Original Article

Determinants of extracellular fluid after hemodialysis in CKD stage G5D patients measured by the bioelectrical impedance (BIA) method: A propensity score matching study

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Abstract

Background: Hemodialysis patients have a higher incidence of extracellular edema than patients with a normal renal function, even if their dry weight (DW) setting is appropriate. However, the factors determining post-dialysis edema in hemodialysis patients have not been fully elucidated. We investigated the determinants of post-dialysis ECW/TBW index (ratio of extracellular body water to total body water) in hemodialysis patients and compared them with non-chronic kidney disease (non-CKD) patients.

Methods: The ECW/TBW index was measured using a bioimpedance body composition analyzer. We measured clinical parameters and the ECW/TBW index in 159 hemodialysis patients and 385 non-CKD patients. We evaluated the relationships with various clinical parameters by a multivariable linear analysis and stepwise regression analysis. Differences in age and BMI between the hemodialysis and non-CKD patients were adjusted by propensity score matching. The modified groups were analyzed by multivariable linear analysis and stepwise regression analyses.

Results: The ECW/TBW index was significantly higher in the hemodialysis patients. A multivariable linear analysis with the ECW/TBW index as the objective variable showed significant associations in age, pre-dialysis Hb, Ht, TP, Alb, Cr, human atrial natriuretic peptide (HANP) and percent creatinine generation rate (%CGR) in hemodialysis patients. After propensity score matching for age and BMI, a strong effect of age was observed in the non-CKD patients, while Alb affected the ECW/TBW index in the hemodialysis patients.

Conclusion: While age strongly influenced the ECW/TBW index in non-CKD patients, that in hemodialysis patients was more strongly influenced by serum Alb than age. High ECW/TBW index is associated with a poor prognosis in hemodialysis patients, suggesting the importance of paying attention to the pre-dialysis albumin concentration in the setting of the body fluid removal for DW.

(Keywords: Bioimpedance, Extracellular body water, Hemodialysis, Propensity score matching)

Introduction

Dry weight (DW) in hemodialysis patients is a concept that was proposed by Thomson et al. in 1967 and was initially defined as the ideal body weight at the time of correction of extracellular fluid volume by hemodialysis therapy[1]. However, the amount of removed water is often reduced during maintenance hemodialysis therapy due to decreasing blood pressure before reaching the DW. Edema remains in patients with adequate DW settings after hemodialysis therapy. In practice, it is sometimes difficult to reach the DW of an edema-free state proposed by Thomson et al., even in patients with a similar salt intake and adequate weight gain[2]. The DW setting has been proposed by measuring the cardiothoracic ratio using X-ray, the inferior vena cava diameter using ultrasonography, and serum human atrial natriuretic peptide (HANP) levels after hemodialysis[3, 4]. However, these parameters are mainly affected by the intravascular fluid volume, and there is no practical marker

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for assessing the extravascular fluid volume. For this reason, there have been few clinical investigations to evaluate the factors associated with the extracellular fluid volume after hemodialysis.

The bioelectrical impedance analysis (BIA) method non-invasively measures total body water (TBW), intracellular water (ICW), and extracellular water (ECW) levels by directly measuring the electrical resistance in the body. It has been reported to be useful for a more detailed evaluation of the fluid volume *in vivo*[5, 6]. The ratio of ICW to ECW, measured by the BIA method is approximately 62:38 in healthy adults and is used to indicate an adequate fluid volume[7]. In addition, it is known that the ratio of ICW to ECW can change with age and disease, and it has been reported that the ECW/ICW ratio tends to increase with older age in healthy individuals[8]. The ECW/TBW index can be defined and quantified using the BIA method by the following equation[9]. The ECW/TBW index (the ratio ECW to TBW) is used as a fluid status indicator, and is homeostatic within a very narrow range, with 0.38 being the normal value for both men and women in normal subjects[9]. Previous studies have shown that a high ECW/TBW index can predict a poor prognosis in patients with conservatively managed chronic kidney disease (CKD)[10]. We previously investigated the relationship between DW and the body water composition measured by BIA in hemodialysis patients and reported that the measurement of the ECW/TBW index was effective in setting the DW[11]. In that study, we calculated the body weight at which the ECW/TBW index was 0.38 in hemodialysis patients; it showed a strong positive correlation ($r=0.99$, $p<0.001$) with the clinically appropriate DW set based on conventional parameters[11]. Furthermore, we have reported that thyroid hormone levels in hemodialysis patients are negatively correlated with the ECW/TBW index measured by the BIA method. Hypothyroidism produces non-pitting edema, and we have reported that the BIA method can also non-invasively detect non-pitting edema in hemodialysis patients[12]. These results suggest that the BIA method may be an effective for evaluating the extracellular fluid volume in hemodialysis patients.

The present study was undertaken to examine the clinical factors associated with the ECW/TBW index using BIA in patients on maintenance hemodialysis, in comparison to patients without CKD. In order to rigorously examine the clinical factors that influence the ECW/TBW index, this study was further validated using a propensity score matching method to match according to BMI, age, and sex—which were significantly different between the two groups—in order to control for the influence of these factors.

Methods

Study design

This retrospective study was conducted using BIA measurement data and clinical blood sampling data of outpatients who attended Kawashima Medicine Clinic (Ibaraki, Japan) from April 2006 to October 2018. This study was approved by the ethics committee of Jichi Medical University (IRB approval number: RIN A16-089/JMU).

Subjects

This study was included hemodialysis patients and non-CKD patients (N=544) who gave their consent to participate. All hemodialysis patients (N=159) were outpatients who received hemodialysis three times per week. Non-CKD patients (N=385) were also outpatients with eGFR >60 ml/min and urinary protein <0.15 g/g · Cr. Patients who did not receive a BIA at the time of blood collection (N=82) and patients with cirrhosis or cancer (N=42) were excluded from the study. Patients undergoing dialysis complicated with atrial fibrillation were also excluded (N=21). Finally, 96 hemodialysis patients and 303 non-CKD patients were included in the analysis (Figure 1).

Sixty-eight patients in each group were included in a propensity score-matching analysis adjusted for age, BMI, and sex.

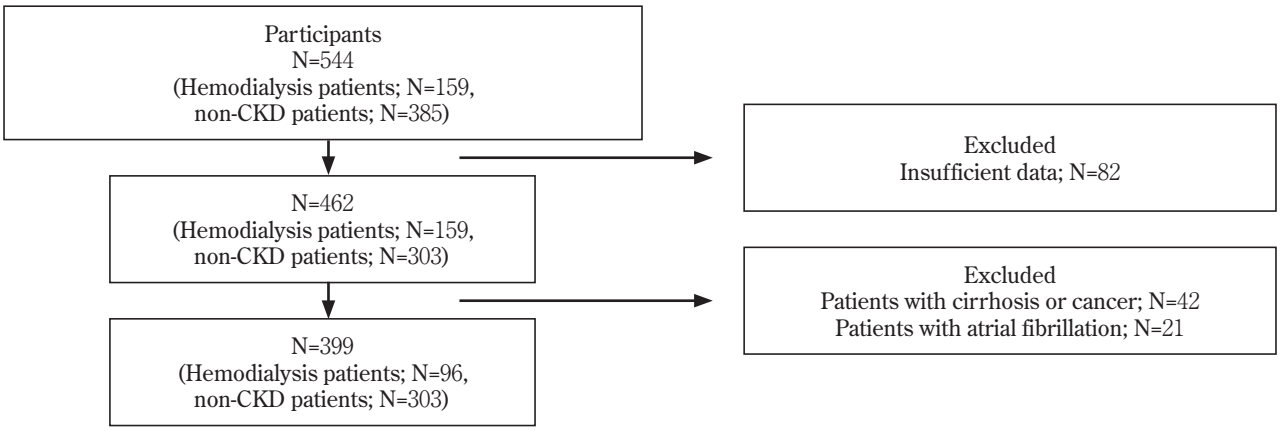

Figure 1. Flowchart of patient recruitment for this study

Laboratory data

The ECW/TBW index and muscle mass was measured in eligible patients using an InBody S20® (Biospace Inc., Seoul, Korea) using the bioelectrical impedance method. Blood test parameters, including serum total protein (TP), serum albumin (Alb), hemoglobin (Hb), hematocrit (Ht), blood urea nitrogen (BUN), and serum creatinine (Cr) were calculated before and after hemodialysis. In hemodialysis patients, we also measured the normalized dialysis dose (Kt/V), normalized protein catabolic rate (nPCR), percent Cr generation rate (CGR), and duration of dialysis therapy. After dialysis, a BIA was conducted and the serum HANP concentration was measured when the patient's weight reached the DW.

Statistical analysis

A statistical analysis was performed to compare the data of dialysis patients and non-CKD patients. All analyses were conducted using JMP14.2 (SAS Institute, Cary, NC, USA). *P* values of <0.05 were considered to indicate statistical significance. Values are shown as the mean ± SD for parametrically-distributed data and as the median [interquartile range] for non-parametrically distributed data. In hemodialysis patients, we also analyzed the correlation between the serum HANP level, Kt/V, nPCR, %CGR and duration of dialysis therapy. A multivariable linear analysis was used to evaluate the determinants of the ECW/TBW index in both groups. In the stepwise method, model-1 was used to analyze all parameters that showed statistically significant differences in each group, while model-2 was used to analyze common parameters that showed statistically significant associations in both groups.

Propensity score matching comparison

As differences in age and BMI existed between the hemodialysis and non-CKD groups, these factors could affect the ECW/TBW index. Therefore, we decided to adjust for age and BMI by propensity score matching. First, a logistic regression analysis was performed, with hemodialysis and non-CKD groups as dependent variables, and age and BMI as independent variables. Then, using 1:1 nearest neighbor matching, the response variable was the ECW/TBW index, the treatment variable was hemodialysis/non-CKD group, and the threshold was 0.05. Matching was performed using the propensity score obtained from the logistic regression analysis. A multivariable linear analysis was performed for 68 adjusted patients in each of the extracted hemodialysis and non-CKD groups. The items for which significant differences were obtained were further analyzed using the stepwise method with Model-1 and Model-2, as described above.

Results

Baseline data of study participants in hemodialysis and non-CKD patients

The median duration of dialysis therapy was 4.6 years. In comparison to the non-CKD patient group, they were older and had lower BMI and muscle mass (age: non-CKD patients 52.0[40.0-62.0] vs. hemodialysis patients 65.0 ± 11.3, p<0.001; BMI: Non-CKD patients 25.2[22.4-27.9] vs. hemodialysis patients 21.5[19.5-23.8], p<0.001; muscle mass, Non-CKD patients 43.2[34.6-50.7] vs. hemodialysis patients 34.0 ± 10.2, p<0.001) (Table 1). ECW/TBW index was statistically significantly higher in hemodialysis patients (ECW/TBW index: non-CKD patients 0.385 ± 0.008 vs. hemodialysis patients 0.398[0.391-0.406], p<0.001) (Table 1).

Multiple regression analysis of factors associated with the ECW/TBW index in hemodialysis and non-CKD patients

A multivariable linear analysis with ECW/TBW index as the objective variable showed significant correlations for age, BMI, muscle mass, Hb, Ht, serum Alb, and serum Cr in the non-CKD patient group. In the hemodialysis group, significant associations were observed in age, pre-dialysis Hb, pre-dialysis Ht, pre-dialysis serum TP, pre-dialysis serum Alb, pre-dialysis serum Cr, and post-dialysis Alb level. In addition, significant correlations were observed in serum HANP levels after hemodialysis and %CGR (Table 2). As for the parameters (serum TP, serum Alb, and serum Cr) that were significantly correlated with the ECW/TBW index in the hemodialysis patient group, the correlation between the pre-dialysis value and the post-dialysis value were examined, which one was stronger correlated factors. The results showed that for all of these parameters, the pre-dialysis parameters showed a much higher correlation than the post-dialysis parameters (Table 2). Therefore, in the subsequent stepwise analysis, only pre-dialysis serum TP, serum Alb, and serum Cr values were used in the dialysis group to exclude the influence of these confounding factors.

Stepwise analysis of factors associated with the ECW/TBW index in hemodialysis and non-CKD patients

A stepwise analysis was performed with the ECW/TBW index as the objective variable. Since Hb and Ht may be cofounding factor, Hb was selected as the factor because of its higher correlation. Muscle mass rather than BMI was chosen for the same reason. In Model 1, we analyzed variables that showed significant associations in each group. The variables identified that pre-dialysis serum Alb, Cr and Hb level, as significant factors in the hemodialysis group, in that order. In contrast, age, muscle mass and serum Cr level in the non-CKD group, showed significant in that order (Table 3). In Model 2, serum albumin, age, Hb and Cr selected. These were common variables that showed significant differences between the two groups. In the

Table 1. General characteristics of non-chronic kidney disease (CKD) and hemodialysis patients

	non-CKD patients (n=303)	Hemodialysis patients (n=96)	P value※
Age (y)	52.0[40.0-62.0]	65.0 ± 11.3	<0.001
Male (n)	171	62	0.090
Female (n)	132	34	0.090
BMI (kg/m^2)	25.2[22.4-27.9]	21.5[19.5-23.8]	<0.001
ECW/TBW index	0.385 ± 0.008	0.398[0.391-0.406]	<0.001
Muscle mass (kg)	43.2[34.6-50.7]	34.0 ± 10.2	<0.001
Pre-dialysis Hb (g/dL)	14.3[13.3-15.4]	10.6[9.5-11.3]	<0.001
Pre-dialysis Ht (%)	44.7[42.0-47.4]	34.1 ± 3.7	<0.001
Pre-dialysis TP (g/dL)	7.3 ± 0.4	6.5 ± 0.6	<0.001
Pre-dialysis Alb (g/dL)	4.4[4.2-4.6]	3.5 ± 0.4	<0.001
Pre-dialysis Cr (mg/dL)	0.68 ± 0.15	9.4 ± 2.6	<0.001
Pre-dialysis BUN (mg/dL)	12.9[11.0-15.0]	58.3 ± 17.5	<0.001
Post-dialysis TP (g/dL)	-	7.0 ± 0.8	-
Post-dialysis Alb (g/dL)	-	3.8 ± 0.4	-
Post-dialysis Cr (mg/dL)	-	3.5[2.8-4.2]	-
Post-dialysis BUN (mg/dL)	-	16.3[12.6-22.6]	-
Duration of dialysis therapy (y)	-	4.6[1.9-8.6]	-
Post-dialysis HANP (pg/mL)	-	57.1[38.0-88.4]	-
Kt/V	-	1.60 ± 0.30	-
nPCR (g/kg/day)	-	0.84 ± 0.15	-
%CGR (%)	-	91.2 ± 24.9	-

mean ± SD for parametrically distributed data, median [interquartile range] for non-parametrically distributed data
BMI: body mass index, Hb: hemoglobin, Ht: hematocrit, TP: total protein, Alb: albumin, Cr: creatinine, BUN: blood urea nitrogen, HANP: human atrial natriuretic polypeptide, nPCR: normalized protein catabolic rate, %CGR: percent creatinine generation rate
※ P value: non-CKD patients vs. hemodialysis patients analyzed by Shapiro-Wilk or Mann-Whitney U test.

Table2. Multivariable linear regression analysis

	non-CKD patients		Hemodialysis patients	
Variable (X)	Correlation coefficient |R|	P value※	Correlation coefficient |R|	P value※
Age	0.36	<0.001	0.35	<0.001
Gender	0.54	<0.001	0.03	0.748
BMI	0.37	<0.001	0.08	0.417
Muscle mass	0.60	<0.001	0.05	0.645
Pre-dialysis Hb	0.45	<0.001	0.36	<0.001
Pre-dialysis Ht	0.42	<0.001	0.33	0.001
Pre-dialysis TP	0.02	0.782	0.28	0.005
Pre-dialysis Alb	0.34	<0.001	0.50	<0.001
Pre-dialysis Cr	0.46	<0.001	0.44	<0.001
Pre-dialysis BUN	0.09	0.137	0.04	0.709
Post-dialysis TP			0.25	0.015
Post-dialysis Alb			0.46	<0.001
Post-dialysis Cr			0.25	0.014
Post-dialysis BUN			0.14	0.177
Duration of dialysis			0.14	0.207
Post-dialysis HANP			0.30	0.003
Kt/V			0.17	0.181
nPCR			0.04	0.777
%CGR			0.43	<0.001

BMI: body mass index, Hb: hemoglobin, Ht: hematocrit, TP: total protein, Alb: albumin, Cr: creatinine, BUN: blood urea nitrogen, HANP: human atrial natriuretic polypeptide, nPCR: normalized protein catabolic rate, %CGR: percent creatinine generation rate

hemodialysis group pre-dialysis serum Alb, Cr and Hb (in that order) showed significant effects. In contrast, age and serum Cr showed significant effects in non-CKD patients (Table 4).

Validation of determinants of the ECW/TBW index by propensity score matching

Our results showed differences in the background factors of age, BMI, and sex between the non-CKD and hemodialysis groups. Since the ECW/TBW index may be easily affected by differences in these background factors, we performed propensity score matching to exclude the effect of these factors. After propensity score matching, 68 patients remained in the non-CKD group and 68 patients remained in the hemodialysis group; there were no statistically significant differences between the two groups in age or BMI (age: non-CKD group 65.0[57.3-71.0] years vs. hemodialysis group 60.6 ± 9.8 years, p=0.180; BMI: non-CKD group 23.5[20.5-26.6] vs. hemodialysis group 22.0[20.1-24.6], p=0.200). When the two groups were compared, the ECW/TBW index was still significantly higher in the hemodialysis group (ECW/TBW index: non-CKD group 0.389 ± 0.008 vs. hemodialysis group 0.396[0.389-0.403], p<0.001) (Table 5).

Multivariate analysis of factors associated with the ECW/TBW index in hemodialysis and non-CKD patients after propensity score matching

We performed a multivariable linear analysis of the propensity score-matched groups using the ECW/TBW index as the objective variable. The results showed that age, sex, BMI, muscle mass, Hb level, Ht level, serum Alb, and serum Cr showed significant correlations in the non-CKD group (Table 6). On the other hand, in the hemodialysis group, age, pre-dialysis Hb, pre-dialysis Ht, pre-dialysis TP, pre-dialysis serum Alb, pre-dialysis Cr, post-dialysis serum Alb, post-dialysis Cr, and %CGR showed significant correlations (Table 6). The correlation coefficients of the blood sampling parameters (serum TP, serum Alb, and serum Cr) that were significantly correlated with the post-dialysis ECW/TBW index in the hemodialysis group, and the correlation coefficients of the pre-dialysis values were significantly higher than those of the post-dialysis values (Table 6). Therefore, in the subsequent stepwise analysis, the serum TP, serum Alb, and serum Cr levels after dialysis were excluded from the hemodialysis group in order to eliminate strong confounding factors.

Table 3. Stepwise method model-1

RANK	non-CKD patients				Hemodialysis patients			
	Factor	standardized coefficient	95% confidential interval	P value※	Factor	standardized coefficient	95% confidential interval	P value※
1	Age	0.321	1.1×10^{4} to 2.7×10^{4}	<0.001	Pre-dialysis Alb	-0.315	-1.5×10^{2} to -3.9×10^{3}	0.001
2	Muscle mass	-0.211	-2.9×10^{4} to -7.1×10^{6}	0.040	Pre-dialysis Cr	-0.246	-1.8×10^{3} to -2.6×10^{4}	0.010
3	Cr	-0.175	-1.7×10^{2} to -1.5×10^{4}	0.046	Pre-dialysis Hb	-0.227	-3.8×10^{3} to -5.2×10^{4}	0.010

Alb: albumin, Cr: creatinine, Hb: hemoglobin
※ P value: Factors vs. ECW/TBW index fluctuaion

In non-CKD patients and hemodialysis patients, the stepwise analysis was performed for all clinical parameters that showed significant differences in multivariable linear regression analysis for ECW/TBW index (In non-CKD patients: Age, Gender, Muscle mass, Hb, Alb, Cr; In hemodialysis patients: Age, Pre-dialysis Hb, Pre-dialysis Alb, Pre-dialysis Cr, Post-dialysis HANP).

Table 4. Stepwise method model-2

RANK	non-CKD patients				Hemodialysis patients			
	Factor	standardized coefficient	95% confidential interval	P value※	Factor	standardized coefficient	95% confidential interval	P value※
1	Age	0.397	1.5×10^{4} to 3.1×10^{4}	<0.001	Pre-dialysis Alb	-0.315	-1.5×10^{2} to -3.9×10^{3}	0.001
2	Cr	-0.338	-2.3×10^{2} to -1.0×10^{2}	<0.001	Pre-dialysis Cr	-0.246	-1.8×10^{3} to -2.6×10^{4}	0.010
3					Pre-dialysis Hb	-0.227	-3.8×10^{3} to -5.2×10^{4}	0.010

Hb: hemoglobin, Alb: albumin, Cr: creatinine
※ P value: Factors vs. ECW/TBW index fluctuation

The stepwise method was performed for ECW/TBW index to analyze the clinical common parameters (Age, Alb, Hb, Cr) which the significant differences were obtained by multivariable linear regression analysis in both non-CKD and hemodialysis patients.

Table 5. Patient profile after propensity score matching

	non-CKD patients (n=68)	Hemodialysis patients (n=68)	P value※
Age (y)	65.0[57.3-71.0]	60.6 ± 9.8	0.180
Male (n)	34	42	0.110
Female (n)	34	26	0.110
BMI (kg/m²)	23.5[20.5-26.6]	22.0[20.1-24.6]	0.200
ECW/TBW index	0.389 ± 0.008	0.396[0.389-0.403]	<0.001
Muscle mass (kg)	36.4[32.0-45.1]	34.7 ± 10.5	0.023
Pre-dialysis Hb (g/dL)	13.9 ± 1.5	10.8[9.5-11.5]	<0.001
Pre-dialysis Ht (%)	43.5 ± 3.9	34.4 ± 3.5	<0.001
Pre-dialysis TP (g/dL)	7.3 ± 0.4	6.5 ± 0.6	<0.001
Pre-dialysis Alb (g/dL)	4.3[4.2-4.6]	3.5 ± 0.4	<0.001
Pre-dialysis Cr (mg/dL)	0.65 ± 0.13	9.7 ± 2.8	<0.001
Pre-dialysis BUN (mg/dL)	14.4 ± 3.6	59.0 ± 19.1	<0.001
Post-dialysis TP (g/dL)	-	7.1 ± 0.8	-
Post-dialysis Alb (g/dL)	-	3.9 ± 0.4	-
Post-dialysis Cr (mg/dL)	-	3.7[2.9-4.4]	-
Post-dialysis BUN (mg/dL)	-	16.7[13.5-22.3]	-
Duration of dialysis therapy (y)	-	5.4[2.7-8.9]	-
Post-dialysis HANP (pg/mL)	-	50.4[31.8-74.4]	-
Kt/V	-	1.60 ± 0.29	-
nPCR (g/kg/day)	-	0.84 ± 0.14	-
%CGR (%)	-	91.2 ± 24.7	-

mean ± SD for parametrically distributed data, median [interquartile range] for non-parametrically distributed data
BMI: body mass index, Hb: hemoglobin, Ht: hematocrit, TP: total protein, Alb: albumin, Cr: creatinine, BUN: blood urea nitrogen, HANP: human atrial natriuretic polypeptide, nPCR: normalized protein catabolic rate, %CGR: percent creatinine generation rate
※P value: non-CKD patients vs. hemodialysis patients analyzed by Shapiro-Wilk or Mann-Whitney U test

Table 6. Multivariable linear regression analysis after propensity score matching

	non-CKD patients		Hemodialysis patients	
Variable (X)	Correlation coefficient |R|	P value※	Correlation coefficient |R|	P value※
Age	0.48	<0.001	0.26	0.030
Gender	0.34	0.005	0.02	0.853
BMI	0.24	0.046	0.06	0.620
Muscle mass	0.48	<0.001	0.12	0.329
Pre-dialysis Hb	0.32	0.009	0.39	0.001
Pre-dialysis Ht	0.28	0.022	0.30	0.012
Pre-dialysis TP	0.04	0.788	0.30	0.014
Pre-dialysis Alb	0.42	0.006	0.50	<0.001
Pre-dialysis Cr	0.40	0.003	0.43	<0.001
Pre-dialysis BUN	0.35	0.302	0.01	0.956
Post-dialysis TP			0.18	0.146
Post-dialysis Alb			0.38	0.002
Post-dialysis Cr			0.24	0.049
Post-dialysis BUN			0.14	0.266
Duration of dialysis			0.08	0.580
Post-dialysis HANP			0.21	0.086
Kt/V			0.16	0.289
nPCR			0.01	0.947
%CGR			0.50	<0.001

BMI: body mass index, Hb: hemoglobin, Ht: hematocrit, TP: total protein, Alb: albumin, Cr: creatinine, BUN: blood urea nitrogen, HANP: human atrial natriuretic polypeptide, nPCR: normalized protein catabolic rate, %CGR: percent creatinine generation rate

Stepwise analysis of factors associated with the ECW/TBW index in hemodialysis and non-CKD patients after propensity score matching

Model 1 of the stepwise analysis showed the significant effects of muscle mass and age in the non-CKD patient group and pre-dialysis serum Alb, Cr, and Hb levels in the hemodialysis group, in that order (Table 7). In Model 2 of the stepwise analysis, the common factors were age, Hb, serum Alb, and Cr. For these blood collection factors, the pre-dialysis values were used for the analysis of the hemodialysis group for the reasons mentioned above. In the non-CKD group, the factors that most significantly affected the ECW/TBW index were age, and serum Cr, in that order. In contrast, in the hemodialysis group, pre-dialysis serum Alb, Cr level, and Hb (in that order) were found to significant influence the post-dialysis ECW/TBW index (Table 8).

Discussion

The present study investigated the factors that affect the post-dialysis ECW/TBW index in hemodialysis patients in comparison to non-CKD patients as controls. The results showed that age had a strong influence on the ECW/TBW index in non-CKD patients. In contrast, the post-dialysis ECW/TBW index in the hemodialysis patients were strongly influenced by pre-dialysis serum Alb, pre-dialysis serum Cr, and pre-dialysis Hb. Although the pre-dialysis Cr and Hb levels were affected by dialysis conditions and erythropoietin dosage, it was very interesting that the pre-dialysis serum Alb levels had a stronger effect on the ECW/TBW index in hemodialysis patients than these factors.

In Japan, dialysis patients are characterized by older age, lower BMI, and show a male predominance in comparison to the general population[13, 14]. Therefore, if we performed a statistical analysis of the non-CKD and hemodialysis groups, it was assumed that these background differences might affect the analysis. Thus, in the present study, we compared hemodialysis patients and non-CKD patients with a normal renal function using usual analysis methods and then added a propensity score matching analysis that corrected for the background factors of hemodialysis patients. Since the pre-dialysis and post-dialysis serum Alb and Cr levels might change, it may be necessary to examine whether the pre-dialysis or post-dialysis levels had a greater influence on the ECW/TBW index. We first analyzed the correlation of the serum Alb and Cr levels measured before and after dialysis with the post-dialysis ECW/TBW index (Table 2). As a result, the serum Alb and serum Cr levels after hemodialysis showed a significant correlation with the post-dialysis ECW/TBW index, but their correlation coefficients were lower in comparison to the pre-dialysis correlation coefficients. Since the serum Alb and Cr values before and after dialysis were strong confounding factors, the pre-dialysis serum Alb and Cr values with higher correlation coefficients were used as factors in the rank correlation analysis. In the stepwise model 1 analysis after propensity score matching between the non-CKD and hemodialysis groups, the factors affecting the ECW/TBW index in the non-CKD group showed a

Table 7. Stepwise method model-1 after propensity score matching

RANK	non-CKD patients				Hemodialysis patients			
	Factor	standardized coefficient	95% confidential interval	P value※	Factor	standardized coefficient	95% confidential interval	P value※
1	Muscle mass	-0.424	-6.5×10^4 to -2.4×10^4	<0.001	Pre-dialysis Alb	-0.34	-1.6×10^2 to -3.9×10^3	0.002
2	Age	0.414	1.6×10^4 to 4.4×10^4	<0.001	Pre-dialysis Cr	-0.30	-2.0×10^3 to -4.0×10^4	0.004
3					Pre-dialysis Hb	-0.28	-4.6×10^3 to -7.6×10^4	0.007

Alb: albumin, Cr: creatinine, Hb: hemoglobin
※P value: Factors vs. ECW/TBW index fluctuation

In non-CKD and CKD G5D patients, all parameters that showed significant differences in ECW/TBW index by multivariable linear regression analysis (In non-CKD patients: Age, Gender Muscle mass, Hb, Alb, Cr: In hemodialysis patients: Age, Pre-dialysis Hb, Pre-dialysis Alb, Pre-dialysis Cr) were used by the stepwise method.

Table 8. Stepwise method model-2 after propensity score matching

RANK	non-CKD patients				Hemodialysis patients			
	Factor	standardized coefficient	95% confidential interval	P value※	Factor	standardized coefficient	95% confidential interval	P value※
1	Age	0.54	2.3×10^4 to 6.5×10^4	<0.001	Pre-dialysis Alb	-0.34	-1.6×10^2 to -3.9×10^3	0.002
2	Cr	-0.29	-3.5×10^2 to -3.3×10^3	0.019	Pre-dialysis Cr	-0.30	-2.0×10^3 to -4.0×10^4	0.004
3					Pre-dialysis Hb	-0.28	-4.6×10^3 to -7.6×10^4	0.007

Hb: hemoglobin, Alb: albumin, Cr: creatinine
※P value: Factors vs. ECW/TBW index fluctuation

The common parameters (Age, Hb, Alb, Cr) significantly different from ECW/TBW index by multivariable linear regression analysis both in non-CKD and hemodialysis patients were analyzed by the stepwise method.

strong correlation in the order of muscle mass and age, whereas in the hemodialysis group muscle mass and age were not extracted. Strong correlations were found in the order of pre-dialysis serum Alb, pre-dialysis serum Cr, and pre-dialysis Hb in the hemodialysis group. This result clearly shows that different factors influenced post-dialysis edema in hemodialysis patients in contrast to non-CKD patients. In the stepwise model 2 analysis after propensity score matching, serum Cr was a common parameter affecting the ECW/TBW index in both the non-CKD and hemodialysis groups. Serum Cr changes depending on the muscle mass volume. It has been reported that the amount of exercise is correlated with muscle mass in the elderly[15]. In this study, the ECW/TBW index was correlated with the serum Cr level, and might reflect muscle mass volume.

Our study found that pre-dialysis serum Alb was the most influential factor in post-dialysis ECW/TBW index. In healthy subjects, serum Alb is affected by the liver function, protein intake, and physical activity[15-17]. In this study, patients with an impaired hepatic function were excluded, and the results of this study were not affected by the hepatic function. Protein intake or physical activity might affect serum Alb levels. In the present study, the nPCR, an index of protein intake, and %CGR, an index of muscle production, were also examined in relation to the post-dialysis ECW/TBW index in hemodialysis patients. Among these parameters, only %CGR showed a significant correlation (Table 6). It is interesting to note that the pre-dialysis serum Cr level, which is dependent on the muscle mass in the body, showed a significant negative correlation with post-dialysis edema, followed by the pre-dialysis serum Alb level. Short-term exercise therapy might only improve the %CGR and long-term continuation of exercise is necessary to increase skeletal muscle mass[18]. Our results suggest the possibility that muscle mass might be associated with post-dialysis edema in hemodialysis patients. In this study, no significant correlation was found between HANP and ECW/TBW index in the hemodialysis group in the selected population after propensity score matching. HANP is known to be an indicator that reflects the circulating blood volume after hemodialysis, and this result indicates that the present study was conducted under the condition of an adequate circulating blood volume after dialysis.

Recently management according to the post-dialysis ECW/TBW index measured by the BIA method has found to be more helpful for preventing reduced life expectancy, hypertension, and atherosclerosis in comparison to the intravascular extracellular fluid volume as an index for DW[19]. On the other hand, another study reported that management according to BIA method significantly improved only systolic blood pressure in dialysis patients[20]. Low pre-dialysis serum Alb levels are known to be a poor prognostic factor for life in dialysis patients[21]; however, the detailed mechanism underlying this association remains unclear. Also, it remains unclear which fluid management by the BIA method had a positive effect on the prognosis of hemodialysis patients. Thus, the prognostic effect of improving serum Alb level and measuring post-dialysis ECW/TBW index needs to be addressed by further investigation in prospective interventional studies. In addition, this study population was limited to Japanese individuals living in a single prefecture, and additional verification is needed to see if the results apply across countries and races.

In conclusion, while age strongly influenced the ECW/TBW index in non-CKD patients, that in hemodialysis patients was more strongly influenced by serum Alb than age. High ECW/TBW index is associated with a poor prognosis in hemodialysis patients, suggesting the importance of paying attention to the pre-dialysis albumin concentration in the setting of the body fluid removal for DW.

Disclosure statement

The authors declare no potential conflicts of interest in association with the research, authorship and/or publication of this article.

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血液透析患者の透析後浮腫値規定因子に関する検討

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要　　約

背景：血液透析（HD）患者においてバイオインピーダンス（BIA）法により測定した透析後浮腫値の決定因子について検討した。
方法：我々はHD患者159名と非慢性腎臓病（非CKD）患者385名を対象とし，BIA法で浮腫値（細胞外水分量／全体水分量の比）を測定した。浮腫値を目的変数として，各種測定項目との関係を重回帰分析およびステップワイズ法で解析した。両群間で相違がみられた年齢，性別，BMIの差について，傾向スコアマッチングで調整を行った後，同様な解析を施行した。
結果：ステップワイズ法で浮腫値に対して非CKD患者では年齢と血清Crが，HD患者では透析前Alb，Cr，Hbが関連していた。傾向スコアマッチングによる解析では，浮腫値に対して非CKD患者では年齢が，HD患者ではAlbがもっとも強い影響を認めた。
結語：非CKD患者では年齢が浮腫値に強く影響を与える一方で，HD患者の浮腫値は年齢よりも血清Alb値により強く影響を受けることが示された。HD患者では高度浮腫は生命予後と関連すると報告されており，血清Alb濃度を考慮したドライウエイト設定が重要であることが示唆された。
（キーワード：バイオインピーダンス法，浮腫値，血液透析，傾向スコアマッチング）

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