ORIGINAL

Clinical characteristics of hyponatremia in patients receiving nutrition support : A cross-sectional study evaluated by bioelectrical impedance analysis

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Abstract : Background & aims : We investigated the contributing factors of hyponatremia in patients on nutrition support using bioelectrical impedance analysis (BIA). Methods : Thirty patients administered enteral or parenteral nutrition support for at least 72 hours were studied. We collected nutritional and electrolyte intake, serum biochemical parameters, and body composition measured by BIA. Patients were classified into two groups according to their serum sodium levels : (1) Normanatremia group, 135–145 mEq/L (n = 18) and (2) Hyponatremia group, less than 135 mEq/L (n = 12), and their characteristics were analyzed. Results : There were no significant differences between the Normonatremia and Hyponatremia groups in terms of energy, protein, and sodium intake. Serum biochemical parameters other than serum sodium and chloride levels were comparable between the two groups. On the other hand, the ratio of extracellular water to total body water (ECW/TBW) obtained by BIA was significantly higher in the Hyponatremia group than in the Normonatremia group. Further, an elevated ECW/TBW significantly and negatively correlated with serum albumin level. Conclusions : Regardless of sodium intake, higher ECW/TBW was associated with hyponatremia in patients on nutrition support. ECW/TBW may be an important clinical parameter relevant to the nutritional care of hyponatremia. J. Med. Invest. 68 : 112-118, February, 2021

Keywords **:** *Hyponatremia, bioelectrical impedance analysis, fluid volume imbalance, the ratio of extracellular water to total body water*

INTRODUCTION

Hyponatremia, the most common electrolyte abnormality in hospitalized patients (1), has recently emerged as a risk factor for mortality (2-10). An increased morbidity and mortality rate has been observed in hyponatremia in hemodialysis patients (2-4) and patients with medical conditions such as heart failure (5), myocardial infarction (6), stroke (7), liver cirrhosis (8), pulmonary embolism (9), and cancer (10). In the clinical setting, many patients receiving nutrition support have these diseases, and hyponatremia has been often seen in these patients. Indeed, we reported that approximately 50% of hospitalized patients on nutrition support had hyponatremia (11).

Hyponatremia might point to a "frail phenotype" or "volume overload." In hemodialysis patients, hyponatremia has been associated with low body mass index (BMI) (2), intradialytic weight loss (2), low lean tissue index (3), and low serum albumin level (2, 4). In addition, hyponatremia has been associated with weight loss in patients on peritoneal dialysis (12) and with disease severity in patients with pulmonary embolism (9). As highlighted by previous studies, hyponatremia is a marker of underlying severe disease that carries a poor prognosis (13), and hyponatremia itself may contribute to adverse outcomes such as mortality and heightened consumption of health care resource (14, 15). Therefore, the treatment of hyponatremia is very important.

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In the clinical treatment of hyponatremia in patients with edema, overly rapid corrections of hyponatremia may worsen the hyponatremia condition. Also, inappropriate treatment of hyponatremia may lead to destructive consequences such as osmotic demyelination syndrome that leads to permanent brain damage or even death (1, 16). Hence, appropriate assessment of the causative factor of hyponatremia is important for the subsequent management of hyponatremia and avoidance of treatment pitfalls.

Bioelectrical impedance analysis (BIA) is widely used in the clinical setting for the evaluation of nutritional status and fluid status (17, 18). BIA is a simple, noninvasive, rapid, portable, and convenient method, which indirectly estimates the body composition and fluid distribution by sending a weak electric current throughout the body (19). Hyponatremia has been often seen in patients receiving nutrition support (11), but no study has revealed the clinical characteristics of hyponatremia in patients on nutrition support. Therefore, we investigated the contributing factor of hyponatremia in patients on nutrition support using BIA. Our study aimed to reveal the clinical characteristics of hyponatremia in patients on nutrition support and to play a constructive part in the appropriate nutritional care of hyponatremia.

MATERIALS AND METHODS

Study Design and Participants

We performed a cross-sectional study of patients who were admitted in general ward at Kobe University Hospital from October 2011 to September 2012. Patients were included if they were administered enteral nutrition (EN) or parenteral nutrition (PN) with the same quality and quantity for at least 72

hours by the Nutrition Support Team (NST). Patients prescribed with oral intake were excluded. Based on the criteria established by the Ministry of Health, Labor and Welfare, nutrition supports are provided by the NST to the following patients : patients with hypoalbuminemia (serum albumin ≤ 3.0 g/dL) and who are identified "at risk for malnutrition" status by subjective global assessment (20) on risk screening, on EN or PN, and any patient who is expected to improve nutritional status by receiving NST interventions.

Based on the European Society of Parenteral and Enteral Nutrition guidelines (19), the following criteria were used to exclude the patients from this study : patients with an amputation, abnormal physical structure, and ascites or noticeable edema. A total of 30 patients were included in the final statistical analysis.

We collected nutritional intake, electrolyte intake, serum biochemical parameters, and results of BIA. Patients were classified into two groups according to their serum sodium levels : (1) Normonatremia group, 135–145 mEq/L (n = 18) and (2) Hyponatremia group, less than 135 mEq/L (n = 12), and their characteristics were analyzed. The study protocol was approved by the Ethics Committee of Kobe University School of Medicine (No. 1277) and complied with the Declaration of Helsinki. All patients were included in this study after providing informed consent.

Serum Chemistry

Fasting blood samples were collected by using an antecubital vein puncture sample from each patient. Blood was collected using 10 mL tubes and centrifuged at 1500 × g for 10 min at 4°C. Complete blood counts were determined immediately after blood collection. Biochemical parameters were measured immediately after centrifugation. Hematological parameters and biochemical assessments were determined in the hospital laboratory using commercially available test kits. In brief, complete blood counts were measured using the XE2100 Hematology analyzer (Sysmex, Kobe, Japan). Biochemical parameters were measured using the TBA200FR NEO Automated Analyzer (Toshiba Medical Systems, Tochigi, Japan).

BIA

The body composition of each patient was assessed using the InBody S20 multi-frequency analyzer (Biospace, Tokyo, Japan) because BIA is a noninvasive and commonly used method for estimating body composition. The analyzer used an 8-point tactile electrode system that measures the total and segmental impedance and phase angle of alternating electric current at four different frequencies. It was used according to the manufacturer's instructions.

Statistical Analysis

All statistical analyses were performed using SPSS 24.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± standard deviation (parametric variables) or median and interquartile range (non-parametric variables). Normality of distribution was assessed with Shapiro-Wilk tests. Differences between groups were analyzed with the two-tail Student's *t*-test for independent variables in case of parametric distribution, while the Mann–Whitney *U*-test was used in case on non-parametric distribution. Categorical variables were described using proportions and were analyzed with the χ^2 test. Correlations were analyzed using Pearson's correlation analysis. *P*-values < 0.05 were considered statistically significant.

RESULTS

Patients Characteristics

We included 30 patients (Normonatremia vs. Hyponatremia : n = 18 vs. 12), and their demographic characteristics are shown in Table 1. There were no significant differences in demographic characteristics between the Normonatremia and Hyponatremia groups. Approximately 50% or more patients in the two groups received a combination of PN and EN. The most common underlying disease in the two groups was malignancy. The prescribed medication which affected serum sodium level was Loop-diuretics alone.

Nutritional Intake · Electrolyte Intake

Sodium intake seemed to be higher in the Hyponatremia group than in the Normonatremia group but no significant differences were observed (Figure 1). Table 2 shows the nutritional and electrolyte intake calculated from the total amount of PN and EN. The ratio of energy to body weight (BW), protein to BW, and sodium to BW were comparable between the two groups.

Biochemical Parameters

In the Normonatremia and Hyponatremia groups, the serum sodium levels were 140 ± 3 mEq/L and 132 ± 2 mEq/L, respectively, while the serum chloride levels were 103 ± 4 mEq/L and 98 ± 4 mEq/L, respectively. Serum potassium, total protein, serum albumin, blood urea nitrogen, serum creatinine, total lymphocyte count, C-reactive protein, and estimated glomerular filtration rate were comparable between the two groups (Table 3).

Body Composition Analysis

The ratio of skeletal muscle mass to BW, body fat mass to BW, body cell mass to BW, and lean body mass to BW were comparable between the two groups (Table 4). As shown in Figure 2, the ratio of extracellular water to total body water (ECW/TBW) was significantly higher in the Hyponatremia group than in the Normonatremia group 0.420 ± 0.009 and 0.407 ± 0.011, respectively ($P < 0.01$). In addition, ECW/TBW in the two groups was higher than the standard value (0.36–0.39).

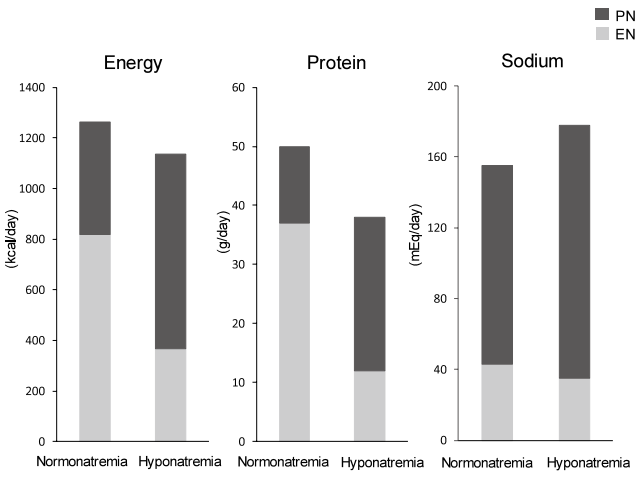

Figure 1. Nutritional intake · Electrolyte intake
EN, enteral nutrition; PN, parenteral nutrition.
Although sodium intake seemed to be higher in the Hyponatremia group than in the Normonatremia group, there were no significant differences.

Table 1. Patients characteristics

		Normonatremia (n = 18)	Hyponatremia (n = 12)	*P*-values
Sex	Men/Woman	13/5	10/2	NS[a]
Age	year	70.0 (62.8-76.8)	72.0 (69.3-81.8)	NS[b]
Body height	cm	159.8 ± 8.0	160.6 ± 9.3	NS[c]
Body weight	kg	54.0 ± 15.3	50.6 ± 9.7	NS[c]
BMI	kg/m^2	21.0 ± 5.3	19.6 ± 3.3	NS[c]
Routes of nutrition support	n (%)			
PN only		5 (27.8%)	6 (50%)	NS[a]
EN only		1 (5.6%)	0 (0%)	NS[a]
PN + EN		12 (66.7%)	6 (50%)	NS[a]
Underlying disease	n (%)			
Malignancy		9 (50.0%)	4 (33.3%)	NS[a]
Clinical stage				
Ⅲ[d]		2 (11.1%)	1 (8.3%)	NS[a]
Ⅳ[d]		1 (5.6%)	2 (16.7%)	NS[a]
Postoperative		5 (27.8%)	0 (0%)	NS[a]
Unknown		1 (5.6%)	1 (8.3%)	NS[a]
Cancer diagnosis				
Head		0 (0%)	1 (8.3%)	NS[a]
Pharyngenal/laryngeal		2 (11.1%)	0 (0%)	NS[a]
Lung		2 (11.1%)	1 (8.3%)	NS[a]
Esophageal		2 (11.1%)	1 (8.3%)	NS[a]
Gastric		2 (11.1%)	1 (8.3%)	NS[a]
Duodenal		1(5.6%)	0 (0%)	NS[a]
Chronic kidney disease		6 (33.3%)	3 (25.0%)	NS[a]
Hemodialysis		2 (11.1%)	1 (8.3%)	NS[a]
Diabetes		3 (16.7%)	4 (33.3%)	NS[a]
Cirrhosis		2 (11.1%)	1 (8.3%)	NS[a]
Cerebrovascular disease		2 (11.1%)	2 (16.7%)	NS[a]
Cardiovascular disease		0 (0%)	2 (16.7%)	NS[a]
Medication	n (%)			
Loop-diuretics		2 (11.1%)	1 (8.3%)	NS[a]

BMI, Body mass index ; PN, parenteral nutrition ; EN, enteral nutrition ; NS, not significant.
Data are presented as mean ± standard deviation, median (interquartile amplitude), or frequency.
[a] χ^2 test.
[b] Mann–Whitney *U*-test.
[c] Student's *t*-tests.
[d] Each patient was staged according to the TNM classification by the Union for International Cancer Control and/or Japanese General Rules for Clinical and Pathological Classification of Cancer.

Table 2. Nutritional intake · Electrolyte intake

		Normonatremia (n = 18)	Hyponatremia (n = 12)	*P*-values
energy	kcal/day	1262 ± 487	1136 ± 515	NS[a]
energy/BW	kcal/kg (BW)/day	24.4 ± 10.3	23.5 ± 12.4	NS[a]
protein	g/day	49.6 ± 20.5	38.7 ± 21.5	NS[a]
protein/BW	g/kg (BW)/day	1.0 ± 0.5	0.8 ± 0.5	NS[a]
sodium	mEq/day	127.7 (100.3-180.0)	162.7 (101.7-245.1)	NS[b]
sodium/BW	mEq/kg (BW)/day	3.1 ± 2.0	3.5 ± 1.6	NS[a]

BW, Body weight ; NS, not significant.
Data are presented as mean ± standard deviation, median (interquartile amplitude).
[a] Student's *t*-tests.
[b] Mann–Whitney *U*-test.

Table 3. Biochemical parameters

		Normonatremia (n = 18)	Hyponatremia (n = 12)	*P*-values
Sodium	mEq/L	140 ± 3	132 ± 2	$P < 0.01$ [a]
Potassium	mEq/L	4.3 ± 0.5	4.0 ± 0.8	NS [a]
Chloride	mEq/L	103 ± 4	98 ± 4	$P < 0.01$ [a]
Total protein	g/dL	5.6 ± 1.0	5.9 ± 1.0	NS [a]
Albumin	g/dL	2.5 ± 0.5	2.2 ± 0.5	NS [a]
Blood urea nitrogen	mg/dL	21.0 (13.0-26.3)	13.0 (11.3-23.8)	NS [b]
Creatinine	mg/dL	0.75 (0.58-1.24)	0.62 (0.45-1.11)	NS [b]
Total lymphocyte count	cell/μL	765 (470-886)	744 (373-1124)	NS [b]
C-reactive protein	mg/dL	2.5 (1.4-5.7)	4.1 (2.0-6.0)	NS [b]
estimated glomerular filtration rate	ml/min/1.73 m^2	74.4 ± 39.6	86.7 ± 48.2	NS [a]

NS, not significant.
Data are presented as mean ± standard deviation, median (interquartile amplitude).
[a]Student's *t*-tests.
[b]Mann–Whitney *U*-test.

Table 4. Body composition analysis

		Normonatremia (n = 18)	Hyponatremia (n = 12)	*P*-values
Skeletal muscle mass	kg/kg (BW)	0.41 ± 0.06	0.40 ± 0.06	NS [a]
Body fat mass	kg/kg (BW)	0.21 (0.14-0.24)	0.21 (0.15-0.25)	NS [b]
Body cell mass	kg/kg (BW)	0.50 (0.49-0.53)	0.49 (0.42-0.52)	NS [b]
Lean body mass	kg/kg (BW)	0.79 (0.76-0.86)	0.79 (0.75-0.85)	NS [b]
ECW	L	12.6 ± 2.8	12.1 ± 2.4	NS [a]
TBW	L	31.0 ± 6.9	28.9 ± 5.7	NS [a]
ECW/TBW		0.407 ± 0.001	0.420 ± 0.009	$P < 0.01$ [a]

BW, Body weight ; NS, not significant
Data are presented as mean ± standard deviation, median (interquartile amplitude).
[a]Student's *t*-tests.
[b]Mann–Whitney *U*-test.

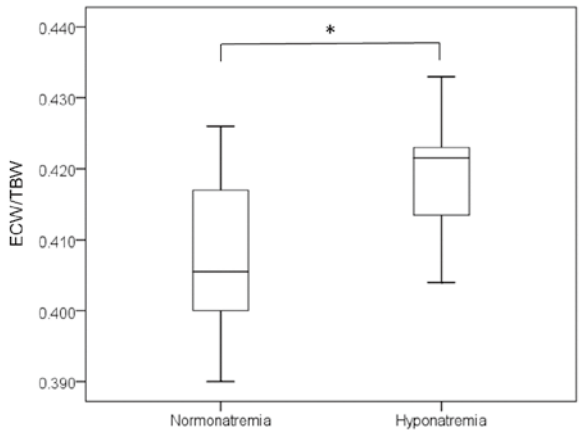

Figure 2. Comparison of ECW/TBW between the Normonatremia group and the Hyponatremia group
ECW/TBW, the ratio of extracellular water to total body water.
*$P < 0.01$, Student's *t*-tests (Normonatremia group vs Hyponatremia group).
ECW/TBW was significantly higher in the Hyponatremia group than in the Normonatremia group 0.420 ± 0.009 and 0.407 ± 0.011, respectively ($P < 0.01$). ECW/TBW standard value (0.36–0.39).

Correlation of ECW/TBW with Serum Albumin Level in All Patients

The relationships between ECW/TBW and serum albumin level were investigated using partial correlation accounting for the influence of age. As shown in Figure 3, ECW/TBW had a significant negative correlation with serum albumin level ($r = -0.643$, $P < 0.01$). Meanwhile, ECW content and the ratio of ECW to BW had no correlation with serum albumin level ($r = 0.004$, $P = 0.984$; $r = 0.237$, $P = 0.208$).

DISCUSSION

In this study, we found that ECW/TBW was significantly higher in the Hyponatremia group than in the Normonatremia group, regardless of sodium intake. Furthermore, an elevated ECW/TBW significantly and negatively correlated with serum albumin level as would be expected with patients with excess ECW. Thus, ECW/TBW may be an important clinical parameter for the evaluation of hyponatremia and fluid status.

Hyponatremia has been associated with low BMI (2), weight loss (2, 12), low lean tissue index (3), and low serum albumin (2, 4) in patients with different diseases, which might result from "fluid volume imbalance". In this study, ECW/TBW in the

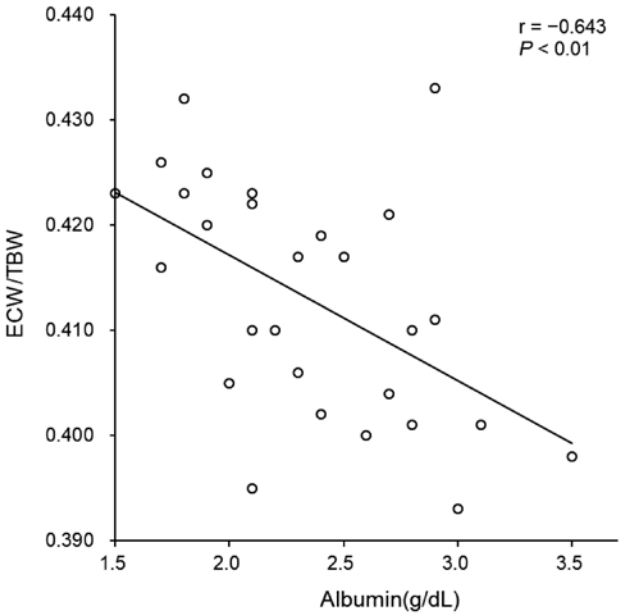

Figure 3. Correlation of ECW/TBW with serum albumin level in all patients
ECW/TBW, the ratio of extracellular water to total body water.
ECW/TBW had a significant negative correlation with serum albumin level ($r = -0.643$, $P < 0.01$).

Normonatremia and Hyponatremia groups was higher than the standard value, which indicated that fluid imbalance between intracellular water (ICW) and ECW was present in the two groups. The cause of fluid volume imbalance is multifactorial and may be associated with systemic inflammation, hypoalbuminemia, capillary leakage, and a decline in lean and/or fat tissue mass (21-24).These factors may have contributed to an elevated ECW/TBW in the two groups. Moreover, the higher ratio of ECW/TBW was associated with hyponatremia, regardless sodium intake. Literature suggests that hyponatremia with chronically ill patients is caused by impaired renal free water excretion which results from inappropriate release of vasopressin such as syndrome of inappropriate antidiuretic hormone and reset osmostat (25). These diseases may have further exacerbated the fluid volume imbalance. However, since they were not diagnosed in this study, it was unclear whether they contributed to hyponatremia. Although hyponatremia is often multifactorial, very interestingly, ECW/TBW showed a significant difference between the two groups.

Previous researchers have shown that the BIA data are associated with patient's nutritional status or clinical outcomes (17, 18). In particular, ECW/TBW, which represents fluid status, has also been found to be a good prognostic factor for diseases such as acute heart failure (26), renal disease (27), liver disease (28) , and malignancy (29). The subjects of this study included patients with systemic inflammation such as malignancy or chronic kidney disease. The higher ECW/TBW ratio in these patients has been reported to have common characteristics as follows. First, fluid retention, such as pleural effusion, ascites, or edema in the peripheral extremities is often seen in patients with malignancy (30) or chronic kidney disease (31) and is generally associated with disease progression, which is indicated as ECW excess. Second, fluid volume imbalance may be closely associated with systemic inflammation, hypoalbuminemia, vascular permeability, protein catabolism, and muscle wasting (21-24). Notably, systemic inflammation seems to play a pivotal role in the fluid volume imbalance by the following mechanisms : Hypoalbuminemia and increased vascular permeability caused by systemic inflammation will enhance extravascular fluid shift, resulting in ECW volume overload (21, 22). In addition, increased protein catabolism and muscle wasting caused by systemic inflammation could deplete body cell mass, which eventually leads to the decrease in ICW, and relative increase in ECW/TBW (23, 24).

In this study, an elevated ECW/TBW showed a significant negative correlation with serum albumin level even after accounting for age. In contrast, ECW content and the ratio of ECW to BW had no correlation with serum albumin level. These findings would support the clinical picture of relative excess ECW due to fluid volume imbalance, regardless of age. Previous studies reported that patients with decreased ICW and relatively increased ECW (ie, relative increase in ECW/TBW) were susceptible to volume overload (29, 32). Therefore, ECW/TBW may be useful as an important clinical parameter for the evaluation of hyponatremia and fluid status.

The final treatment for hyponatremia in patients receiving nutritional support is corrective treatment for serum sodium concentration and fluid balance to improve their prognosis. Based on our results, we suggest ECW/TBW as an indicator of fluid balance. Although clinical assessment of fluid status has been applied as one of the diagnostic parameters of algorithm for the diagnosis of hyponatremia (1), the method for the assessment has not been clarified. The indicator of fluid balance using ECW/TBW may help the evaluation of hyponatremia in the clinical setting.

One of the clinical practice pitfalls, which could endanger hyponatremic patients, is overly rapid correction of hyponatremia. NST patients often receive PN management. They often already have a fluid volume imbalance. Excessive serum sodium correction with PN can cause a rapid rise in serum sodium level, eventually resulting in overcorrection of hyponatremia, and exposes the patients to harmful risks such as edema and worsening of hyponatremia. Therefore, we suggest prioritizing corrective treatment for fluid balance before sodium replenishment. In other words, we suggest interventions aimed at improving ECW/TBW ratio, rather than interventions aimed solely at increasing serum sodium concentration. Assessment of fluid status by ECW/TBW may prevent excessive serum sodium correction and may help the evaluation of hyponatremia in patients on nutrition support.

Our study had some limitations. First, our study was limited by its observational nature, which allowed us to establish associations, but not causality. Further studies are needed to demonstrate causality between hyponatremia and fluid volume imbalance. Second, it was not possible to classify the patients according to ECW/TBW owing to the small sample size. It would be better to compare the ECW/TBW with various indicators such as nutritional status and clinical outcomes and to monitor them in clinical practice.

In conclusion, regardless of sodium intake, higher ECW/TBW was associated with hyponatremia in patients on nutrition support. Further, an elevated ECW/TBW significantly and negatively correlated with serum albumin level, as would be expected with patients with excess ECW. ECW/TBW may be an important clinical parameter relevant to the nutritional care of hyponatremia.

CONFLICTS OF INTEREST

None declared.

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