Hemodynamic and Biochemical Benefits of the Objective Measurement of Fluid Status in Hemodialysis Patients

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Subtle fluid imbalance can cause poor clinical outcomes among hemodialysis patients. However, the traditional subjective assessment of fluid status may be inadequate. We evaluated whether the objective measurement and optimization of fluid status could be beneficial for hemodynamic and biochemical parameters in hemodialysis patients. We enrolled 120 hemodialysis patients, who were clinically euvolemic for at least 3 months. Based on the results of a body composition monitor, we divided the patients into the following two groups: the hyperhydrated group (post hemodialysis fluid overload ≥ 1.1 L) and the dehydrated group (post hemodialysis fluid overload < -1.1 L). We reduced the patient's body weight in the hyperhydrated group and raised the body weight in the dehydrated group towards normohydration (-1.1 L $\leq$ fluid overload < 1.1 L) for 16 weeks. Forty-four of 120 patients were in the hyperhydrated group, and 18 of 120 patients in the dehydrated group. After 16 weeks, systolic blood pressure and pulse pressure decreased in the hyperhydrated group, while there was no increase in blood pressure in the dehydrated group after the intervention. Serum levels of monocyte chemoattractant protein-1, an inflammatory marker, gradually decreased in the hyperhydrated group, and serum adiponectin levels, an anti-atherogenic biomarker, increased in the two groups. We found that hyperhydrated patients contributed over 1/3 of the participants despite enrolling clinically euvolemic patients and that body composition monitor-guided optimization of body fluid status may lead to improvement of inflammatory markers and anti-atherogenic adipokines as well as hemodynamic parameters in hemodialysis patients.

Keywords: adipokines; blood pressure; body composition; hemodialysis; inflammation

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In hemodialysis (HD) patients, chronic fluid overload can cause left ventricular hypertrophy (Jaeger and Mehta 1999), whereas dehydration is linked to the development of intradialytic adverse events such as hypotension (Passauer et al. 1998). Therefore, subtle fluid imbalance can lead to poor clinical outcomes among these patients. The kidney is the primary organ that controls volume status in the body. In HD patients, who have lost their renal function and depend on dialysis machines for most of their renal functions, adequate volume assessment is very important for maintaining normohydration. However, the traditional assessment of fluid status in HD patients depends on physicians' subjective evaluation, which means that that assessment may depend on physicians' experiences or be relatively insensitive.

Recently, a body composition monitor (BCM), a type

of multi-frequency bioimpedance analysis device, was used for the objective assessment of fluid status in dialysis patients (Tattersall 2009). A large observational study has demonstrated that hyperhydration measured by the BCM is associated with higher mortality in HD patients (Wizemann et al. 2009). Another small longitudinal study found that the ratio of intracellular water to body weight (reflecting malnutrition) may have a negative effect on cardiac biomarkers and that the ratio of extracellular water to body weight (reflecting hyperhydration) may have a positive effect on those markers. Moreover, they showed that cardiac biomarkers were related to inflammation (Jacobs et al. 2010). In a recent interventional study, BCM-guided volume reduction led to better control of hypertension in hyperhydrated patients, but no biomarkers were measured (Machek et al. 2010). In contrast, Bednarek-Skubowska et

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al. (2010) showed that levels of cardiac biomarker were unrelated to the volumes of the body fluid compartments in HD patients; controversy remains regarding the relationship between biomarkers and body composition, and these studies were based on the observation studies (Bednarek-Skublewska et al. 2010; Jacobs et al. 2010), instead of on interventional studies.

Therefore, we evaluated the BCM-guided volume assessment in clinically normohydrated HD patients and the effect of BCM-guided volume control on changes in clinical and chemical biomarkers for 16 weeks in these patients.

Subjects and Methods

Study design

We enrolled 120 patients who received HD for more than 6 months at 3 major dialysis centers (Gachon University Gil Hospital, Seoul National University Hospital, and Seoul National University Bundang Hospital). All of the patients' dry weights were stable, and they were clinically normohydrated for at least 3 months. Inclusion criteria were as follows: age 18 years old or greater, no change in dialysate composition, and less than a 5% change in dry weight within 3 months. Exclusion criteria were as follows: any diagnosed acute or chronic inflammatory state within 3 months, hospitalization-related dialysis within 3 months, diseases that produce local fluid accumulation and edema, active malignancy, currently taking diuretics, currently taking any medication with the potential to influence body composition, malnutrition, pregnancy, insertion of a cardiac pacemaker or defibrillator, or the amputation of any extremity. All of the patients provided informed consent, and the study was approved by the institutional review boards of each hospital.

BCM measurement

A BCM (Fresenius Medical Care, Bad Homburg, Germany) was used to determine the extracellular and total body water. Fluid overload was calculated using a physiological BCM model that is based on tissue properties (Chamney et al. 2007). Patients rested for 5 minutes before performing the BCM measurement, and electrodes were fixed to the hand and foot on one side of the body in a supine position. All of the nurses in the centers were trained to use the BCM. If any erroneous measurement was detected by the BCM on the basis of a measurement quality indicator, the nurse repeated the measurement.

Study protocol

This study was a multicenter 16-week interventional trial. When the measured post-HD fluid overload ranged between -1.1 L and 1.1 L, the fluid status was considered to be normohydration (Passauer et al. 2010). Based on the amount of fluid overload, we divided the patients into the following two groups: the hyperhydrated group (fluid overload ≥ 1.1 L) and the dehydrated group (fluid overload < -1.1 L). Dry weight was calculated as follows: dry weight = (post-HD body weight) - (post-HD fluid overload). We restricted food intake during BCM measurement. We optimized body weight towards each patient's dry weight by adjustment of the amount of ultrafiltration for the first 8 weeks, and we maintained each patient's dry weight for the subsequent 8 weeks. During the intervention in the first 8 weeks, post-dialytic weight was adjusted gradually in steps of < 0.5 kg/week, and the antihypertensive drugs were adjusted in parallel with changes in the fluid status.

We collected clinical data including hemoglobin, blood urea nitrogen, creatinine, albumin, cholesterol, glucose, C-reactive protein, calcium, phosphorus, parathyroid hormone, and electrolytes. We measured BCM before and 30 minutes after HD sessions every 4 weeks and extracellular water, intracellular water, estimate of fluid overload, lean tissue index, fat tissue index, and fat content were recorded.

All parameters were measured at the midweek dialysis session. Every 8 weeks, the acquired serum samples were centrifuged and the supernatants were collected and immediately frozen at -70°C until subsequent analysis. All of the samples were run in duplicate to measure biochemical parameters. Leptin, adiponectin, and resistin levels were determined using Bio-Plex Pro human diabetes assays (Bio-Rad Laboratories, Hercules, CA, USA), with intra-assay coefficients of variation (CVs) of 5.38%. Serum interleukin-6 (IL6) and monocyte chemotactic protein-1 (MCP1) concentrations were measured using the Bio-Plex multiplex cytokine assay (Bio-Rad Laboratories), with intra-assay CVs of 6.73%. Serum lipopolysaccharide quantification for the measurement of endotoxin was performed using a Limulus Amebocyte assay (Cambrex, Verviers, Belgium), with an intra-assay CVs of 4.95%.

Statistical analysis

Continuous variables are expressed as the means $\pm$ S.D., whereas categorical variables are presented as absolute values and percentages. Differences between groups were tested with one-way analysis of variance (ANOVA) for continuous variables and with the chi-square test for categorical variables. Intra-group differences for continuous variables were assessed using the Wilcoxon signed ranks test and repeated measures ANOVA for paired samples. Linear regression analysis was performed according to Spearman's test. Due to their skewed distribution, the values were log transformed.

The SPSS (SPSS version 12.0, Chicago, IL, USA) package was used for statistical analysis. A *P*-value of < 0.05 was considered significant. All probabilities were two-tailed.

Results

Baseline characteristics and clinical course

The demographic features and BCM parameters of each study group are shown in Table 1. The mean age was 55.6 years, and half of the patients had diabetes mellitus. Dialysis vintage was approximately 5 years, and the prevalence of anuria was 83%. Of the patients, 36.6% (44/120) were in the hyperhydrated group, and 15.0% (18/120) were in the dehydrated group. Fig. 1 presents the trends throughout the study. In 44 hyperhydrated patients, 7 patients did not complete the study due to the following reasons: transfer to another hospital, 3; hospitalization, 2; and withdrawal of informed consent, 2. In 18 dehydrated patients, 2 patients did not complete the study due to transplantation (1) and hospitalization (1). Fifty-three of 62 patients (85.5%) completed the study and were included in the data analysis. The percentage of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker usage was 10% in the dehydrated group, and 73.3% in the hyperhydrated group. All enrolled patients underwent three dialysis sessions per week.

Table 1. Baseline characteristics of the patients.

	Total	Dehydration	Normohydration	Hyperhydration	P
N	120	18	58	44	
Post-hemodialysis fluid overload (L)	0.89 ± 2.15	-1.90 ± 0.61	0 ± 0.58	2.99 ± 1.69	< 0.001
Male (%)	67 (55.4)	8 (42.1)	30 (52.6)	28 (63.6)	0.255
Age (year)	56.4 ± 13.2	53.3 ± 14.3	55.9 ± 14.1	58.4 ± 11.3	0.360
Cause of end stage renal disease (%)					0.106
Diabetes	55 (45.5)	4 (21.1)	27 (47.4)	23 (52.3)	
Hypertension	20 (16.5)	3 (15.8)	11 (19.3)	6 (13.6)	
Glomerulonephritis	16 (13.2)	6 (31.6)	7 (12.3)	3 (6.82)	
Others	30 (24.8)	6 (31.6)	12 (21.1)	12 (27.3)	
Dialysis vintage (year)	4.97 ± 4.73	5.98 ± 5.64	4.1 ± 3	5.71 ± 5.95	0.146
Height (cm)	163 ± 8.90	160 ± 8.69	163 ± 8.27	164 ± 9.67	0.274
Body weight (kg)	57.2 ± 9.43	55.1 ± 8.32	58.6 ± 10.8	56.4 ± 7.97	0.365
Urine output (mL/day)	120 ± 216	106 ± 189	122 ± 234	123 ± 207	0.956
Anuria (%)	100 (82.6)	15 (79.0)	48 (84.2)	36 (81.8)	0.863

Values are mean $\pm$ s.d.

Fig. 1. Flow diagram of patients enrolled in the study.

Change in the parameters

Changes in post-HD fluid overload of both the dehydrated and hyperhydrated groups after the 16-week intervention are shown in Fig. 2. In the hyperhydrated group, post-HD fluid overload was significantly decreased after the 8-week intervention (2.99 ± 1.69 L at week 0, 1.21 ± 1.43 L at week 8, and 0.74 ± 2.35 L at week 16). In the dehydrated group, post-HD fluid overload was increased, but there was no significant difference (-1.90 ± 0.61 L at week 0, -1.41 ± 1.13 L at week 8, and -1.29 ± 1.08 L at week 16). Systolic blood pressure and pulse pressure after the HD session were significantly decreased after the 16-week intervention in hyperhydrated patients (Table 2). The number of anti-

hypertensive drugs was also decreased in the hyperhydrated group. In dehydrated patients, there was no increase in blood pressure parameters after the 16-week intervention.

The fat tissue index at the post-HD session was markedly increased in the dehydrated patients. This result suggests that fat content may be the main contributor to an increase in body weight. In hyperhydrated patients, extracellular water at pre- and post-HD sessions and intracellular water at post-HD sessions were decreased after the intervention, while fat tissue index and fat content at the time of the post-HD session were increased after the intervention (Table 3).

In both groups, serum MCP1 levels decreased gradu-

Fig. 2. Changes in post-hemodialysis fluid overload.

Post-hemodialysis fluid overload was decreased in the hyperhydrated group (HH) and increased in the dehydrated group (DH) after 16 weeks of BCM-guided intervention ($n = 44$ at week 0, 40 at week 8, and 37 at week 16 in HH; $n = 18$ at week 0, 17 at week 8, and 16 at week 16 in DH).

Table 2. Changes in haemodynamic parameters in dehydrated and hyperhydrated patients.

Parameters	Week 0	Week 8	Week 16	* <i>P</i>
Dehydration				
Systolic BP _{pre} (mm Hg)	128 ± 15.5	132 ± 23.1	130 ± 22.3	0.638
Diastolic BP _{pre} (mm Hg)	72.9 ± 13.4	74.0 ± 17.9	70.7 ± 14.9	0.272
Pulse Pressure _{pre} (mm Hg)	55.8 ± 11.8	58.6 ± 15.4	59.7 ± 14.0	0.778
Hypotensive event (per week)	0.53 ± 1.01	0.27 ± 0.8	0.19 ± 0.40	0.300
No. of anti-hypertensive drugs	1.29 ± 1.45	1.2 ± 1.42	1.33 ± 1.5	0.666
Hyperhydration				
Systolic BP _{pre} (mm Hg)	150 ± 16.2	146 ± 18.7	143 ± 21.0 [†]	0.025
Diastolic BP _{pre} (mm Hg)	71.4 ± 11.0	71.4 ± 13.0	70.7 ± 11.2	0.611
Pulse Pressure _{pre} (mm Hg)	78.6 ± 13.4	72.5 ± 21.4	71.7 ± 20.4 [†]	0.022
Hypotensive event (per week)	0.18 ± 0.64	0.21 ± 0.52	0.28 ± 0.74	0.664
No. of anti-hypertensive drugs	4.38 ± 2.67	4.41 ± 2.59	4.05 ± 2.53 ^{†‡}	0.182

Values are mean ± S.D.

BP, blood pressure; pre, pre-hemodialysis; post, post-hemodialysis.

**P* < 0.05 using repeated-measures analysis of variance.

[†]*P* < 0.05 vs. week 0, and [‡]*P* < 0.05 vs. week 8 using the Wilcoxon signed ranks test.

ally during the 16-week period (Table 4). Although serum levels of IL6 were significantly decreased after the 8-week intervention period, these levels fluctuated in both groups during the subsequent 8-week period. In the hyperhydrated patients, endotoxin levels were also decreased during the

first 8-week period, although these effects were not sustained during the subsequent 8-week period. In the dehydrated group, serum adiponectin levels gradually increased during the 16-week intervention, while serum leptin and resistin levels were not changed. In the hyperhydrated

Table 3. Changes in parameters of body composition in the dehydrated and hyperhydrated patients.

	Week 0	Week 8	Week 16	<i>P</i>
Dehydration				
ECW _{pre} (L)	13.5 ± 2.02	13.5 ± 2.08	13.6 ± 2.10	0.497
ICW _{pre} (L)	16.2 ± 3.63	15.9 ± 2.71	15.5 ± 2.60	0.305
ECW/ICW _{pre}	0.85 ± 0.11	0.86 ± 0.10	0.88 ± 0.06	0.141
Lean tissue index _{pre} (L)	13.2 ± 2.74	12.9 ± 1.98	12.4 ± 1.73	0.222
Fat tissue index _{pre} (L)	9.06 ± 4.04	9.61 ± 3.44	9.86 ± 3.32	0.178
Fat content _{pre} (%)	28.5 ± 10.4	30.2 ± 8.01	31.1 ± 7.94	0.167
Ultrafiltration (L/session)	2.47 ± 0.69	2.05 ± 0.84	2.27 ± 0.61	0.155
ECW _{post} (L)	11.6 ± 1.90	11.6 ± 1.82	11.5 ± 1.8	0.810
ICW _{post} (L)	16.6 ± 3.28	16.1 ± 2.85	15.8 ± 2.69	0.059
ECW/ICW _{post}	0.71 ± 0.09	0.73 ± 0.09	0.73 ± 0.07	0.192
Lean tissue index _{post} (L)	13.4 ± 2.27	13.1 ± 2.11	12.7 ± 1.77	0.076
Fat tissue index _{post} (L)	8.89 ± 3.87	9.35 ± 3.55 [†]	9.63 ± 3.55 [†]	0.009
Fat content _{post} (%)	28.9 ± 9.78	30.4 ± 8.93 [†]	31.3 ± 8.83 [†]	0.014
Hyperhydration				
ECW _{pre} (L)	17.0 ± 3.06	15.5 ± 2.44 [†]	15.4 ± 2.63 [†]	< 0.001
ICW _{pre} (L)	15.7 ± 3.68	15.9 ± 3.22	16.3 ± 4.37	0.422
ECW/ICW _{pre} (L)	1.11 ± 0.21	0.99 ± 0.14 [†]	0.99 ± 0.19 [†]	0.001
Lean tissue index _{pre} (L)	12.3 ± 2.64	12.5 ± 2.26	12.2 ± 2.33 [‡]	0.384
Fat tissue index _{pre} (L)	7.51 ± 3.51	7.59 ± 3.53	8.07 ± 3.74 [‡]	0.217
Fat content _{pre} (%)	24.9 ± 9.78	25.3 ± 9.38	26.8 ± 9.61 ^{†‡}	0.149
Ultrafiltration (L/session)	1.65 ± 1.35	1.84 ± 1.02	1.93 ± 1.23	0.512
ECW _{post} (L)	15.8 ± 2.73	14.3 ± 2.12 [†]	14.1 ± 2.25 [†]	< 0.001
ICW _{post} (L)	16.5 ± 4.33	15.8 ± 5.55 [†]	14.8 ± 3.72 ^{†‡}	0.018
ECW/ICW _{post} (L)	1.00 ± 0.23	0.96 ± 0.19	0.99 ± 0.19	0.316
Lean tissue index _{post} (L)	12.7 ± 2.7	11.7 ± 2.53 [†]	11.3 ± 2.61 ^{†‡}	< 0.001
Fat tissue index _{post} (L)	7.20 ± 2.81	7.73 ± 3.36 [†]	8.08 ± 3.51 ^{†‡}	0.001
Fat content _{post} (%)	24.8 ± 8.12	27.2 ± 10.1 [†]	28.5 ± 10.3 ^{†‡}	< 0.001

Values are mean ± S.D.

ECW, extracellular water; ICW, intracellular water; pre, pre-hemodialysis; post, post-hemodialysis.

Table 4. Changes in cytokines in the dehydrated and hyperhydrated patients.

Parameters	Week 0	Week 8	Week 16	* <i>P</i>
Dehydration				
Interleukin-6 (ln[pg/mL])	1.29 ± 2.58	0.04 ± 1.15 [†]	1.29 ± 0.76 [‡]	0.100
MCP1 (ln[pg/mL])	5.89 ± 1.53	5.33 ± 0.48 [†]	5.37 ± 0.50	0.095
Leptin (ln[pg/mL])	10.3 ± 1.78	9.99 ± 1.65	10.1 ± 1.71	0.817
Adiponectin (ln[pg/mL])	14.0 ± 0.14	15.8 ± 0.31 [†]	16.1 ± 0.40 ^{†‡}	< 0.001
Resistin (ln[pg/mL])	10.2 ± 0.49	10.1 ± 0.46	10.2 ± 0.52	0.661
Endotoxin (ln[EU/mL])	1.05 ± 0.50	1.01 ± 0.40	1.07 ± 0.30	0.908
Hyperhydration				
Interleukin-6 (ln[pg/mL])	1.13 ± 1.32	0.04 ± 1.16 [†]	1.23 ± 0.55 [‡]	< 0.001
MCP1 (ln[pg/mL])	5.64 ± 0.77	5.27 ± 0.37 [†]	5.21 ± 0.42 [†]	0.005
Leptin (ln[pg/mL])	8.89 ± 1.58	8.37 ± 1.55 [†]	8.66 ± 1.60 [‡]	0.013
Adiponectin (ln[pg/mL])	14.0 ± 0.15	15.8 ± 0.33 [†]	16.3 ± 0.44 ^{†‡}	< 0.001
Resistin (ln[pg/mL])	10.1 ± 0.52	10.0 ± 0.50	10.0 ± 0.58	0.782
Endotoxin (ln[EU/mL])	0.96 ± 0.43	0.89 ± 0.39 [†]	0.92 ± 0.34 [‡]	0.232

Values are mean ± S.D.

MCP1, monocyte chemotactic protein-1.

**P* < 0.05 using by repeated-measures analysis of variance tests.[†]*P* < 0.05 vs. week 0, and [‡]*P* < 0.05 vs. week 8 using the Wilcoxon signed ranks test.

Table 5. Changes in biochemical parameters in dehydrated and hyperhydrated patients.

	Week 0	Week 8	Week 16	* <i>P</i>
Dehydration				
Hemoglobin (g/dL)	10.9 ± 0.79	10.6 ± 0.98	10.2 ± 0.84	0.111
Blood urea nitrogen (mg/dL)	72.6 ± 18.6	68.8 ± 14.5	60.3 ± 19.5 ^{†‡}	0.012
Creatinine (mg/dL)	10.5 ± 2.25	10.5 ± 2.10	10.0 ± 2.04 ^{†‡}	0.097
Albumin (g/dL)	3.89 ± 0.32	3.85 ± 0.35	3.85 ± 0.40	0.525
Cholesterol (mg/dL)	162 ± 25.6	150 ± 28.1	155 ± 20.12	0.145
C-reactive protein (mg/dL)	0.18 ± 0.19	0.34 ± 0.44	0.20 ± 0.22	0.757
Calcium (mg/dL)	9.03 ± 0.63	8.99 ± 0.71	8.56 ± 0.77	0.187
Phosphorus (mg/dL)	4.95 ± 1.15	4.35 ± 1.53	5.10 ± 2.15	0.888
Sodium (mmol/L)	138 ± 2.85	138 ± 2.41	139 ± 2.05 [†]	< 0.001
Potassium (mmol/L)	5.09 ± 0.72	4.83 ± 0.67	5.03 ± 0.78	0.891
total CO ₂ (mmol/L)	19.9 ± 3.57	19.61 ± 3.49	17.1 ± 4.84	0.797
Parathyroid hormone (pg/dL)	254 ± 271	294 ± 293	268 ± 286	0.445
Kt/Vurea	1.68 ± 0.17	1.73 ± 0.22	1.79 ± 0.17	0.097
nPNA (g/kg/day)	1.35 ± 0.18	1.31 ± 0.18	1.25 ± 0.23	0.289
Hyperhydration				
Hemoglobin (g/dL)	10.6 ± 1.04	10.7 ± 1.23	11.2 ± 4.09	0.641
Blood urea nitrogen (mg/dL)	59.8 ± 19.0	64.3 ± 15.0	60.5 ± 17.6	0.240
Creatinine (mg/dL)	8.83 ± 2.34	9.01 ± 2.38	8.82 ± 2.66	0.682
Albumin (g/dL)	3.89 ± 0.39	3.89 ± 0.5	3.79 ± 0.4 [‡]	0.204
Cholesterol (mg/dL)	146 ± 33.6	143 ± 28.8	149 ± 33.2	0.475
C-reactive protein (mg/dL)	0.16 ± 0.26	0.32 ± 0.55	0.54 ± 0.82	0.297
Calcium (mg/dL)	8.65 ± 0.7	8.42 ± 0.74 [†]	8.53 ± 0.65 [‡]	0.016
Phosphorus (mg/dL)	4.59 ± 1.18	4.97 ± 1.41	5.15 ± 1.86	0.284
Sodium (mmol/L)	137 ± 4.14	138 ± 4.48	137 ± 3.69	0.397
Potassium (mmol/L)	5.13 ± 0.82	5.15 ± 0.79	5.16 ± 0.82	0.926
total CO ₂ (mmol/L)	20.0 ± 3.98	19.0 ± 3.94 [†]	18.8 ± 3.68	0.098
Parathyroid hormone (pg/dL)	181 ± 352	190 ± 349	203 ± 433	0.262
Kt/Vurea	1.48 ± 0.18	1.57 ± 0.26	1.50 ± 0.27	0.217
nPNA (g/kg/day)	0.99 ± 0.19	1.13 ± 0.21 [†]	1.01 ± 0.17 [‡]	0.001

Values are mean ± s.d.

nPNA, normalized protein equivalent of nitrogen appearance.

group, similar to the dehydrated group, serum adiponectin levels gradually increased throughout the entire period. There was no significant change in other parameters in either group, including hemoglobin, albumin, and cholesterol (Table 5). The normalized protein equivalent of nitrogen appearance (nPNA) was slightly increased in the hyperhydrated group and unchanged in the dehydrated group.

As shown in Fig. 3, serum endotoxin levels were positively associated with serum MCP1 and IL6 ($r = 0.556$, $P < 0.001$ and $r = 0.641$, $P < 0.001$, respectively). However, serum endotoxin levels were negatively associated with serum adiponectin ($r = -0.326$, $P = 0.005$).

Discussion

We demonstrated that the objective assessment of fluid status can detect hyperhydrated or dehydrated state in subjectively euvolemic HD patients, and we also found that

BCM-guided optimization of fluid status may lead to the improvement of inflammatory markers and anti-atherogenic adipokines as well as hemodynamic parameters in HD patients.

Machek et al. (2010) showed that volume-guidance towards normohydration leads to better control of hypertension in hyperhydrated patients and less intradialytic adverse events in the dehydrated patients. This result is consistent with our data. However, the authors assessed the changes in hydration status retrospectively, which suggests that the data were not followed up on a regular basis and that they had no data on biochemical biomarkers. Our study design was prospective, and blood samples were collected every 8 weeks.

After the optimization of patients' volume status, systolic blood pressure, and pulse pressure in the hyperhydrated patients were significantly decreased without con-

Fig. 3. Association between endotoxins and other cytokines in hemodialysis patients.

There were positive correlations between monocyte chemotactic peptide-1 and endotoxin (A), and between interleukin-6 and endotoxin (B), while there was a negative correlation between adiponectin and endotoxin (C) ($n = 73$). Due to their skewed distribution, the values were log transformed.

comitant increases in the dose of anti-hypertensive medication. In the dehydrated patients, there was a reduction in hypotensive episodes after the intervention, although this reduction was not statistically significant. This result may arise because most of the hyperhydrated patients reduced their fluid overload sequentially, while some of the dehydrated patients failed to reach normohydration after the 16-week intervention (Fig. 2).

MCP1, a monomeric polypeptide of 9 to 15 kDa, is the prototype of the C-C chemokine b subfamily and also exhibits its most potent activity for monocytes (Ikeda et al. 2002). MCP1 is produced by various types of cells within the arterial wall, including vascular smooth muscle cells, endothelial cells and macrophages in response to wide ranges of stimuli. IL6 is a 26-kDa cytokine that is produced by many different cells in the body (Ikeda et al. 2001). It has been well documented that elevated levels of acute-phase proteins are associated with unfavorable short- and long-term prognoses in patients with end-stage renal disease (Pecoits-Filho et al. 2002). Hyperhydration is reported to be related to inflammation in patients with peritoneal dialysis (Vicente-Martinez et al. 2004). In this study, although IL6 levels were not changed, MCP1 levels in hyperhydrated patients were significantly decreased after the 8-week intervention; those changes were maintained for the subsequent 8 weeks.

In chronic kidney disease patients, endotoxin enters the circulation via bacterial translocation (the passage of intact bacteria and macromolecules such as endotoxin across the intestinal barrier) (Kotanko et al. 2006). In congestive heart failure, bowel edema and hypoperfusion may be the two main factors influencing bowel wall permeability (Krack et al. 2005). In HD patients, predialysis endotoxin levels could be associated with ultrafiltration volume or hypotensive events during the dialytic session (McIntyre et al. 2011). In this current study, endotoxemia was positively associated with IL6 and MCP1 levels and negatively associated with adiponectin levels. This result suggests that endotoxin may be a mediator of inflammation in the presence of hyperhydration; however, further study is needed to evaluate the association between volume control and inflammation.

The post-HD fat tissue index was increased in both dehydrated and hyperhydrated patients. In addition, nPNA, a nutritional marker in HD patients, was increased in the hyperhydrated patients after the 16-week intervention. Cheng et al. (2005) found that optimized fluid status was associated with an improvement in nutritional status in peritoneal dialysis patients. Fat has some favorable effects on storing energy and counteracts the inflammatory effects of circulating endotoxins (Mohamed-Ali et al. 1999). These data suggest that the correction of fluid imbalance may be closely related to the improvement of nutrition, especially in hyperhydrated patients.

Adipocytes synthesize and release adipokines, which have been linked to blood pressure control. Adiponectin is

protective against hypertension through an endothelium-dependent mechanism, and plays an important role in the regulation of vascular tone (Ouchi et al. 2003). Shatat et al. (2009) showed that lower serum adiponectin levels were associated with higher blood pressures. In the hyperhydrated patients in the current study, serum adiponectin levels were increased and pre-HD systolic blood pressures and pulse pressures were decreased after a 16-week period. However, it is unclear whether the increased levels of adiponectin directly influence the change in blood pressure or is an epiphenomenon with increased fat tissue index.

This study had several limitations. There were no data on changes in biochemical parameters of normohydrated patients during the 16-week intervention period, which would be informative and important. This study is an interventional trial and not a randomized controlled study, which means that all the hyperhydrated patients were treated. Therefore, we focused on the changes according to the interventional period. Sixteen weeks may not be a sufficiently long period to evaluate hard clinical outcomes. Further long-term randomized controlled trials are needed.

In conclusion, our data show that hemodynamic and biochemical parameters improved after the correction of HD patients' fluid imbalance, which was not detected clinically. Further prospective interventional trials are needed to evaluate the improvement of hard clinical endpoints with the change in volume status.

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Conflict of Interest

The authors declare no conflict of interest.

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