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Positive association of residual kidney function with hemoglobin level in patients on peritoneal dialysis independent of endogenous erythropoietin concentration

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Abstract

Background: How residual kidney function (RKF) functions in the prevention of anemia in peritoneal dialysis (PD) patients is unclear. In this study, we investigated the association between RKF and hemoglobin (Hb) level.

Methods: We performed a cross-sectional analysis of the association between RKF, defined as the mean renal creatinine and urea clearance (rCUC), and the Hb level in 50 PD patients registered retrospectively. The independent variable was mean rCUC as continuous or categorical variable by tertile, and the dependent variable was Hb level as continuous or dichotomous variable using Hb cutoff of 10 g/dL. We conducted a multivariable regression analysis and calculated the c-statistic for Hb level < 10 g/dL using a receiver operating characteristic curve.

Results: In multivariable regression analysis, mean rCUC was significantly associated with Hb level independent of dose of erythropoiesis-stimulating agent (ESA) and endogenous erythropoietin (eEPO) concentration. Multivariable adjusted least square means of the Hb level were higher with increase in the mean rCUC tertile. The c-statistic (95% confidential interval) for a Hb level < 10 g/dL was significantly greater in the model with mean rCUC than without [0.931 (0.789–0.980) vs. 0.856 (0.697–0.939), $P = 0.044$].

Conclusion: A decline in RKF is associated with anemia in PD patients independent of ESA dose and eEPO concentration.

Trial registration: UMIN000018902

Keywords: Anemia, Creatinine clearance, Erythropoietin, Hemoglobin, Kt/V, Residual kidney function

Background

The introduction of erythropoiesis-stimulating agent (ESA) to clinical settings for renal anemia has allowed the easy management of anemia in patients with chronic kidney disease (CKD). Anemia control is considered important for the prediction of mortality and increase in quality of life in CKD patients. However, recent studies

have demonstrated that a large dose of ESA results in a high mortality rate and high incidence of cardiovascular events such as stroke in hemodialysis (HD) patients [1] and those with non-dialysis-dependent CKD [2–4].

The importance of residual kidney function (RKF) in the survival of chronic dialysis patients, especially peritoneal dialysis (PD) patients, was recently reported [5–7]. The “Cardiovascular and Metabolic Clinical Practice Guidelines for Peritoneal Dialysis Patients” by the International Society for Peritoneal Dialysis in 2015 also emphasize the importance of RKF in cardiovascular disease and mortality, recommending that PD patients undergo monitoring of RKF at least once every 6 months [8].

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Wang and Lai [5] also stressed the importance of RKF in anemia management. Lopez-Menchero et al. [9] reported that in addition to ESA use and iron levels, RKF also correlated significantly with hemoglobin (Hb) levels in PD patients. A recent report by Penne et al. [10] showed a strong relation between RKF and improved anemia control in HD patients. However, how RKF functions and how the endogenous erythropoietin (eEPO) concentration is involved in the prevention of anemia in CKD patients is unclear.

This study investigated the association between RKF and Hb levels from the perspective of the mechanism by measuring eEPO concentrations in PD patients.

Methods

Study participants

The study population comprised 50 patients aged > 18 years who were treated with PD at our hospital between May 2006 and March 2011 and had been followed for at least 6 months. Patients, who did not have any bone marrow disease or cirrhosis of the liver, were registered retrospectively. This study is a subanalysis of our multicenter cohort study (Fukuoka Peritoneal Dialysis Database Study), which was conducted in accordance with the Declaration of Helsinki, was approved by the Institutional Review Boards of Kyushu University Hospital (no. 26-223), and was registered at the University Hospital Medical Information Network (UMIN000018902).

Data collection

Blood, 24-h urine, and peritoneal dialysate samples were collected from PD patients at least every 6 months to evaluate their dialysis and peritoneal status as well as medical condition [11]. Demographic, clinical, and prescription data at each 6-monthly examination were also recorded based on the guidelines [12]. Venous blood was collected at a regular outpatient clinic visit after fasting, and part of the blood sample was centrifuged at $3000\times g$ at 4 °C for 15 min and stored at -80 °C until analysis, except for those used for standard biochemical analyses.

Calculation of Hb levels and ESA dose

Hb levels were assessed based on mean values during the last 3 months of the observation period. Darbepoetin alfa was administered as the ESA in all 50 patients to achieve and maintain a Hb level of approximately 11 g/dL according to the guidelines for anemia in CKD [13, 14]. The ESA dose was evaluated based on the weekly dose calculated from the total dose during the last 3 months of the observation period.

Measurements of RKF, dialysis adequacy, and peritoneal membrane solute transport

RKF and dialysis adequacy, which were measured every 6 months in each patient, were calculated as the weekly

urea clearance (Kt/V) and creatinine clearance (Ccr) from 24-h urinary and dialysate clearance, by direct measurement of urea in the urine and each dialysate exchange. The volume of urea distribution in a patient, which is the patient's total body water (TBW), was calculated according to the equations of Hume and Weyers—men: $TBW (L) = 0.297 \text{ body weight (kg)} + 0.195 \text{ body height (cm)} - 14.013$; women: $TBW (L) = 0.184 \text{ body weight (kg)} + 0.345 \text{ body height (cm)} - 35.27$ [15]. RKF was defined as the mean renal creatinine and urea clearance (rCUC). Peritoneal membrane solute transport was assessed by the peritoneal equilibration test. A standard 4-h dwell period was used (first exchange of the day), with a 2.27% glucose concentration 2-L volume exchange. The patients used their usual overnight dialysis regimes, and both the overnight and the test drainage volumes were measured. The dialysate-to-plasma ratio of creatinine at the completion of the 4-h dwell period (D/P_{cr}) was used as the estimate of low molecular weight solute transport.

Measurement of serum eEPO concentration

Serum eEPO concentration was measured by a chemiluminescent enzyme immunoassay (SRL Inc., Fukuoka, Japan).

Statistical analysis

Results are expressed as the mean \pm standard deviation, median (interquartile range [IQR]), or number (percentage) as appropriate. The trend among mean rCUC groups was assessed using Cochran-Armitage test for the categorical variables and Jonckheere-Terpstra test for continuous variables. The primary outcome variable was the mean Hb level during the last 3 months of the observation period. Both univariable and multivariable linear regression analyses were conducted to assess the associations between the Hb level and the variables. Variables showing a *P* value of < 0.05 in the univariable analysis were included in addition to cardiothoracic ratio (CTR), ESA dose, and log-transformed eEPO concentration in the multivariable analyses. To investigate whether the accuracy of predicting Hb levels improved after addition of the mean rCUC into a basic model (model 1) including the potential risk factors that were significantly associated with Hb levels in the univariable analysis in addition to CTR, ESA dose, and eEPO concentration, we calculated the c-statistic for Hb levels < 10 g/dL using a receiver operating characteristic curve. For two-tailed tests, *P* < 0.05 was considered significant in all analyses. All statistical analyses were conducted using JMP 11.2 software (SAS Institute, Tokyo, Japan) and RStudio Version 0.99.896.

Results

The characteristics and laboratory data of the 50 patients according to the tertiles of mean rCUC are

Table 1 Clinical characteristics according to tertiles of mean rCUC

	Total (N = 50)	T1 (mean rCUC < 11.7 L/ week/1.73m ²), n = 17	T2 (mean rCUC 11.8–29.8 L/ week/1.73m ²), n = 17	T3 (mean rCUC ≥ 29.9 L/ week/1.73m ²), n = 16	P for trend
Male sex, n (%)	37 (74.0)	12 (70.6)	11 (64.7)	14 (87.5)	0.277
Age, years	54 ± 14	53 ± 14	55 ± 15	55 ± 15	0.499
Dialysis duration, months	20.2 ± 11.6	23.4 ± 12.3	18.1 ± 9.7	18.8 ± 12.5	0.213
Original disease					
DN, n (%)	16 (32.0)	7 (41.2)	6 (35.3)	3 (18.8)	0.167
Non-DN, n (%)	34 (68.0)	10 (58.8)	11 (64.7)	13 (81.2)	
Blood pressure, mmHg					
Systolic	139 ± 14	141 ± 11	137 ± 18	139 ± 13	0.845
Diastolic	81 ± 11	82 ± 9	78 ± 16	82 ± 7	0.581
Daily alcohol consumption, n (%)	20 (40.0)	5 (29.4)	8 (47.1)	7 (43.8)	0.394
Current smoker, n (%)	9 (18.0)	3 (17.7)	2 (11.8)	4 (25.0)	0.593
Past histories of CVD, n (%)	8 (16.0)	2 (11.8)	4 (23.5)	2 (12.5)	0.939
History of peritonitis, n (%)	8 (16.0)	1 (5.9)	3 (17.7)	4 (25.0)	0.133
Body mass index, kg/m ²	22.9 ± 2.9	22.4 ± 2.4	22.1 ± 2.7	24.2 ± 3.2	0.124
CTR, %	48.2 ± 5.4	49.8 ± 4.7	48.3 ± 4.6	46.6 ± 6.7	0.075
Dialysis modality					
APD, n (%)	22 (44.0)	11 (64.7)	8 (47.1)	9 (56.3)	0.614
CAPD, n (%)	28 (56.0)	6 (35.3)	9 (52.9)	7 (43.7)	
Use of icodextrin, n (%)	41 (82.0)	16 (94.1)	13 (76.5)	12 (75.0)	0.150
Use of HG dialysate, n (%)	17 (34.0)	11 (64.7)	4 (23.5)	2 (12.5)	0.002
Dose of ESA, µg/week	34 ± 18	37 ± 16	32 ± 16	31 ± 23	0.206
Total Kt/V, /week	1.71 ± 0.34	1.66 ± 0.42	1.61 ± 0.31	1.87 ± 0.23	0.011
Renal Kt/V, /week	0.46 ± 0.37	0.10 ± 0.11	0.42 ± 0.18	0.88 ± 0.27	< 0.001
Peritoneal Kt/V, /week	1.25 ± 0.38	1.56 ± 0.41	1.19 ± 0.21	0.99 ± 0.22	< 0.001
Renal Ccr, L/week, /week	29.2 ± 26.9	5.1 ± 4.9	27.4 ± 8.9	56.8 ± 27.8	< 0.001
Urine volume, L/day	0.80 ± 0.64	0.22 ± 0.24	0.76 ± 0.38	1.44 ± 0.55	< 0.001
Mean rCUC, L/week/1.73m ²	22.7 ± 19.4	4.2 ± 4.2	20.5 ± 6.2	44.5 ± 16.5	< 0.001
D/Pcr	0.73 ± 0.16	0.76 ± 0.16	0.72 ± 0.17	0.70 ± 0.16	0.328
Prescriptions, n (%)					
RAS inhibitors	48 (96.0)	17 (100.0)	15 (88.2)	16 (100)	0.972
Calcium channel blockers	37 (74.0)	15 (88.2)	10 (58.8)	12 (75.0)	0.370
β blockers	23 (46.0)	11 (64.7)	6 (35.3)	6 (37.5)	0.113
Calcium-containing PBs	44 (88.0)	13 (76.5)	16 (94.1)	15 (93.8)	0.123
Non-calcium containing PBs	29 (58.0)	14 (82.4)	6 (35.3)	9 (56.3)	0.119
Iron preparations	11 (22.5)	7 (41.2)	2 (11.8)	2 (13.3)	0.054
Vitamin D	27 (54.0)	9 (52.9)	7 (41.2)	11 (68.8)	0.375
Cinacalcet hydrochloride	4 (8.0)	1 (5.9)	1 (5.9)	2 (12.5)	0.488

Values are expressed as mean ± standard deviation or number (percentage) as appropriate

Abbreviations: APD automated peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, Ccr creatinine clearance, CTR cardiothoracic ratio, CVD cardiovascular disease, DN diabetic nephropathy, D/Pcr dialysate-to-plasma creatinine ratio, ESA erythropoiesis-stimulating agent, HG high-glucose (2.5%), Kt/V urea clearance, PBs phosphate binders, RAS renin-angiotensin system, rCUC renal creatinine and urea clearance

shown in Tables 1 and 2, respectively. Total Kt/V, renal Kt/V, renal Ccr, urine volume, sodium, and chloride were significantly higher with greater mean rCUC, while the prevalence of diabetic nephropathy

(DN) and high-glucose dialysate users, peritoneal Kt/V, serum creatinine, brain natriuretic peptide (BNP), and β₂-microglobulin (BMG) were lower with greater mean rCUC.

Table 2 Laboratory data according to tertiles of mean rCUC

	Total (N = 50)	T1 (mean rCUC < 11.7 L/week/1.73m ²), n = 17	T2 (mean rCUC 11.8–29.8 L/week/1.73m ²), n = 17	T3 (mean rCUC ≥ 29.9 L/week/1.73m ²), n = 16	P for trend
Total protein, g/dL	6.4 ± 0.7	6.5 ± 0.6	6.2 ± 0.6	6.4 ± 0.7	0.539
Albumin, g/dL	3.5 ± 0.4	3.5 ± 0.4	3.4 ± 0.5	3.6 ± 0.4	0.270
Blood urea nitrogen, mg/dL	65 ± 13	63 ± 10	68 ± 17	67 ± 12	0.460
Creatinine, mg/dL	11.5 ± 3.0	13.1 ± 3.1	11.1 ± 2.3	10.1 ± 3.0	0.003
Uric acid, mg/dL	6.8 ± 1.1	6.7 ± 1.2	6.7 ± 1.0	6.9 ± 1.1	0.341
Sodium, mEq/L	136 ± 4	134 ± 3	137 ± 3	139 ± 2	< 0.001
Potassium, mEq/L	4.4 ± 0.6	4.4 ± 0.7	4.2 ± 0.6	4.7 ± 0.5	0.306
Chloride, mEq/L	98 ± 5	94 ± 3	98 ± 4	102 ± 4	< 0.001
Calcium, mg/dL	9.5 ± 0.4	9.5 ± 0.4	9.5 ± 0.5	9.5 ± 0.4	0.643
Phosphate, mg/dL	5.4 ± 1.2	5.4 ± 1.7	5.3 ± 0.7	5.4 ± 1.2	0.894
Glucose, mg/dL	108 ± 31	112 ± 35	105 ± 26	107 ± 34	0.408
Total cholesterol, mg/dL	182 ± 44	168 ± 33	195 ± 58	183 ± 37	0.355
Triglyceride, mg/dL	126 ± 73	126 ± 84	114 ± 53	138 ± 82	0.569
LDL-C, mg/dL	96 ± 27	85 ± 22	105 ± 26	100 ± 30	0.176
HDL-C, mg/dL	52 ± 18	53 ± 14	53 ± 22	52 ± 16	0.794
Hb, g/dL	10.2 ± 1.1	9.8 ± 1.0	10.0 ± 1.2	10.9 ± 0.7	< 0.001
C-reactive protein, mg/dL	0.08 (0.03–0.13)	0.07 (0.04–0.15)	0.08 (0.03–0.22)	0.06 (0.03–0.11)	0.631
Serum iron, µg/dL	87 ± 26	84 ± 26	87 ± 31	88 ± 22	0.735
TIBC, µg/dL	283 ± 34	301 ± 34	268 ± 37	281 ± 22	0.074
TSAT, %	30.7 ± 9.3	28.2 ± 8.8	32.2 ± 10.3	31.7 ± 8.7	0.213
Ferritin, ng/mL	130 (80–220)	108 (73–205)	216 (89–306)	113 (59–177)	0.643
Whole PTH, pg/mL	94 (55–151)	89 (55–128)	92 (37–173)	97 (52–163)	0.801
BNP, pg/mL	86 (37–298)	222 (67–468)	101 (34–433)	47 (20–116)	0.023
eEPO, U/mL	16.0 (13.6–25.1)	22.1 (13.9–24.9)	17.7 (13.9–24.3)	18.6 (14.0–23.7)	0.618
BMG, mg/L	23.2 (18.1–28.8)	28.6 (26.6–37.3)	22.8 (19.9–29.6)	17.6 (14.6–18.9)	< 0.001
HbA1c, %	5.4 ± 0.7	5.3 ± 0.8	5.5 ± 0.7	5.5 ± 0.8	0.128

Values are expressed as mean ± standard deviation or median (interquartile range) as appropriate

Abbreviations: *BMG* β₂-microglobulin, *BNP* brain natriuretic peptide, *eEPO* endogenous erythropoietin, *Hb* hemoglobin, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PTH* parathyroid hormone, *rCUC* renal creatinine and urea clearance, *TIBC* total iron binding capacity, *TSAT* transferrin saturation

The mean Hb levels were higher with greater mean rCUC (Table 2). This trend remained statistically significant [least square mean ± standard error: 9.7 ± 0.2, 10.2 ± 0.2, and 10.8 ± 0.2 in T1, T2, and T3, respectively; *P* for trend = 0.002] even after adjustment for model 1 (dialysis duration, current smoking habit, dose of ESA, log-transformed ferritin, log-transformed BNP, log-transformed eEPO, total Kt/V, and CTR) by analysis of covariance (Fig. 1).

Univariable regression analysis revealed that dialysis duration, current smoker, total Kt/V, renal Kt/V, renal Ccr, mean rCUC, and urine volume were positively associated and that log-transformed ferritin and log-transformed BNP were negatively associated with Hb levels. In the multivariable regression analysis, containing model 1 plus mean rCUC, dialysis duration and mean rCUC remained

significant (Table 3). We did not enter renal Kt/V, renal Ccr, and urine volume in the multivariable model because of their multicollinearity with mean rCUC (*r* = 0.919, 0.980, and -0.756) in the multivariable analysis.

To evaluate the impact of the mean rCUC on the accuracy of assessment, we compared the discriminatory abilities between model 1 (dialysis duration, current smoking habit, dose of ESA, log-transformed ferritin, log-transformed BNP, log-transformed eEPO, total Kt/V, and CTR) and the following models: model 1 plus mean rCUC, urine volume, renal Kt/V, renal Ccr, or log-transformed BMG. The c-statistic (95% confidential interval) for a Hb level < 10 g/dL was significantly greater in model 1 plus mean rCUC than model 1 [0.931 (0.789–0.980) vs. 0.856 (0.697–0.939), *P* = 0.044]. However, no significant increases in the c-statistic (95% confidential

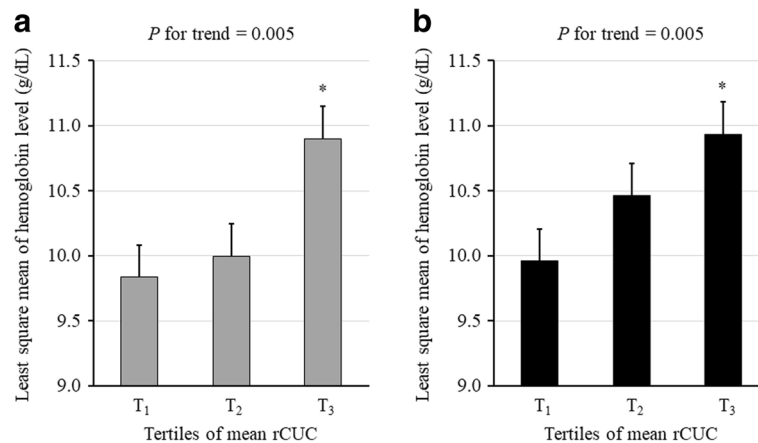


Fig. 1 Hb level according to the tertiles of mean rCUC. Least square means of Hb level according to the tertiles of mean rCUC in the univariable model (a) and the multivariable-adjusted regression model (b). A linear regression model was used to compare the least square mean among the tertile groups. * $P < 0.01$ vs. T1. Abbreviations: Hb hemoglobin, rCUC renal creatinine and urea clearance, T tertile

interval) were found in model 1 plus urine volume [0.906 (0.776–0.964), $P = 0.192$], renal Kt/V [0.924 (0.767–0.978), $P = 0.061$], renal Ccr [0.929 (0.795–0.978), $P = 0.058$], or log-transformed BMG [0.880 (0.738–0.950), $P = 0.491$] compared with model 1.

Discussion

The present study suggests that RKF represents an important correlate of Hb level in PD patients and that this correlation is independent of ESA dose and eEPO concentration. Therefore, the findings suggest that hematopoiesis-inhibiting uremic toxins, which are mainly removed by RKF, but not by PD, are a major cause of anemia in PD patients.

Ifudu et al. [16] reported an independent positive correlation between dialysis dose and hematocrit level when investigating the contribution of hematocrit in 135 HD patients receiving ESA. A comparison of 20 patients whose dialysis dose was increased with 20 patients with similar baseline characteristics whose dialysis dose was unaltered showed that the hematocrit level was significantly increased in the former group after 6 weeks, but remained unchanged in the latter group, demonstrating the importance of dialysis dose on anemia management. In a retrospective study by Matsuo et al. [17], in which 53 patients on PD monotherapy were moved to a combined regimen of HD + PD following a diagnosis of underdialysis and/or overhydration with declining RKF, a significant increase in Hb levels (from 8.2 to 10.7 g/dL) was found without an increase in ESA dose. The present study of PD monotherapy, however, found no evidence to suggest a significant correlation between dialysis dose (peritoneal Kt/V) and Hb level. We consider that this was because of the superior solute clearance of HD compared with PD. Evenepoel et al. [18] reported that high-flux HD delivered significantly higher clearance of all retention

solutes, especially BMG and p-cresol compared with peritoneal dialysis, although renal clearances, conversely, were significantly higher in patients in PD.

A significant association of total Kt/V, calculated by the addition of renal Kt/V to peritoneal Kt/V, with Hb level, was observed in the univariable regression analysis. However, the significant association was diminished in the multivariable regression analysis (Table 3). Furthermore, no association was found between peritoneal Kt/V and Hb level. According to these findings, maintaining RKF, but not an increase in dialysis dose, is important for the control of Hb levels in PD patients. Taken together, these findings show that standard PD is insufficient to eliminate factors influencing anemia, suggesting the presence of a hematopoiesis-inhibiting substance that is typically removed and eliminated by RKF, but not by PD.

The mechanism of the association between RKF and Hb remains to be elucidated. In the present study, log-transformed BMG was closely correlated with mean rCUC ($r = -0.736$, $P < 0.001$), suggesting the possibility of this factor as an important cause of low RKF-associated anemia. However, a significant association was not observed in the univariable regression analysis (Table 3) and also in the multivariable regression analysis when log-transformed BMG was entered instead of mean rCUC (Additional file 1: Table S1).

However, Pawlak et al. [19] described the contribution of quinolinic acid in the development of anemia in CKD patients. Quinolinic acid is an intermediate of the metabolic pathway responsible for the conversion of tryptophan into nicotinic acid and is an *N*-methyl-D-aspartate (NMDA) receptor agonist with putative neuroexcitatory and neurotoxic properties [20]. Another candidate for the potential contributing factor of anemia is indoxyl sulfate, a representative uremic toxin. Chiang et al. [21]

Table 3 Univariable and multivariable regression analysis for Hb levels

	Univariable		Multivariable		
	β -coefficient	<i>P</i>	β -coefficient	Standardized β	<i>P</i>
Male sex	-0.223	0.534			
Age, years	0.005	0.658			
Primary disease of kidney disease, DN	-0.383	0.254			
Dialysis duration, months	0.038	0.004	0.033	0.346	0.008
Body mass index, kg/m ²	-0.020	0.713			
Systolic blood pressure, mmHg	-0.014	0.199			
Diastolic blood pressure, mmHg	0.007	0.605			
Daily alcohol consumption	0.405	0.204			
Current smoker	0.927	0.020	0.240	0.170	0.211
Past histories of CVD	0.553	0.194			
History of peritonitis	-0.134	0.756			
CTR, %	-0.032	0.277	0.037	0.181	0.280
Dose of ESA, μ g/week	-0.002	0.823	0.001	0.010	0.943
Dialysis modality, APD	-0.078	0.805			
Use of icodextrin	0.319	0.435			
Use of HG dialysate	0.258	0.437			
Total Kt/V, /week	1.038	0.021	0.330	0.104	0.425
Renal Kt/V, /week	1.400	< 0.001			
Peritoneal Kt/V, /week	-0.501	0.232			
Renal Ccr, L/week, /week/1.73m ²	0.017	0.003			
Mean rCUC, L/week	0.024	0.002	0.018	0.321	0.045
Urine volume, L/day	0.630	0.009			
D/Pcr	-0.881	0.371			
Total protein, g/dL	0.322	0.183			
Albumin, g/dL	0.517	0.150			
Blood urea nitrogen, mg/dL	-0.020	0.103			
Creatinine, mg/dL	-0.092	0.077			
Uric acid, mg/dL	0.123	0.393			
Sodium, mEq/L	0.048	0.272			
Potassium, mEq/L	0.082	0.752			
Chloride, mEq/L	0.055	0.109			
Calcium, mg/dL	0.098	0.802			
Phosphate, mg/dL	-0.136	0.291			
Glucose, mg/dL	0.001	0.835			
Total cholesterol, mg/dL	-0.0001	0.969			
Triglyceride, mg/dL	0.003	0.209			
LDL-C, mg/dL	0.005	0.390			
HDL-C, mg/dL	-0.010	0.283			
Ln C-reactive protein, mg/dL	-0.123	0.329			
Serum iron, μ g/dL	-0.004	0.539			
TIBC, μ g/dL	-0.005	0.252			
TSAT, %	-0.004	0.813			

Table 3 Univariable and multivariable regression analysis for Hb levels (Continued)

Ln ferritin, ng/dL	-0.569	0.009	-0.276	-0.177	0.221
Ln whole PTH, pg/mL	-0.018	0.924			
Ln BNP, pg/mL	-0.216	0.021	-0.146	-0.220	0.233
Ln eEPO, U/mL	-0.042	0.897	-0.046	-0.021	0.884
Ln BMG, mg/L	-0.545	0.200			
HbA1c, %	0.098	0.649			
Use of RAS inhibitors	1.248	0.116			
Use of calcium channel blockers	-0.431	0.227			
Use of β blockers	-0.153	0.629			
Use of calcium-containing PBs	-0.135	0.780			
Use of non-calcium-containing PBs	-0.145	0.650			
Use of iron preparations	0.044	0.908			
Use of vitamin D	-0.108	0.733			
Use of cinacalcet hydrochloride	0.175	0.764			

Variables with a *P* value of <0.05 in the univariable analysis were included in addition to CTR, ESA dose, and log-transformed eEPO in the multivariable analyses. Renal Kt/V, renal Ccr, and urine volume were excluded from multivariable analysis because of their multicollinearity with mean rCUC. The values written in italic letter show significant association with Hb levels. A *P* value of <0.05 was considered statistically significant

Abbreviations: *APD* automated peritoneal dialysis, *BMG* β_2 -microglobulin, *BNP* brain natriuretic peptide, *CTR* cardiothoracic ratio, *Ccr* creatinine clearance, *DN* diabetic nephropathy, *D/Pcr* dialysate-to-plasma creatinine ratio, *eEPO* endogenous erythropoietin, *ESA* erythropoiesis-stimulating agent, *Hb* hemoglobin, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *HG* high-glucose (2.5%), *Kt/V* urea clearance, *LDL-C* low-density lipoprotein cholesterol, *Ln* log-transformed, *PBs* phosphate binders, *PTH* parathyroid hormone, *RAS* renin-angiotensin system, *rCUC* renal creatinine and urea clearance, *TIBC* total iron binding capacity, *TSAT* transferrin saturation

demonstrated that indoxyl sulfate treatment suppressed EPO mRNA expression and decreased the nuclear accumulation of hypoxia-inducible factor- α proteins and hypoxia-responsive element-luciferase activity following hypoxia. This suggested a potential connection between a uremic toxin and the desensitization of the oxygen-sensing mechanism in EPO-producing cells, which may explain anemia in CKD patients. However, these mechanisms are mediated by decreased eEPO production and do not explain the lack of a relationship between eEPO concentration and Hb levels observed in the present study.

More recently, two observational reports on anemia in PD patients have been published [22, 23]. Huang et al. [22] reported that serum indoxyl sulfate was negatively correlated with Hb level in 90 non-anuric PD patients but did not show the association of Kt/V and Hb levels. Meanwhile, Ryta et al. [23] reported the association of total Kt/V with Hb levels both in 2180 prevalent and 88 incident PD patients. However, this report unfortunately did not show the association of renal Kt/V and Hb level. The findings of the two reports are slightly different from the present study but support our speculation that accumulation of uremic toxins may be involved in anemia in PD patients.

While several studies have reported the role of iron metabolism, renin-angiotensin system inhibitors, BMG levels, serum albumin levels, parathyroid hormone, C-reactive protein, and other factors in anemia management

[24–26], we did not find any correlations of these factors in the present study.

Distribution of original disease was different among three tertiles; that is, prevalence of DN increased with a decrease in mean rCUC, although not significant. To date, there have been a few reports on the association between Hb levels and diabetes, in which diabetic patients were reported to require less ESA than non-diabetic patients [27], whereas no association was reported between diabetes and anemia [28]. In our study, no significant association was observed between DN and Hb levels in the univariable analysis, and the association between mean rCUC and Hb level was robust even when the variable “diabetic nephropathy” was added to the multivariable model. Thus, we consider that this bias would not affect this association.

This study had some limitations. It had a cross-sectional design, which limited the interpretation of the results with respect to cause and effect. Another limitation is the small number of subjects included in our study. Moreover, we could not identify the uremic toxin that might inhibit erythropoiesis or shorten the red blood cell life span. Nevertheless, there are some strengths in this study that eEPO concentration was measured and the involvement of eEPO concentration was examined in the association between RKF and Hb level. To the best of our knowledge, this study is the first report which focused on these associations.

Conclusion

The findings in the present study demonstrated that a decline in RKF is associated with a low Hb level independent of ESA dose and eEPO concentration. This suggests the existence of a uremic toxin as an inducer of anemia, which is probably eliminated mainly by RKF, but not by PD. Further research is needed to clarify the specific mechanism responsible for anemia in PD patients.

Additional file

Additional file 1: Table S1. Univariable and multivariable regression analysis for Hb levels. (DOCX 33 kb)

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Availability of data and materials

Data share is not allowed by our institutional review board.

Authors' contributions

KaT and KuT contributed to the research idea and study design. KaT, KuT, HY, SY, ST, AT, ME, KF, and KM carried out the data acquisition. KuT and HY participated in the data cleaning. KaT and KuT interpreted the data. KaT and HY participated in the statistical analysis. TK carried out the supervision. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KaT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (approval number of the Ethics Committee of Kyushu University Hospital: 26-223) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is a subanalysis of our multicenter cohort study (Fukuoka Peritoneal Dialysis Database Study), which was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN00018902).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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