EVALUATING HYPONATREMIA IN NON-DIABETIC UREMIC PATIENTS ON PERITONEAL DIALYSIS

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◆ **Background:** An approach to hyponatremia in uremic patients on peritoneal dialysis (PD) necessitates the assessment of intracellular fluid volume (ICV) and extracellular volume (ECV). The aim of the study was to evaluate the association of plasma sodium (Na⁺) concentration and body fluid composition and identify the causes of hyponatremia in non-diabetic PD patients.

◆ **Methods:** Sixty non-diabetic uremic patients on PD were enrolled. Baseline body fluid composition, biochemistry, hand-grip test, peritoneal membrane characteristics, dialysis adequacy, Na⁺ and water balance, and residual renal function (RRF) were measured. These parameters were reevaluated for those who developed hyponatremia, defined as serum Na⁺ concentration < 132 mmol/L and a decline in serum Na⁺ > 7 mmol/L, during monthly visits for 1 year. Body fluid composition was determined by multi-frequency bioelectrical impedance (BIA).

◆ **Results:** There was no significant correlation between serum Na⁺ concentrations and any other parameters except a negative correction with overnight ultrafiltration (UF) amount ($p = 0.02$). The ICV/ECV ratio was positively correlated with serum albumin ($p < 0.005$) and hand grip strength ($p < 0.05$). Over 1 year, 9 patients (M:F = 3:6, aged 35 – 77) with 4 different etiologies of hyponatremia were identified. Hyponatremic patients with a body weight (BW) loss had either an increased ICV/ECV ratio associated with primarily a negative Na⁺ balance ($n = 2$) or a reduced ratio of ICV/ECV associated with malnutrition ($n = 2$). In contrast, hyponatremic patients with a BW gain had either a reduced ICV/ECV ratio associated with a rapid loss of RRF and a higher peritoneal permeability ($n = 2$) or a normal to increased ICV/ECV ratio associated with high water intake ($n = 3$).

◆ **Conclusion:** Besides BW change and ultrafiltration rate, the assessment of ICV/ECV ratio is valuable in identifying the etiologies of hyponatremia in PD and provides a guide for optimal therapy.

KEY WORDS: Bio-impedance; peritoneal dialysis; hyponatremia; non-diabetes; nutrition; residual renal function.

Hyponatremia is the most common electrolyte disorder in hospitalized patients and has been shown to have substantial impacts on morbidity and mortality (1). To develop hyponatremia, there must be a positive balance for electrolyte-free water (EFW) and/or a negative balance for total body major cations, sodium (Na⁺) and potassium (K⁺). The positive EFW balance could come from either a large input of free water or a lower than expected excretion rate of water. In patients with normal renal function or mild renal insufficiency, the reduced water clearance depends primarily on the action of anti-diuretic hormone (ADH) (2). In advanced renal failure, however, ADH has a negligible effect on reducing the excretion rate of water and a net gain of EFW is suggested as being primarily responsible for the development of hyponatremia (3). Therefore, hyponatremia is rarely investigated in uremic patients on maintenance dialysis, especially on peritoneal dialysis (PD).

Discovering the underlying causes of hyponatremia is challenging in PD patients. Several factors affecting the total body water (TBW) and Na⁺ homeostasis perplex the diagnosis and treatment of hyponatremia in PD patients, including dietary water and salt intake, residual renal function (RRF), and the convection and diffusion of water and Na⁺ across the peritoneal membrane under the treatment of PD (4). Since water distribution across the cell membrane largely relies on the intracellular and extracellular effective osmoles, the assessment of extracellular volume (ECV) and intracellular volume (ICV) theoretically helps diagnose underlying etiologies of hyponatremia in PD patients (5). In clinical practice, however, it is difficult to determine ECV and ICV in PD patients, and physicians need a simple, rapid, reliable, and effective bedside tool for hyponatremic PD patients. Multi-frequency bioelectrical impedance analysis (BIA), increasingly used to assess body fluid distribution in the general population, has been validated as a reliable test in PD patients (6–9). In this study, we investigated the association between serum Na⁺

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concentration and pertinent parameters with the aid of BIA in a cross-sectional analysis and prospectively identified different causes of hyponatremia in PD patients.

PATIENTS AND METHODS

PATIENTS

The study protocol was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital, National Defense Medical Center, in Taiwan, R.O.C. The selection of eligible patients on PD is shown in a flow diagram (Figure 1). Sixty non-diabetic uremic patients undergoing PD with standard glucose solutions for more than 3 months were enrolled in this study. Patients on automated PD or icodextrin dialysis were excluded, as were patients with acute illness requiring admission. There were 26 men and 34 women aged 19 to 77 years (47.2 ± 13.6 years). Duration of PD treatment ranged from 3 to 146 months (mean 24.4 ± 26.6 months). Causes of renal failure were chronic glomerulonephritis in 30 patients, hypertensive nephropathy in 16 patients, chronic interstitial nephropathy in 20 patients, Chinese herb nephropathy in 13 patients, obstructive nephropathy in 1 patient, and idiopathic nephropathy in 10 patients.

All patients used 3 – 5 exchanges daily with 1.5-L or 2-L exchange volume of Baxter dialysate (Baxter Healthcare Corporation, Deerfield, IL, USA) containing 1.5%, 2.5%, or 4.25% dextrose. Dialysate Na^+ concentration was 132 mmol/L. All patients continued their regular medications, such as anti-hypertensives, erythropoietin, phosphate binders, and lipid-lowering agents. Twenty-eight patients were on anti-hypertensive agents, including 12 calcium channel blockers, 10 β -adrenergic blockers, 16 angiotensin-converting enzyme inhibitors, 10 angiotensin-II receptor blockers, 2 α -adrenergic blockers, and 6 furosemide. Baseline body fluid composition, nutritional status, biochemical parameters, peritoneal

membrane characteristics, dialysis adequacy, RRF, Na^+ , and water balance were measured at the beginning of the study. These patients then received monthly outpatient follow-up with regular general plasma biochemical checkup for 1 year. The endpoint of our study was the development of new onset hyponatremia defined as serum Na^+ concentration < 132 mmol/L and a decline in serum $\text{Na}^+ > 7$ mmol/L compared with the previous month. To avoid laboratory error or mild day-to-day variation, every report of hyponatremia in these PD patients was rechecked. For those with new onset hyponatremia, the above-mentioned parameters were re-collected for analysis. Sixty healthy subjects with matching age, gender, and body mass index (BMI) were also evaluated using BIA for comparison.

METHODS

Assessment of Body Fluid Status and Other Composition:

Body fluid composition was measured using BIA (Inbody 3.0, Biospace Co. Ltd., USA), through 8 tactile electrodes under upright posture. Bioelectrical impedance analysis was performed with an “empty” abdomen (no dialysate in abdominal cavity) in the fasting state and after urination. With the patient standing on the sole electrodes and gripping the hand electrodes, the microprocessor-controlled switches and impedance analyzer were started and segmental resistances of right arm, left arm, trunk, right leg, and left leg were measured with 50 logarithmic frequency from 5 to 500 kHz. Total body water, ICV, ECV, lean body mass, and body fat weight using equations in the BIA software were measured. Mean values of 2 measurements were used for data analysis. To analyze the reproducibility of the study, BIA was performed 5 times at intervals of 3 minutes in 10 continuous ambulatory PD patients. The mean standard deviation and coefficient of variation of each set of readings were 0.11 and 0.28%.

Nutritional Status: Multiple markers to identify malnutrition in this study included serum albumin < 38 g/L, serum phosphate < 1.13 mmol/L, serum $\text{K}^+ < 3.5$ mmol/L, a reduced lean body mass ($> 5\%$), and diminished skeletal muscle function ($> 15\%$ reduction of hand grip strength) (10). Anthropometric measurements included height, weight, and BMI. Skeletal muscle function was estimated by means of handgrip strength using a handgrip dynamometer (Jamar, Sammons, Preston, Bolingbrook, IL, USA). Left and right handgrip strengths were averaged.

Biochemical Parameters: Fasting blood samples obtained for the analysis of serum electrolytes, creatinine, urea, total cholesterol, albumin, and total protein were measured by standard laboratory techniques with an automatic analyzer (AU 5000 chemistry analyzer, Olympus, Tokyo, Japan). Serum albumin concentration was determined by bromocresol green method (normal range 38 to 53 g/L). C-reactive protein (CRP) was measured using the Tina-quant (Latex) ultrasensitive assay (Roche Diagnostics GmbH, Mannheim, Germany).

Figure 1 — Flow diagram of assessment for eligibility. BIA = bioelectrical impedance analysis; Na^+ = plasma sodium.

Membrane Transport Status: The transport characteristics of the peritoneal membrane were sorted by using a standard peritoneal equilibration test (PET) as described by Twardowski *et al.* (11). Patients were classified as a high transporter when the ratio of dialysate/plasma (D/P) creatinine at the fourth hour was higher than the mean value plus 1 standard deviation, and as a low transporter when the D/P creatinine ratio was lower than the mean value minus 1 standard deviation.

Dialysis Adequacy: Dialysis adequacy was evaluated using weekly total solute removal. Small-solute clearance was measured by means of total Kt/V urea as the sum of peritoneal Kt/V and renal Kt/V as well as weekly creatinine clearance (WCC).

Residual Renal Function: Residual renal function was measured using mean urea and creatinine clearance.

Water and Na⁺ Balance: The water and Na⁺ balances were obtained by calculating the difference between total water intake and total water removal and the difference between total Na⁺ intake and total Na⁺ removal, respectively. Water and Na⁺ intake were assessed by a well-trained dietitian. Total water removal was estimated as the sum of daily urine volume and daily ultrafiltration (UF). Total Na⁺ removal was estimated as the sum of daily urine Na⁺ excretion and daily dialytic Na⁺. The daily dialytic Na⁺ removal was calculated as follows: $(V_{dr} \times C_{dr}) - (V_{in} \times C_{in})$, where V_{dr} represents the volume of the drained dialysate (L/24 hours), C_{dr} the Na⁺ concentration of the drained dialysate (mmol/L), V_{in} the volume of the instilled dialysate (L/24 hours), and C_{in} the Na⁺ concentration of the instilled dialysate (mmol/L). The daily urine Na⁺ excretion was calculated as follows: $U_{Na} \times V$, where U_{Na} represents urine Na⁺ concentration (mmol/L) and V denotes daily urine volume (L/24 hours). The average of daily water and Na⁺ balance obtained from each patient on PD was calculated.

STATISTICAL ANALYSIS

Data were expressed as mean $\pm$ standard deviation. Paired *t*-test was used for analysis of follow-up data. Pearson's linear correlation coefficients were calculated to evaluate the association between serum Na⁺ concentration and body fluid composition (TBW, ICV, and ECV). A *p* value < 0.05 was considered significant.

RESULTS

PATIENTS' CHARACTERISTICS

The characteristics of the patients on PD and the normal healthy controls are shown in Table 1. The ratio of ECV/TBW was significantly higher in patients on PD than the healthy controls despite similar BMI and body weight (BW). In patients on PD, the mean serum Na⁺ concentrations were 139.3 ± 3.0 mmol/L, ranging from 132 to 145 mmol/L. Their BW was 57.2 ± 10.8 kg, TBW 30.5 ± 6.1 L, ICV 20.2 ± 3.9 L, and ECV

10.3 ± 2.1 L. The ICV/ECV and ECV/TBW ratios were 1.97 ± 0.02 and 0.33 ± 0.03 , respectively. The mean D/P creatinine ratio was 0.64 ± 0.11 . The PD was adequate with Kt/V 2.3 ± 0.4 and WCC 71.2 ± 20.9 L/week/1.73 m². Residual renal function was 2.4 ± 1.5 mL/min. Their estimated daily water intake and total (dialysate/renal) fluid removal was 1.7 ± 0.4 and 1.5 ± 0.4 , respectively. Their estimated daily Na⁺ intake and calculated total Na⁺ removal were 104 ± 18 and 122 ± 21 mmol/day, respectively.

TABLE 1
Baseline Characteristics in Patients on PD and Healthy Controls

	PD patients (n = 60)	Healthy controls (n = 60)
Demographic data		
Age (years)	47.2 $\pm$ 13.6	48.7 $\pm$ 11.7
Gender (male/female)	26/34	26/34
SBP (mmHg)	141 $\pm$ 21 ^a	118 $\pm$ 12
DBP (mmHg)	88 $\pm$ 14 ^a	78 $\pm$ 9
Biochemical parameters		
Na ⁺ (mmol/L)	139.3 $\pm$ 3.0 ^a	142.1 $\pm$ 1.8
K ⁺ (mmol/L)	4.4 $\pm$ 0.8	4.2 $\pm$ 0.2
Phosphate (mmol/L)	1.71 $\pm$ 0.48 ^a	1.18 $\pm$ 0.05
Urea nitrogen (mmol/L)	26.1 $\pm$ 6.8 ^a	4.7 $\pm$ 1.0
Creatinine (μ mol/L)	1,052 $\pm$ 309 ^a	69 $\pm$ 9
Albumin (g/L)	38 $\pm$ 4 ^a	43 $\pm$ 2
CRP (mg/dL)	0.32 $\pm$ 0.1 ^a	0.12 $\pm$ 0.02
Body fluid composition		
BW (kg)	57.2 $\pm$ 10.8	58.1 $\pm$ 7.4
BMI	22.9 $\pm$ 2.01	22.2 $\pm$ 1.97
TBW (kg)	30.5 $\pm$ 6.1	30.8 $\pm$ 1.9
ICV (kg)	20.2 $\pm$ 3.9	21.0 $\pm$ 2.7
ECV (kg)	10.3 $\pm$ 2.1	9.8 $\pm$ 1.7
ECV/TBW	0.33 $\pm$ 0.03 ^b	0.32 $\pm$ 0.01
ICV/ECV	1.97 $\pm$ 0.02 ^a	2.14 $\pm$ 0.01
Hand-grip test (kg)	32 $\pm$ 2.8	—
Membrane transport (D/P Cr)	0.64 $\pm$ 0.11	—
Adequacy of dialysis		
Kt/V	2.3 $\pm$ 0.4	—
WCC (L/week/1.73 m ²)	71.2 $\pm$ 20.9	—
RRF (mL/min/1.73 m ²)	2.4 $\pm$ 1.5	—
Na ⁺ /H ₂ O balance		
Water intake (L)	1.7 $\pm$ 0.4	—
Water output (L)	1.5 $\pm$ 0.4	—
Na ⁺ intake (mmol/day)	104 $\pm$ 18	—
Na ⁺ output (mmol/day)	122 $\pm$ 21	—

PD = peritoneal dialysis; SBP = systolic blood pressure; DBP = diastolic blood pressure; Na⁺ = plasma sodium; K⁺ = plasma potassium; CRP = C-reactive protein; BW = body weight; BMI = body mass index; TBW = total body water; ICV = intracellular cell volume; ECV = extracellular volume; D/P Cr = dialysate-to-plasma ratio of creatinine; WCC = weekly creatinine clearance; RRF = residual renal function.

^a *p* < 0.001

^b *p* < 0.01

CORRELATION BETWEEN CLINICAL AND BIOCHEMICAL PARAMETERS

There was no significant correlation between serum Na⁺ concentrations and body fluid composition including TBW, ICV, ECV, ICV/ECV, and ECV/TBW ratio as well as hand-grip strength, Kt/V, and RRF. A statistical trend was present in the relationship between serum Na⁺ and D/P creatinine ($p=0.06$). There was also a significant correlation between serum Na⁺ concentration and overnight UF amount ($r=-0.27$, $p=0.02$). The ICV/ECV ratio was found to be positively correlated with serum albumin ($p<0.001$) and hand-grip strength ($p<0.001$) (Figure 2). There was also a significant correlation between net daily dialysate volume removed and net daily PD Na⁺ removal ($r=0.71$, $p<0.001$).

IDENTIFICATION OF HYPONATREMIA

Over a 1-year follow-up, hyponatremia was identified in 9 out of the 60 PD patients (M:F=3:6, aged 37–77). Serum Na⁺ levels decreased from 138.3 ± 1.6 mmol/L at baseline to 129.1 ± 1.2 mmol/L ($p<0.001$). The time to develop hyponatremia ranged from 3 to 10 months. The patients' characteristics are shown in Table 2. An analysis of body water distribution, PD characteristics, and laboratory features, allowed the PD patients with hyponatremia to be divided into 2 groups: those with BW loss and those with BW gain. Each group could be further divided into 2 subgroups with different etiologies (Tables 3–5, Figure 3).

Patients with BW Loss: Four hyponatremic patients with BW loss could be divided into 2 subgroups according to different ICV/ECV ratios. Two patients with increased ICV/ECV ratio

(a)

(b)

Figure 2 — A positive correlation between the ratio of ICV to ECV and serum albumin concentrations (a) and hand-grip muscle strength (b). ICV = intracellular volume; ECV = extracellular volume.

TABLE 2
Clinical Characteristics of PD Patients who Developed Hyponatremia

	A	B	C	D	E	F	G	H	I
Gender	F	F	M	F	F	M	M	F	F
Age	40	51	77	68	38	37	54	53	57
BMI	21.9	24.1	20.1	23.8	21.2	22.4	23.8	23.7	18.1
Etiology of ESRD	CGN	CGN	CTIN	HN	FSGS	LN	CGN	CGN	CGN
Length of PD (months)	5	19	21	9	5	7	31	22	27
Time to develop hyponatremia (months)	4	7	8	10	4	3	6	4	8
History of hypertension	+	+	—	+	+	+	+	+	—
Diuretics	—	+	—	+	+	+	—	+	—
Lipid-lowering agents	—	—	—	—	+	—	—	+	+
Episodes of peritonitis	—	—	+	+	—	—	—	—	—
PD exchanges/day	4	4	4	4	5	5	4	4	5
Edema	—	—	+	+	+	+	—	—	—
Pre-BP (mmHg)	130/80	150/96	140/80	160/90	160/100	150/94	140/90	150/92	126/76
Post-BP (mmHg)	90/50	100/60	130/70	136/80	180/110	170/98	50/94	160/90	130/80

PD = peritoneal dialysis; BMI = body mass index; ESRD = end-stage renal disease; CGN = chronic glomerulonephritis; CTIN = chronic tubulointerstitial nephritis; HN = hypertensive nephrosclerosis; FSGS = focal segmental glomerulosclerosis; LN = lupus nephritis; BP = blood pressure.

TABLE 3
Changes in Body Fluid Composition in PD Patients with Hyponatremia

	Na ⁺ (mmol/L)		BW (kg)		TBW (kg)		ICV (kg)		ECV (kg)		ICV / ECV		ECV / TBW	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Type I Hyponatremia														
A	138	130	56.7	53.0	30.1	28.5	20.4	19.7	9.7	8.8	2.10	2.24	0.32	0.31
B	137	129	61.5	58.7	34.5	30.9	23.1	21.3	11.4	9.6	2.03	2.25	0.33	0.31
Type II Hyponatremia														
C	140	127	54.3	50.9	31.9	29.6	20.5	18.3	11.4	11.3	1.80	1.62	0.36	0.38
D	139	129	57.7	54.4	31.1	29.8	20.2	18.6	10.9	11.2	1.85	1.66	0.35	0.38
Type III Hyponatremia														
E	141	131	53.5	55	34.1	35.3	22.2	22.6	11.8	12.6	1.88	1.79	0.34	0.35
F	137	129	58.2	59.8	36.4	37.9	24.0	26.5	12.4	13.4	1.93	1.83	0.34	0.35
Type IV Hyponatremia														
G	136	128	64.4	68.7	38.9	41.6	26.1	27.5	12.8	14.1	2.04	1.95	0.33	0.34
H	138	129	59.1	61.1	31.9	32.3	21.3	21.5	10.6	10.8	2.0	1.99	0.33	0.33
I	139	130	46.2	50.5	23.7	27.9	15.7	18.5	8.0	9.4	1.96	1.97	0.34	0.34

PD = peritoneal dialysis; Na⁺ = plasma sodium; BW = body weight; TBW = total body water; ICV = intracellular cell volume; ECV = extracellular volume.

TABLE 4
Changes in Dialysis Adequacy and Nutritional Parameters in PD Patients with Hyponatremia

	WCC (L/week/1.73 m ²)		Kt/V		HGT (kg)		Alb (g/L)		K ⁺ (mmol/L)		InP (mmol/L)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Type I Hyponatremia												
A	67	49	2.34	2.19	31	34	39	41	4.7	3.8	2.58	2.30
B	42	48	1.76	2.29	36	34	36	38	4.8	4.4	1.87	1.91
Type II Hyponatremia												
C	66	59	2.14	1.97	28	18	39	31	4.7	3.4	1.55	0.78
D	71	65	2.33	2.17	23	16	37	30	4.1	3.2	1.62	1.00
Type III Hyponatremia												
E	57	50	1.83	1.75	30	22	34	30	6.0	4.0	1.87	2.55
F	66	66	1.86	1.77	32	19	30	29	4.2	4.1	2.10	2.33
Type IV Hyponatremia												
G	57	53	1.92	1.80	43	42	37	36	4.4	4.5	1.52	1.62
H	61	59	2.20	2.37	35	38	41	40	5.2	4.1	1.68	1.68
I	58	53	2.23	2.07	28	32	39	37	4.9	5.0	1.74	1.58

PD = peritoneal dialysis; WCC = weekly creatinine clearance; HGT = hand-grip test; Alb = albumin; InP = inorganic phosphate.

(mean 2.07 – 2.25) had a significant decline in ECV (mean 10.6 – 9.2 L) and ECV/TBW (mean 0.33 – 0.31). Both had a relatively low peritoneal membrane transport (mean D/P creatinine ratio 0.52) associated with a higher total Na⁺ removal (mean 145 – 187 mmol/day) and a lower blood pressure (SBP 140 – 95 mmHg). We called this subgroup type I hyponatremia. Another 2 patients with BW loss, designated as type II hyponatremia, were found to have a reduced ICV/ECV ratio (mean 1.83 – 1.64). They had a predominantly low ICV (mean 20.4 – 18.5 L), relatively normal to increased ECV (mean 11.2 – 11.3 L), and an increased ECV/TBW ratio (0.36 – 0.38). They showed clinical evidence of malnutrition such as a decrease in lean body mass (mean 39.1 – 37.0 kg), a reduction in hand-grip

strength (mean 26 – 17 kg), hypoalbuminemia (albumin 38 – 31 g/L), hypophosphatemia (1.59 – 0.89 mmol/L), and hypokalemia (4.4 – 3.3 mmol/L). Both patients had experienced bacterial peritonitis, 2 and 5 days respectively, prior to the development of hyponatremia.

Patients with BW Gain: Based on the ICV/ECV ratio, we divided the 5 hyponatremic PD patients with increased BW into 2 groups. Two patients, defined as type III hyponatremia, with decreased ICV/ECV ratio (mean 1.91 – 1.81) had a predominantly increased ECV (mean 12.1 – 13.0 L). In contrast to our other hyponatremic PD patients, both patients had a relatively high baseline peritoneal membrane transport, which became

TABLE 5
Changes in Total Sodium and Water Removal, Residual Renal Function, and Membrane Permeability in PD Patients with Hyponatremia

	Total Na ⁺ Removal (mmol/L)		Total Water Removal (mL)		RRF (mL/min/1.73 m ²)		D/P Cr	
	Before	After	Before	After	Before	After	Before	After
Type I Hyponatremia								
A	170	196	2,200	2,350	1.20	0	0.48	0.48
B	120	178	1,400	1,800	0.12	0.14	0.64	0.55
Type II Hyponatremia								
C	137	128	1,340	1,400	0.80	0.20	0.57	0.61
D	149	130	1,620	1,500	2.10	0.50	0.53	0.59
Type III Hyponatremia								
E	96	88	1,500	1,100	1.60	0	0.74	0.79
F	149	120	1,600	1,300	1.63	0.56	0.75	0.89
Type IV Hyponatremia								
G	116	139	1,970	2,210	1.36	0.94	0.56	0.54
H	129	168	1,800	2,100	2.06	1.74	0.54	0.50
I	133	136	1,500	1,700	0	0	0.60	0.55

PD = peritoneal dialysis; Na⁺ = plasma sodium; RRF = residual renal function; D/P Cr = dialysate-to-plasma ratio of creatinine.

Figure 3 — Algorithm to approach the hyponatremia in non-diabetic PD patients. PD = peritoneal dialysis; ICV/ECV = ratio of intravascular volume to extracellular volume; Na⁺ = plasma sodium; K⁺ = plasma potassium; NaCl = sodium chloride; KCl = potassium chloride.

even higher during the 1-year follow-up (D/P creatinine ratio 0.75 – 0.84), and a rapid loss of RRF (1.62 – 0.28 mL/min). They also had a tendency to display inadequate dialysis, with decreasing Kt/V (mean 1.85 – 1.76) and WCC (mean 62 – 58 L/week) along with a lower total water (1,550 – 1,200 mL/day)

and Na⁺ removal (123 – 104 mmol/day) even though PD dosage was increased to 5 exchanges of 2-L dialysate. Their blood pressure obviously rose (155 – 175 mmHg) with difficulty in controlling it despite using multiple anti-hypertensive medications. Another 3 patients (type IV hyponatremia) had increased

ICV (21.0 – 22.5 L) and ECV (mean 10.5 – 11.4 kg), but a relatively unchanged ratio of ICV/ECV (mean 2.0 – 1.97) and ECV/TBW (0.33 – 0.34). In contrast to type III hyponatremia, the D/P creatinine ratios in type IV patients were relatively low (0.53) but their average daily removal of water (2,000 mL) and Na⁺ (148 mmol) were prominently higher. They were also found to have a higher daily water intake, approximately 2.5 L to 3.0 L.

DISCUSSION

In this study, we searched for parameters that could be helpful in the differential diagnosis of hyponatremia in PD patients. There was no significant correlation between serum Na⁺ concentration and any single parameter of body composition and nutrition. This finding points to the fact that hyponatremia cannot be considered simply as a marker of volume and nutrition states in non-diabetic PD patients because of the complex relationship between Na⁺ homeostasis and body fluid regulation. Based on BW change and ICV/ECV ratio, we did, however, identify 4 different types of hyponatremia over a 1-year follow-up period (see below).

In PD patients, BW change is an important clue for the differential diagnosis of hyponatremia. Without a change in lean body and fat mass, BW loss during the development of hyponatremia reflects TBW loss. However, isolated loss of TBW would not cause hyponatremia unless there is a concomitant loss of extracellular Na⁺, evidenced by contracted ECV (12,13). Without additional Na⁺ and water loss via the gastrointestinal tract, the kidney and PD may be the major routes of Na⁺ and water loss. Since RRF is usually very low in PD patients, urine Na⁺ and water loss may not be large enough to be the sole mechanism of hyponatremia (14). The amount of Na⁺ and water loss during PD should be proportional to the amount of UF, confirmed by our findings of a significant correlation between the net daily removal of fluid and Na⁺ (2,3,15). Two of our patients with hyponatremia were characterized by BW loss and increased ICV/ECV ratio (type I hyponatremia). They did have higher daily UF and dialytic Na⁺ loss associated with negative Na⁺ balances, likely resulting from the low peritoneal membrane transport status. Mass balance of Na⁺ also depends on Na⁺ intake, and strong self-control in dietary Na⁺ intake may aggravate the negative Na⁺ balance.

Two of our patients had hyponatremia with decreased BW but a decreased ICV/ECV ratio, accompanied by the presence of malnutrition. Without contracted ECV, their low ICV/ECV ratio was indicative of reduced ICV. Cell volume is maintained by intracellular effective osmoles (primarily K⁺ and phosphate) (16). Without hyperglycemia or mannitol therapy in our patients, a loss of intracellular effective osmoles should account for reduced ICV (17). In malnourished patients with low protein intake, intracellular K⁺ and phosphate will be lost concomitantly to be electroneutral, producing a primary deficit of K⁺ and phosphate (18). Reduced intracellular tonicity will cause intracellular water shifting to extracellular components,

subsequently diluting extracellular osmoles, mainly Na⁺. As anticipated, our patients with this type II hyponatremia had hypokalemia and hypophosphatemia, suggestive of a deficit of K⁺ and phosphate due to malnutrition or hypercatabolic status. Therefore, PD patients with hyponatremia and an unexpected decrease of ICV or ICV/ECV ratio may point to malnutrition. In fact, both of them had preceding peritonitis with hypercatabolism and protein loss prior to hyponatremia. The significant positive correlation between ICV/ECV ratio and serum albumin and hand-grip strength in this study further suggested that reduced ICV/ECV ratio may be a good indicator of protein malnutrition.

Rather than negative Na⁺ balance, positive water balance should be considered as a primary mechanism of hyponatremia in PD patients having BW gain without an increase of lean body mass. Patients on PD are prone to having a positive water balance due to either excessive water intake or inadequate UF (19). Two patients with type III hyponatremia were found to have higher peritoneal membrane transport (D/P creatinine 0.8 and 0.9, respectively) and lower daily water removal. High peritoneal transport not only reduces UF but allows glucose uptake from dialysate (20). Furthermore, Na⁺ removal in high peritoneal transport status may become lower (21). Inadequate UF would lower water clearance and subsequently directly cause EFW accumulation, which distributes to ICV and ECV based on tonicity balance. However, increased plasma osmoles (glucose from dialysate and Na⁺ from decreased clearance) leads to dominant ECV expansion, which would cause a reduced ICV/ECV ratio, poorer hypertension control, and edema. Rapid loss of RRF was also noted in those patients. Residual renal function is a well-established determinant of survival rate in PD patients (22–24). Previous studies have shown that PD patients with higher peritoneal membrane permeability had quicker loss of RRF, lower serum albumin, and higher cardiovascular morbidity and mortality (25,26).

Another 3 PD patients with type IV hyponatremia were found to have BW gain without obvious change in ICV/ECV ratio. It was suspected that excessive EFW intake was responsible for the pathogenesis of their hyponatremia. Without additional solute gain or loss, EFW gain will be distributed to both ECV and ICV in proportion to their size (one-third to the ECV and two-thirds to the ICV component) and consequently result in a stable ICV/ECV ratio. Unlike the patients with high peritoneal transport (type III hyponatremia), there was no edema or difficulty in blood pressure control among our PD patients with type IV hyponatremia. Of note, those patients with type IV hyponatremia had higher RRF. We also found a significant negative correlation between serum Na⁺ concentration and overnight UF amount. Higher total water removal through either better RRF or larger UF amount might make the 3 patients feel freer to drink water (27). In addition, the greater dialysate removal of water will be associated with more Na⁺ removal. If dietary Na⁺ remains constant in type IV patients, negative Na⁺ balance may not develop.

If hyponatremia is present without an appreciable change in BW, a pure loss of Na⁺ and/or K⁺ salts with no change in TBW

may be the primary mechanism, which was not identified in this study (type V hyponatremia) (28).

The therapeutic approach to hyponatremia in PD patients should be guided by an understanding of the underlying etiology of the hyponatremia. For type I hyponatremia associated with excessive Na^+ and water loss via UF, the goal of therapy is to keep a high Na^+ intake or increase PD dialysate Na^+ concentration. For type II hyponatremia secondary to protein-calorie malnutrition, aggressive nutritional support, correction of hypokalemia, and control of underlying infection or inflammation are more important than correction of hyponatremia (29). For type III hyponatremia due to a high peritoneal membrane transporter and low UF rate, modification of dialysis modality is the cornerstone of management because this type of hyponatremia is an epiphenomenon. Icodextrin-based dialysate could be the dialysate of choice if PD is continued (30). Switching to hemodialysis or renal transplantation may be the management of choice if PD is discontinued. For type IV hyponatremia due to high water intake, the target therapy is to reduce water intake rather than increase dialysate water removal. Because dialysate Na^+ removal is accompanied by increased dialysate water removal, recurrent hyponatremia will develop if the Na^+ intake is not increased simultaneously. For type V hyponatremia, only sodium chloride (NaCl) or potassium chloride (KCl) supplement is needed.

This study has some limitations. First, there are day-to-day and time-sensitive variations in serum Na^+ concentration, especially in the non-fasting state. However, in this study, serum Na^+ concentration was obtained in the fasting state. Hyponatremia was reconfirmed when serum Na^+ was < 132 mmol/L. Second, we did not evaluate the cause of hyponatremia when the serum Na^+ concentration was > 132 mmol/L. Third, the technical variability of BIA at different time periods may limit the accuracy of ICV and ECV. Fourth, we could not compare the difference between those who developed hyponatremia and those who did not develop hyponatremia.

In conclusion, many factors influence the development of hyponatremia in people undergoing PD. The ICV/ECV ratio, a composite index reflecting extracellular volume and nutritional status, is associated with different causes of hyponatremia in non-diabetic PD patients. The use of ICV/ECV ratio seemed to be helpful in distinguishing the different subgroups. A diagnostic approach to hyponatremia in non-diabetic PD patients is provided (Figure 3). The therapeutic approach to hyponatremia in PD patients should be guided by the underlying etiology of the hyponatremia.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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