Kt/V and Ccr as dependent variables. Model 1 was adjusted for age and sex, and Model 2 comprised Model 1 in addition to adjustments for plus LP(a) and BNP levels. There was a linear relationship between serum FA levels and residual kidney Kt/V in both models after the adjustments (Model 1: P=0.035; Model 2: P=0.036), and no linear regression was performed between serum FA and Ccr levels in either model (Model 1: P=0.081; Model 2: P = 0.100) (Table 3).

**Table 3** Linear Regression Analysis Results

Parameter	Model 1			AdjR2	Model 2			AdjR2
	B	SE	P		B	SE	P	
Residual kidney Kt/V*	0.045	0.021	0.035	0.027	0.045	0.021	0.036	0.110
Ccr	1.924	1.095	0.081	0.049	1.782	1.074	0.100	0.086

**Notes:** Model 1 adjusted for age and sex. Model 2 was Model 1 plus adjustments for LP(a) and BNP. The beta coefficients refer to how many deviations a dependent variable will have per deviation increase in the predictor variable. SE refers to the standard error. The adjusted R2 represents the goodness of fit, which is used to measure the degree of the estimated models fitting the observations. Differences were considered to be statistically significant at \*P<0.05.

## Discussion

RRF is the endocrine and clearance function of the remnant nephrons after renal function damage. For PD patients, maintaining good RRF contributes to the improvement of nutritional level, water and electrolyte balance, assurance of dialysis adequacy and loss of morbidity and mortality of dialysis-related complications.<sup>16</sup> FA is absorbed into the body through glomerular filtration and reabsorption of the proximal tubule, while FA transporters located in the proximal tubule contribute to FA reabsorption and maintain homeostasis. Studies have found a decrease in the expression of FA transporters and the serum FA level in an acute kidney injury rat model,<sup>17</sup> which provides us with an important reference to explore the relationship between RRF and serum FA levels in patients undergoing PD due to chronic renal failure. In this study, we assessed Scr, BUN, cytC, Kt/V and other indicators to reflect RRF in CAPD patients directly or indirectly and then analysed their relationships with serum FA to provide a reasonable interpretation.

Kt/V is an important index used to evaluate PD adequacy, which reflects the ability to eliminate small molecule toxins during dialysis. It includes the Kt/V of the residual kidney and peritoneum function, which represents the urea removal capacity provided by the residual kidney and peritoneum function, respectively. The increase in residual kidney Kt/V improves the anaemia of CAPD patients, according to a study by Karel al.<sup>18</sup> In addition, residual kidney Kt/V has the ability to improve the viability and serum albumin and nutritional level of CAPD patients.<sup>19,20</sup> In our study, the relationship between the residual kidney Kt/V level and serum FA deficiency was significant, and we found an obviously positive correlation between the two parameters. On the one hand, deficiency of folate results in megaloblastic anemia, and there have been many reports on the use of folate supplements for anemia treatment. On the other hand, we also observed a decrease in the urea level after FA supplementation in DN mice,<sup>21</sup> while linear regression analysis showed that the residual kidney Kt/V changed with the change in serum FA. This allowed us to consider that the elevated residual kidney Kt/V improves anemia in CAPD patients,<sup>18</sup> during which serum FA likely plays an important role. Serum FA can improve the Kt/V level, which is reflected as an indicator of urea removal capacity. However, peritoneal Kt/V was significantly increased in the FA-deficient group and was negatively correlated with serum FA, which was related to the fact that the total Kt/V of PD inpatients in our center were stable caused by the nicely quality control of PD consistently. The increase in residual kidney Kt/V will inevitably lead to a corresponding decrease in peritoneal Kt/V when the total Kt/V value is stable, which consequently reaches the opposite conclusion of residual kidney Kt/V. Similarly, this conjecture has been made in previous studies, namely, that the peritoneal Kt/V has the function of keeping the total Kt/V level stable when the residual kidney Kt/V decreases.<sup>19,22</sup>

CytC is a non-glycosylated, low-molecular-weight basic protein (13 kDa) that is used as a marker for the glomerular filtration rate, and it has significant effects in the evaluation of RRF and predicting clinical outcomes in PD patients,<sup>23,24</sup> moreover, it is characterized by a significant negative correlation with residual kidney Kt/V.<sup>25</sup> In the present study, we found that the relationship between the cytC level and serum FA deficiency was significant, and both showed an obvious negative correlation. It is further speculated that some kind of correlation between them may exist.

Scr, always used as the indicator of renal function, has also been mentioned to be related to serum FA in a previous study. In addition to the study by Mierzecki et al that FA supplementation reduced Scr in subjects with atherosclerotic hazards,<sup>14</sup> serum FA also decreased in AKI rats with the rise of Scr and showed a significantly negative correlation in another study by Yang et al.<sup>17</sup> Moreover, M Achón et al found a reduction in Scr in rats fed high-dose FA after 4 weeks.<sup>26</sup>

Our statistical results were similar to those of previous studies, except that the subjects were CAPD patients, which was the main difference in our research.

Ccr, together with Kt/V, constitutes an index for small solute clearance during PD and plays an important role in improving dialysis adequacy. Clinically, a weekly total Kt/V > 1.7 and Ccr > 60 are considered adequate dialysis. Consequently, broadly similar trends for Kt/V and Ccr should be observed, but our study showed completely different results. There were no significant differences in Ccr levels between the FA deficiency group and the nondeficiency group. Univariate correlation analysis and simple linear regression analysis also revealed no relationship between Ccr and FA level, and we surmise that this finding is probably attributed to renal physiology. A previous retrospective study found that the results of Kt/V and Ccr dialysis were contradictory in nearly 23% of PD patients, and further analysis suggested that the reason may have been related to the role of renal filtration and reabsorption.<sup>27</sup> The creatinine produced during human metabolism is excreted mainly through glomerular filtration and renal tubular secretion, while urea can be partially reabsorbed by renal tubules after glomerular filtration, which causes a discrepancy in the statistical analysis results between assessments of Kt/V and Ccr.

To the best of our knowledge, this is the first investigation to directly analyse the correlation between serum FA and RRF in CAPD patients. Although this is only a cross-sectional study that cannot investigate the causal relationship, it certainly indicates the significance of the serum FA level in CAPD patients. A series of prospective studies will be carried out on this basis to further explore the influence of FA supplementation on the quality of life of PD patients.

In conclusion, there is a relationship between serum FA and RRF in CAPD patients. Prospective studies or trials should be performed to clarify the importance of FA supplementation on RRF during peritoneal dialysis.

## Confidentiality Statement

Patients' clinical data were stored in our professional medical database, the process of data collection was supervised of the experts for the full time, which ensured the clinical data cannot be compromised. All attempts to access these data for private purposes are not allowed. The datasets generated and analyzed during this study are not publicly available because of professional discretion, as they were part of patients' records, but are available as a de-identified data sheet from the corresponding author on reasonable request.

## Abbreviations

PD, peritoneal dialysis; FA, folate; CAPD, continuous ambulatory peritoneal dialysis; RRF, residual renal function; Hb, hemoglobin; MCV, mean corpuscular volume; Ccr, creatinine clearance; cytC, cystatin C; Scr, serum creatinine; CVD, cardiovascular disease; DN, diabetic nephropathy; NDN, non-diabetic nephropathy; BUN, urea nitrogen; RBP, retinol-binding protein; BNP, brain natriuretic peptide; LP(a), lipoprotein a.

## Data Sharing Statement

The datasets analysed during the current study available from the corresponding author on reasonable request.

## Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of The First Affiliated Hospital of Naval Medical University. Because of the retrospective nature of the study, patient consent for inclusion was waived.

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## Disclosure

The authors report no conflicts of interest in this work.

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