Kidney & Blood Pressure Research

Kidney Blood Press Res 2012;36:231-241
DOI: 10.1159/000343412
Published online: November 19, 2012
Accepted: October 19, 2012

1420-4096/12/0361-0231$38.00/0

Original Paper

Associations of Proteinuria, Fluid Volume Imbalance, and Body Mass Index with Circadian Ambulatory Blood Pressure in Chronic Kidney Disease Patients

Yasushi Ohashi Takatoshi Otani Reibin Tai Takayuki Okada Kentarou Tanaka Yoshihide Tanaka Ken Sakai Atsushi Aikawa

Department of Nephrology, Toho University School of Medicine, Tokyo, Japan

Key Words
Ambulatory blood pressure monitoring • Body composition • Bioelectrical impedance • Fluid balance • Chronic kidney disease

Abstract
Background/Aims: Obesity and hypervolemic status are the main causes of hypertension in patients with chronic kidney disease (CKD). However, it is difficult to differentiate between them. We aimed to assess the associations of body mass index (BMI) and total body water (TBW) with ambulatory blood pressure (ABP). ***Methods:*** Body composition by bioelectrical impedance analysis (BIA) and 24-h ABP were measured in 40 patients with CKD. TBW was assessed using corrected TBW_{BIA} adjusted for body surface area ($cTBW_{BIA}$) and the TBW_{BIA}/TBW_{Watson} ratio obtained using an anthropometric formula (Watson). ***Results:*** Elevated ABP (average 24-h BP ≥ 135/85 mmHg) was noted in 23 patients, who were more likely to have a higher $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson} ratio than patients without elevated BP. Patients with nocturnal non-dipping (<10% drop in BP during sleep) were more likely to have a higher TBW_{BIA}/TBW_{Watson} ratio. Proteinuria and the TBW_{BIA}/TBW_{Watson} ratio were significant independent factors for 24-h ABP. BMI had a positive correlation with the $cTBW_{BIA}$, TBW_{BIA}/TBW_{Watson} ratio and furosemide use. ***Conclusion:*** Hypertension is dependent on proteinuria and fluid volume imbalance. The TBW_{BIA}/TBW_{Watson} ratio can serve as an indicator of fluid volume-dependent hypertension. BMI is affected by TBW, in which case BMI can become less involved with 24-h ABP.

Yasushi Ohashi, MD

Department of Nephrology, Toho University School of Medicine, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541 (Japan), Tel. + 81 3 3762 4151, Fax + 81 3 5471 3056
E-Mail ys-0084@med.toho–u.ac.jp

Kidney & Blood Pressure Research

Kidney Blood Press Res 2012;36:231-241
DOI: 10.1159/000343412
Published online: November 19, 2012

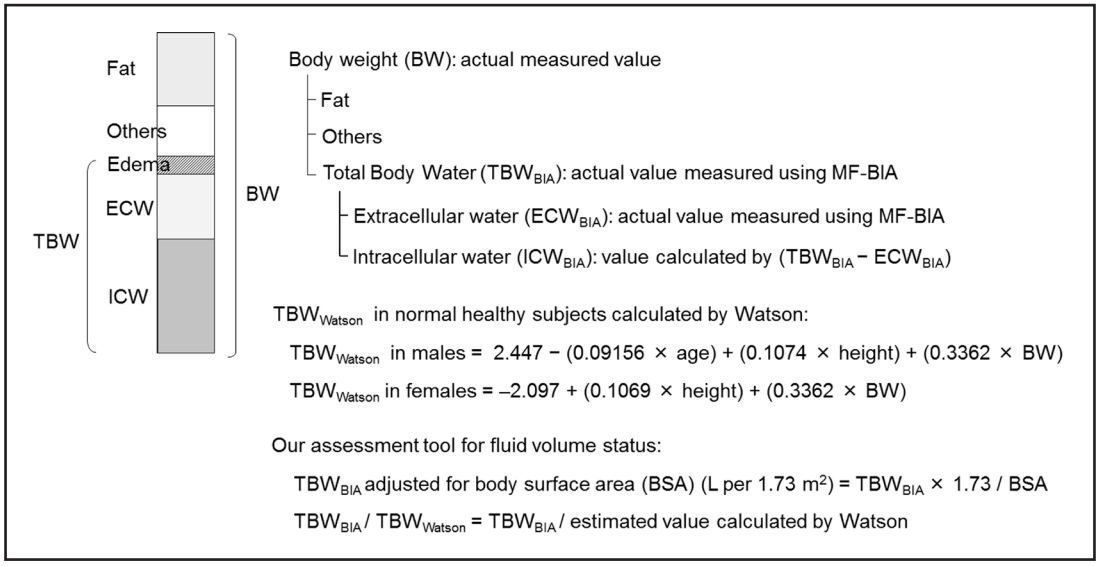
Introduction

Hypertension occurs in approximately 80–85% of patients with chronic kidney disease (CKD) [1]. Hypertension in CKD results from excess fluid volume with sodium retention, increased renin-angiotensin activity, enhanced sympathetic nervous activity [2], secondary hyperparathyroidism [3], erythropoietin treatment [4], impaired nitric oxide synthesis [5], and endothelium-mediated vasodilatation [5]. Lastly, hypertension itself causes or contributes to the development of CKD [6]. Moreover, patients with CKD may not demonstrate the normal nocturnal decline in blood pressure (BP), and are consequently at possible risk of hypertensive complications [7]. In the general population, body mass index (BMI) is closely associated with hypertension, which promotes atherosclerotic cardiovascular disease (CVD) and is associated with increased mortality [8–10]. Obesity may also be associated with developing CKD [11–13]. For dialysis patients, however, several studies have reported that the BMI is inversely related with mortality [14, 15] and BP [16]. These studies have suggested that dialysis patients, especially those with the malnutrition-inflammation syndrome, often lose weight [14, 15] or that obese patients sequester excess fluid volume in extracellular space more effectively than do lean people and therefore do not develop hypertension [16]. Thus, the BMI is likely to become less involved with BP and mortality with progression of CKD. Unlike the general population, changes in the body weight (BW) in CKD patients may be caused not only by changes in muscle and fat but also by the fluid status, suggesting that the BMI in such patients might not be merely a marker for obesity. Among the various factors that cause hypertension in patients with CKD, it is often difficult to differentiate between the influence of fluid volume imbalance that promotes fluid volume-dependent hypertension and the influence of either obesity or the malnutrition and inflammation syndrome promoting atherosclerosis-dependent hypertension.

The isotopic dilution technique (D_2O) and dual energy X-ray absorptiometry (DEXA) are reliable methods for the measurement of total body water (TBW) [17]. However, these techniques are invasive and inconvenient to perform. Multi-frequency bioelectrical impedance analysis (MF-BIA) has been observed to be a suitable noninvasive alternative to these techniques [18]. MF-BIA can effectively distinguish between intra- and extracellular components. The values of TBW_{BIA}, intracellular water (ICW_{BIA}), and extracellular water (ECW_{BIA}) measured by MF-BIA have a high correlation with the corresponding values measured by D_2O and DEXA [18]. In fact, the fat-free mass and the ratio of ECW to TBW measured by MF-BIA have been used for the assessment of fluid volume status in CKD patients [19, 20]. However, fluid volume status cannot be distinguished from these indicators because the balance of ECW and ICW appears to change depending on the edematous status as well as the body type of patients, such as obese or lean [21, 22]. In particular, individuals with the lean body type show an increased ECW_{BIA}/TBW_{BIA} ratio with a decreased ICW_{BIA} regardless of their edematous state [21, 22]. A recent study has proposed a new 3-compartment model comprising normally hydrated adipose tissue mass, normally hydrated lean tissue mass and excess fluid mass [21]; the difference between the expected normal ECW obtained by calculation and the measured ECW value is used to assess the fluid volume status [23]. However, these methods need complicated formulae and the appropriate reference values. Thus, a reliable indicator of fluid volume status corresponding to body type in CKD patients remains unavailable.

Anthropometric formulae used in combination with tracer dilution techniques (e.g., Watson) have been widely used to calculate the TBW_{Watson} in CKD patients [24]. The Watson formula, which is routinely used when calculating dialysis efficiency, was originally derived from pooled data of healthy volunteers; it provides information regarding adequate fluid volume balance. Consequently, TBW_{BIA} is the actual value of fluid volume and TBW_{Watson} provides the adequacy of fluid volume. The TBW_{BIA}/TBW_{Watson} ratio, which can be calculated using anthropometric formulae, may possibly be a practical tool for assessing the fluid volume.

Fig. 1. Frame format of the body fluid composition, assessment tools, and equations.



The present study aimed to assess the associations of body fluid composition and the BMI with 24-h ambulatory blood pressure (ABP) in CKD patient and to provide a reliable tool for assessing the fluid volume status.

Materials and Methods

Study design

We randomly selected 40 ambulatory patients with CKD from our kidney center to participate in this study. Informed consent was obtained from all the patients. This study was approved by the Ethics Committee of Toho University Omori Medical Center, Tokyo, Japan. CKD was diagnosed if any of the following parameters were met: estimated glomerular filtration rate (eGFR) <60 mL·min^{-1} per 1.73 m^2 for at least 3 months; presence of proteinuria (spot urine/protein ratio ≥300 mg/g creatinine); or the presence of structural kidney disease (e.g., adult polycystic kidney disease), according to the Kidney Disease Outcomes Quality Initiative and the position statement of Kidney Disease: Improving Global Outcomes [25]. The participants were surveyed for age, gender, height, body weight, BMI, underlying disease, BP, serum albumin (Alb), total cholesterol (TC) to high-density lipoprotein (HDL) ratio, low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratio, uric acid (UA), eGFR, proteinuria, and prescription of diuretics and antihypertensive agents. Hyperuricemia was diagnosed when the uric acid level was >7.0 mg/dL and >6.0 mg/dL in male and female patients, respectively. The eGFR was calculated according to the revised formula of [194 × Cr$^{-1.094}$ × Age$^{-0.287}$] (×0.739 for women) for Japanese patients according to the Modification of Diet in Renal Disease method [26].

To assess the components of body fluid composition, we used the assessment methods and equations described in Figure 1. MF-BIA was performed in the standard manner with the patient lying supine on a flat nonconductive bed for at least 15 min. For the determination of TBW$_{BIA}$, we used a segmental MF-BIA instrument (Inbody S20®;Biospace Co. Ltd., Seoul, Korea; www.biospaceamerica.com), which has 8 tactile electrodes. The microprocessor-controlled switches and impedance analyzer were activated and the segmental resistances of the arms, trunk, and legs were measured at 4 frequencies (5, 50, 250, and 500 kHz). Thus, a set of 20 segmental resistances was measured for each individual. These data were then used to calculate TBW$_{BIA}$ from the sum of the measurements for each body segment by using MF-BIA software. The measured TBW$_{BIA}$ was expressed as actual values, percentages of BW, and corrected values for body surface area (BSA) (cTBW$_{BIA}$). TBW$_{Watson}$ was calculated according to the Watson formula [24]; then, the TBW$_{BIA}$/TBW$_{Watson}$ ratio was calculated. The cTBW$_{BIA}$ and TBW$_{BIA}$/TBW$_{Watson}$ ratio were used to assess the fluid volume status.

ABP was measured every 20 min (6:00 AM to 10:00 PM) during the day and every 30 min at night (10:00 PM to 6:00 AM) using automated ABP monitors on the arm. In this study, patients with <8 h of ABP recordings were considered to have inadequate measurements and were excluded from the analysis. Average 24-h ABP values of ≥135/85 mmHg were considered as elevated ABP [27] regardless of antihypertensive agent use. Nocturnal non-dipping was defined as a decrease of <10% in systolic BP during sleep as compared with that during the awaking period [28].

Statistical Analysis

Data were statistically analyzed using JMP version 9.0 software (SAS Institute Inc, Cary, NC). Homogeneity of variances was analyzed using Bartlett's test. When the variances of the 2 groups were assumed to be equal, statistical significance for the 2 groups was assessed using Student's *t*-test for continuous variables, as appropriate, and Pearson's χ^2 test or Fisher's exact test for categorical variables. The measured values were expressed as mean ± standard deviation (SD) and percentages. The significance of the correlations between the $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson} ratio values and the variables of 24-h ABP were analyzed using Pearson product-moment correlation coefficient. The variables that showed a *p*-value of <0.20 in the correlation coefficients were analyzed using stepwise linear regression analysis to exclude confounding factors. The analyzed values were expressed as standardized partial regression coefficient ±standard error (SE) in the stepwise multivariate linear regression model. A *p*-value of <0.05 was considered statistically significant.

Results

Associations of demographic characteristics with circadian blood pressure

Table 1 presents the relevant baseline characteristics of the 40 study participants in relation to the presence or absence of elevated ABP and nocturnal non-dipping. Twenty-three (57.5%) patients showed elevated ABP; these patients were more likely to be younger and have diabetes mellitus (DM), lower eGFR, increased proteinuria, and lower Alb levels than the patients without elevated ABP. The 2 groups did not differ significantly with respect to the lipid profile, uric acid level, and prescription of diuretics and antihypertensive agents. In this population, 26 (65.0%) patients showed nocturnal non-dipping; these patients were more likely to have DM and lower Alb levels than patients with nocturnal dipping.

Associations of demographic characteristics with body fluid composition and BMI

Tables 2 and 3 present the associations of demographic variables with the $cTBW_{BIA}$, the TBW_{BIA}/TBW_{Watson} ratio, and the BMI. The $cTBW_{BIA}$ showed an independent positive association with male gender, BMI, and furosemide use and negative association with age. In contrast, the TBW_{BIA}/TBW_{Watson} ratio was independently positively associated with DM and furosemide use. The BMI was negatively correlated with age and was positively correlated with furosemide use, any 1 or more diuretics use, and any 3 or more antihypertensives use. However, there were no independent demographic factors for the BMI after adjusting for age, DM, TC/HDL ratio, furosemide use, and any 3 or more antihypertensives use.

Associations of body fluid composition and BMI with circadian blood pressure

Figure 2 presents the body fluid composition obtained by MF-BIA and the Watson formula and BMI in relation to the presence or absence of elevated ABP and nocturnal non-dipping. The $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson} ratio values were more likely to be significantly higher in patients with elevated ABP ($cTBW_{BIA}$: 33.1 ± 5.5 L vs. 35.2 ± 5.1 L, $p < 0.05$, and TBW_{BIA}/TBW_{Watson} ratio: 0.952 ± 0.064 vs. 1.010 ± 0.050, $p < 0.01$). Further, the TBW_{BIA}/TBW_{Watson} ratio was more likely to be significantly higher in patients with nocturnal non-dipping than in those without nocturnal non-dipping (0.952 ± 0.054 L vs. 1.000 ± 0.060 L, $p < 0.05$), but there was no significant difference in the $cTBW_{BIA}$ between patients with and without nocturnal non-dipping. BMI showed no significant differences between the presence and absence of elevated ABP and nocturnal non-dipping.

Table 1: Clinical characteristics according to the presence of elevated average 24-h blood pressure and nocturnal non-dipping

Characteristics	Overall	24-h ambulatory BP		*p*	Nocturnal dipping		*p*
		<135/85 mmHg	≥135/85 mmHg		≥10%	<10%	
Number, n	40	17 (42.5)	23 (57.5)		14 (35.0)	26 (65.0)	
Age, years	68.7 ± 11.6	73.1 ± 11.3	65.5 ± 11.0	0.040	70.3 ± 12.2	67.9 ± 11.4	0.539
Gender female, n (%)	7 (17.5)	3 (17.6)	4 (17.4)	1.000	3 (21.4)	4 (15.4)	0.679
BW, kg	64.1 ± 11.2	61.6 ± 11.8	66.0 ± 10.6	0.223	62.0 ± 10.4	65.3 ± 11.7	0.386
BMI, kg/m^2	24.4 ± 3.5	23.8 ± 3.7	24.9 ± 3.3	0.359	23.7 ± 2.9	24.8 ± 3.7	0.354
Diabetes mellitus, n (%)	17 (42.5)	3 (17.6)	14 (60.9)	0.010	3 (21.4)	14 (53.9)	0.048
eGFR, mL/min per 1.73 m^2	26.0 ± 16.6	32.1 ± 18.7	21.6 ± 13.1	0.042	30.9 ± 20.0	23.4 ± 13.7	0.170
Proteinuria, g/g creatinine	1.9 ± 2.7	0.3 ± 0.7	3.1 ± 3.0	<0.001	1.2 ± 2.7	2.4 ± 2.6	0.178
Alb, g/dL	3.8 ± 0.5	4.0 ± 0.3	3.6 ± 0.6	0.003	4.0 ± 0.3	3.6 ± 0.6	0.039
TC/HDL	4.1 ± 1.8	3.8 ± 2.1	4.3 ± 1.7	0.439	4.3 ± 2.5	4.0 ± 1.4	0.732
LDL/HDL	2.4 ± 1.3	2.1 ± 1.7	2.6 ± 1.1	0.413	2.4 ± 1.8	2.4 ± 1.0	0.872
Hyperuricemia, n (%)	27 (67.5)	9 (52.9)	18 (78.3)	0.082	9 (64.3)	18 (69.2)	0.723
Diuretics							
Thiazide, n (%)	3 (7.5)	0 (0.0)	3 (13.0)	0.248	1 (7.1)	2 (7.7)	1.000
Furosemide, n (%)	13 (32.5)	4 (23.5)	9 (39.1)	0.333	4 (28.6)	9 (34.6)	1.000
Aldosterone antagonist, n (%)	3 (7.5)	1 (5.9)	2 (8.7)	1.000	1 (7.1)	2 (7.7)	1.000
Any 1 of the above diuretics, n (%)	15 (37.5)	5 (29.4)	10 (43.5)	0.325	6 (42.9)	9 (34.6)	0.873
Any 2 of the above diuretics, n (%)	2 (5.0)	0 (0.0)	2 (8.7)		0 (0.0)	2 (7.7)	
Antihypertensives							
ACE inhibitors, n (%)	8 (20.0)	4 (23.5)	4 (17.4)	0.703	3 (21.4)	5 (19.2)	1.000
AT1-R blocker, n (%)	34 (85.0)	13 (76.5)	21 (91.3)	0.373	11 (78.6)	23 (88.5)	0.646
Ca channel blocker, n (%)	27 (67.5)	10 (58.8)	17 (73.9)	0.496	8 (57.1)	19 (73.1)	0.480
β-blocker, n (%)	6 (15.0)	3 (17.6)	3 (13.0)	1.000	2 (14.3)	4 (15.4)	1.000
α-blocker, n (%)	5 (15.0)	1 (5.9)	4 (17.4)	0.373	1 (7.1)	4 (15.4)	0.640
Number of antihypertensives, n	2.5 ± 1.3	1.8 ± 0.8	2.1 ± 1.0	0.310	1.8 ± 0.9	2.1 ± 1.0	0.293

Values are expressed as mean ± SD and percentages. Abbreviations: BP, blood pressure; BW, body weight; BMI, body mass index; eGFR, estimated glomerular filtration rate; Alb, serum albumin; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme; AT1-R, angiotensin II type 1 receptor

Table 4 presents the associations of demographic characteristics and body fluid status with the average systolic 24-h ABP and the average diastolic 24-h ABP. Model 1 in Table 4 shows the β-coefficients of variables for these dependent variables concerning the $cTBW_{BIA}$, and Model 2 in Table 4 shows these values for variables concerning the TBW_{BIA}/TBW_{Watson} ratio. After adjusting for multiple variables by stepwise linear regression analysis, proteinuria of ≥1.0 g/g creatinine remained a significant independent factor for the average systolic and diastolic 24-h ABP in Model 1 and 2, and age remained a significant independent factor for the average diastolic 24-h ABP in Model 1. The TBW_{BIA}/TBW_{Watson} ratio remained significant independent factors for the average systolic 24-h ABP in Model 2. However, there were no significant independent factors for nocturnal non-dipping.

Associations of the $cTBW_{BIA}$ *and the* TBW_{BIA}/TBW_{Watson} *ratio with BMI*

Correlations of the BMI with the $cTBW_{BIA}$ and the TBW_{BIA}/TBW_{Watson} ratio are presented in Figure 3. The BMI was intermediately correlated with the $cTBW_{BIA}$ ($r = 0.520$, $p < 0.001$), which was an independent associate factor, and weakly correlated with the TBW_{BIA}/TBW_{Watson} ratio ($r = 0.323$, $p < 0.05$).

Discussion

This present study revealed the association of body fluid composition with 24-h ABP and the association between TBW and BMI in patients with CKD. The study results suggested the following: (1) Patients with elevated ABP are more likely to have higher $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson} ratio values, and patients with nocturnal non-dipping are more likely to

Kidney & Blood Pressure Research

Kidney Blood Press Res 2012;36:231-241
DOI: 10.1159/000343412
Published online: November 19, 2012

Table 2: Correlations of demographic variables with $cTBW_{BIA}$, TBW_{BIA}/TBW_{Watson}, and BMI

Variables	$cTBW_{BIA}$ (L per 1.73 m^2)		TBW_{BIA}/TBW_{Watson}		BMI (kg/m^2)	
	β	*p*	β	*p*	β	*p*
Age, years	−0.510	<0.001	−0.320	0.044	−0.378	0.016
Male gender	0.554	<0.001	0.293	0.067	−0.029	0.860
Diabetes mellitus	0.361	0.022	0.386	0.014	0.232	0.150
BMI, kg/m^2	0.523	<0.001	0.330	0.038	–	–
eGFR, mL/min per 1.73 m^2	−0.046	0.777	−0.138	0.396	0.085	0.603
Proteinuria ≥ 1.0g/g creatinine	0.265	0.099	0.267	0.096	0.198	0.221
Alb, g/dL	−0.254	0.114	−0.370	0.019	0.078	0.630
TC/HDL	0.013	0.949	0.111	0.580	0.258	0.193
LDL/HDL	<0.001	0.997	0.121	0.549	0.238	0.231
Hyperuricemia	0.097	0.557	−0.064	0.698	0.030	0.854
Thiazide	0.101	0.534	0.004	0.982	0.141	0.387
Furosemide	0.356	0.024	0.379	0.016	0.358	0.023
Aldosterone antagonist	0.053	0.743	<0.001	0.999	−0.118	0.913
Any 1 or more of the above diuretics	0.211	0.192	0.276	0.084	0.375	0.017
ACE inhibitors	0.188	0.245	0.112	0.492	0.177	0.274
AT1-R blocker	0.139	0.393	0.239	0.137	−0.125	0.441
Ca channel blocker	0.025	0.881	−0.038	0.816	0.062	0.702
β-blocker	0.068	0.675	0.182	0.260	0.066	0.687
α-blocker	0.032	0.845	0.094	0.563	0.302	0.059
Any 3 or more antihypertensives	0.258	0.107	0.302	0.059	0.325	0.041

Abbreviations: $cTBW_{BIA}$, total body water determined using bioelectrical impedance analysis adjusted for body surface area; TBW_{BIA}, total body water determined using bioelectrical impedance analysis; TBW_{Watson}, total body water determined using Watson formula; BMI, body mass index; eGFR, estimated glomerular filtration rate; Alb, serum albumin; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin converting enzyme; AT1-R, angiotensin II type 1 receptor

Table 3: Stepwise multivariate linear regression models for $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson}* (*Only statistically significant differences are presented. Explanatory variables were selected on the basis of a *p* value of <0.20 in the prior univariate analysis. Variables included in the stepwise multivariate linear regression models for $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson} were age, male gender, diabetes mellitus, body mass index, proteinuria ≥ 1.0 g/g creatinine, furosemide, and angiotensin II type 1 receptor (AT1-R) blocker. Albumin, number of diuretics, and number of antihypertensives were not included in these analyses because these variables may possibly have had multicollinearity for proteinuria, furosemide, and AT1-R blocker, respectively)

	β	SE	*p*
$cTBW_{BIA}$, L per 1.73m^2			
Age, years	−0.414	0.029	<0.001
Male gender	0.574	0.404	<0.001
BMI, kg/m^2	0.307	0.160	0.003
Furosemide	0.211	0.539	0.024
TBW_{BIA}/TBW_{Watson}			
Diabetes mellitus	0.334	0.009	0.026
Furosemide	0.326	0.009	0.030

Abbreviations: : $cTBW_{BIA}$, total body water by using bioelectrical impedance analysis adjusted for body surface area; BMI, body mass index; TBW_{BIA}, total body water determined using bioelectrical impedance analysis; TBW_{Watson}, total body water determined using the Watson formula

have higher TBW_{BIA}/TBW_{Watson} ratios, whereas BMI is not associated with elevated ABP and nocturnal non-dipping; (2) proteinuria is an independent factor for average 24-h ABP, and TBW_{BIA}/TBW_{Watson} ratio is an independent factor for average systolic 24-h ABP; and (3) BMI has a positive correlation with the $cTBW_{BIA}$ and the TBW_{BIA}/TBW_{Watson} ratio.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2012;36:231-241
DOI: 10.1159/000343412
Published online: November 19, 2012

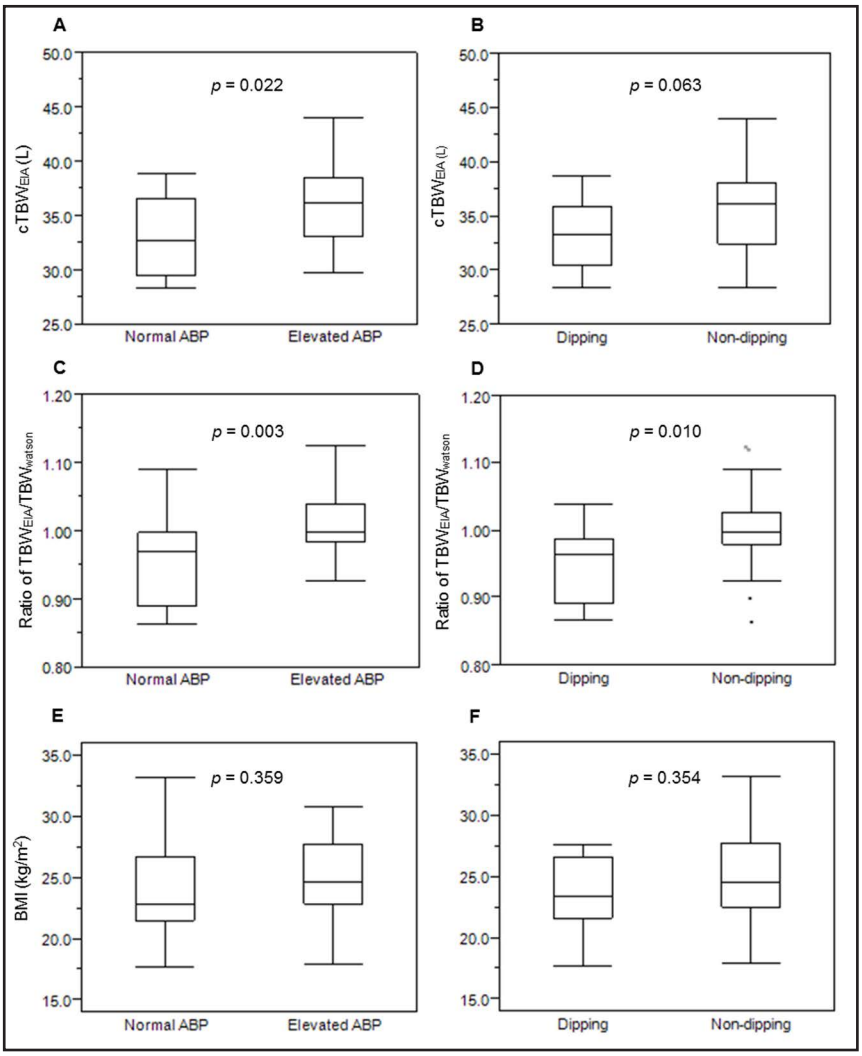


Fig. 2. Box plots of $cTBW_{BIA}$ (A and B), TBW_{BIA}/TBW_{Watson} (C and D) and BMI (E and F) according to the presence of elevated ABP and nocturnal non-dipping. ABP, ambulatory blood pressure; $cTBW_{BIA}$, total body water by using bioelectrical impedance analysis adjusted for body surface area; TBW_{BIA}, total body water determined using bioelectrical impedance analysis; TBW_{Watson}, total body water determined using the Watson formula.

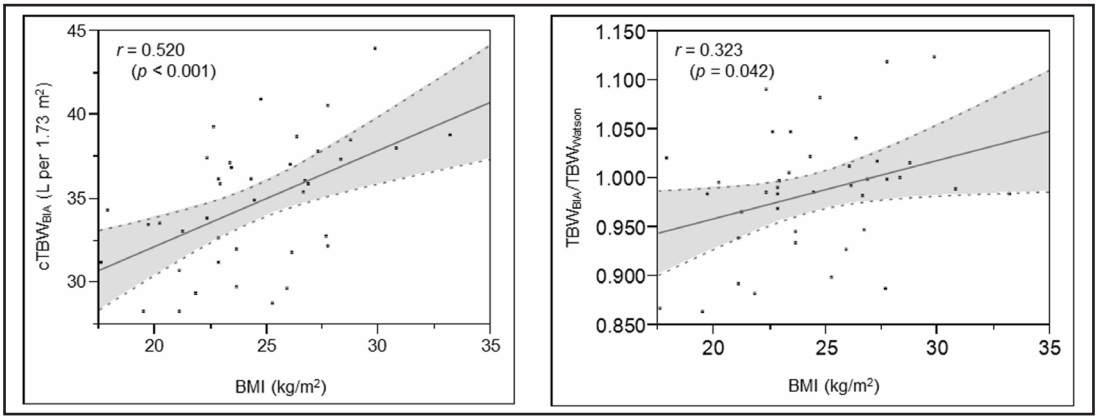


Fig. 3. Correlations of BMI with $cTBW_{BIA}$ and TBW_{BIA}/TBW_{Watson}. Abbreviations: $cTBW_{BIA}$, total body water by using bioelectrical impedance analysis adjusted for body surface area; TBW_{BIA}, total body water determined using bioelectrical impedance analysis; TBW_{Watson}, total body water determined using the Watson formula.

Obesity is an independent risk factor for hypertension [8–10] and CKD [11–13]. Nevertheless, the relationship between BMI and BP is attenuated in advanced CKD, and BMI

Table 4: Stepwise multivariate linear regression models for average 24-h blood pressure* (*Only statistically significant differences are presented. Explanatory variables were selected on the basis of a *p* value of <0.20 in the prior univariate analysis. Model 1 shows the β coefficients for average 24-h blood pressure by variables involving $cTBW_{BIA}$, and model 2 shows those by variables involving TBW_{BIA}/TBW_{Watson}. Variables included in the stepwise multivariate linear regression models for average 24-h systolic blood pressure (BP) were age, diabetes mellitus, estimated glomerular filtration rate (eGFR), proteinuria ≥ 1.0 g/g creatinine, hyperuricemia, and $cTBW_{BIA}$ or TBW_{BIA}/TBW_{Watson} and for average 24-h diastolic BP were age, diabetes mellitus, eGFR, proteinuria ≥ 1.0 g/g creatinine, and $cTBW_{BIA}$ or TBW_{BIA}/TBW_{Watson})

	β	SE	*p*
Model1			
Average 24-h SBP, mmHg			
Proteinuria ≥ 1.0g/g creatinine	0.626	2.220	<0.001
Average 24-h DBP, mmHg			
Age, years	−0.449	0.122	0.003
Proteinuria ≥ 1.0g/g creatinine	0.286	1.398	0.047
Model 2			
Average 24-h SBP, mmHg			
Proteinuria ≥ 1.0g/g creatinine	0.556	2.207	<0.001
TBW_{BIA}/TBW_{Watson}	0.263	35.776	0.043
Average 24-h DBP, mmHg			
Age, years	−0.449	0.122	0.003
Proteinuria ≥ 1.0g/g creatinine	0.286	1.398	0.047

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TBW_{BIA}, total body water determined using bioelectrical impedance analysis; TBW_{Watson}, total body water determined using the Watson formula

is inversely associated with BP and mortality in dialysis patients [16]. The interrelationship of malnutrition inflammation and arteriosclerosis (MIA) in leaner dialysis patients is known as one of the best answers for the paradox between BMI, hypertension, and mortality [14, 15]. In addition, unlike the general population, we assumed that hypertension in CKD patients is related more closely to fluid volume status than to BMI. Our data suggest that proteinuria and fluid volume imbalance are more important dependent factors for 24-h ABP than BMI in patients with CKD and that the association of proteinuria with 24-h ABP is independent with respect to fluid volume status. Hyperfiltration with increased BP may lead to increased proteinuria, or proteinuria may mediate a persistent increase in renin-angiotensin activity [29].

In our study, BMI was correlated with the $cTBW_{BIA}$ and the TBW_{BIA}/TBW_{Watson} ratio, and furosemide use was positively correlated with BMI. This finding supported our assertion that BMI is partially affected by the fluid volume status in CKD patients. Moreover, BMI was not associated with elevated ABP or nocturnal non-dipping. This result suggests that factors other than obesity, such as proteinuria and fluid volume imbalance, are associated with 24-h ABP. Furthermore, the $cTBW_{BIA}$, i.e., the ratio of TBW to BSA, was observed to decrease with age (Tables 2 and 3). It is thus difficult to assess body composition and elucidate the relationship between BP, fluid volume status, and nutritional status in patients with CKD.

Although many studies have investigated the fluid volume status by using MF-BIA in CKD patients, only a few studies have reported the association between the fluid volume status and the circadian rhythm of BP. One of the reasons for the dearth of studies is possibly the absence of a practical and reliable indicator of the fluid volume imbalance. We assessed the fluid volume status in CKD patients using the TBW_{BIA}/TBW_{Watson} ratio calculated using the Watson formula adjusted for height, weight, age, and gender [24]. This ratio may diminish the impact of these factors on the measurement of fluid volume status, and the difference between TBW_{BIA} and TBW_{Watson} reflects changes in the TBW in terms of the imbalance in the fluid volume status. $cTBW_{BIA}$ adjusted for BSA may be a practical indicator because reference values are not required for its use. However, this parameter cannot be adjusted for the factors of age and gender. The TBW_{BIA}/TBW_{Watson} ratio showed a significant association with 24-h

systolic ABP, being more likely to be higher in patients with elevated ABP and nocturnal non-dipping. This finding was partly supported by the results of previous studies, which reported that CKD induced the salt-sensitive type of hypertension that causes elevated nocturnal BP due to a defect in the sodium excretory capability [30]. The TBW_{BIA}/TBW_{Watson} ratio can serve as an indicator of fluid volume-dependent hypertension. In this regard, however, the TBW_{BIA}/TBW_{Watson} ratio should be interpreted with caution because of the SD obtained using the Watson formula (3.76 in men and 3.60 in women) [20]. Further, the TBW_{BIA}/TBW_{Watson} ratio was less than 1.0 in all the patients, suggesting that TBW_{Watson} may have been overestimated in the general Japanese population. A previous study reported differences in TBW_{Watson} across individuals depending on race [31]. If the TBW_{BIA}/TBW_{Watson} ratio is applied more practically, a precise value of TBW in the Japanese population can be estimated, so that a reference range for the TBW_{BIA}/TBW_{Watson} ratio can be established in the future by using catamnestic data.

Previous studies have reported the indications and limitations of body composition analysis using MF-BIA [32–35]. Cooper et al. compared the results of TBW assessment in CKD patients by using different methods such as D_2O, Watson formula, MF-BIA, and calculating the TBW as 58% of the BW [32]. According to their reports, the Watson formula significantly underestimated the TBW. However, the mean TBW measured using MF-BIA did not differ significantly from the mean D_2O value, and the reliability of the results did not vary enormously. Woodrow et al. reported more errors with BIA than with D_2O and DEXA for TBW measurement in CKD patients [32, 33]. However, these reports did not completely deny the value of TBW assessment by MF-BIA. MF-BIA is more accurate than anthropometric measurements and can be performed simply, conveniently, and non-invasively, in contrast to D_2O and DEXA measurements. In this study, we did not assess D_2O and DEXA because this study did not focus on the mechanical accuracy and advantages of MF-BIA. Even if the values for body composition established by D_2O and DEXA are used, no complete consensus exists regarding a suitable indicator of fluid volume imbalance.

Our study has several limitations: this is a retrospective, cross-sectional study based on pre-existing medical records obtained from a single center, and the sample size is small. A prospective, multicenter epidemiological study on a larger scale is required to identify and establish the reference threshold for the TBW_{BIA}/TBW_{Watson} ratio. In addition, we observed that the estimated TBW may have an error margin in comparison to the actual value of TBW in the Japanese population. However, despite these limitations, we consider that the TBW_{BIA}/TBW_{Watson} ratio has a practical use as an indicator of fluid volume-dependent hypertension.

Conclusion

Hypertension is dependent primarily on proteinuria and fluid volume imbalance in patients with CKD. The TBW_{BIA}/TBW_{Watson} ratio can serve as an indicator of fluid volume-dependent hypertension. Unlike the general population, BMI is influenced by not only fat but also by TBW, in which case BMI can become less involved with 24-h ABP.

Conflict of Interests

The authors do not have any financial or other interests. The authors alone are responsible for the content and writing of this paper.

Acknowledgements

We wish to thank Dr. Sonoo Mizuiri for giving us the chance to initiate this study.

References

1 Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, Chen SC, Qiu Y, Wang C, Li S, Vassalotti JA, Collins AJ: In: Kidney Early Evaluation Program Investigators: CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis 2008;51:S13–S20.

2 Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ: Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int 2004;65:1568–1576.

3 Raine AE, Bedford L, Simpson AW, Ashley CC, Brown R, Woodhead JS, Ledingham JG: Hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure. Kidney Int 1993;43:700–705.

4 Vaziri ND: Mechanism of erythropoietin-induced hypertension. Am J Kidney Dis 1999;33:821–828.

5 Passauer J, Pistrosch F, Büssemaker E, Lässig G, Herbrig K, Gross P: Reduced agonist-induced endothelium-dependent vasodilation in uremia is attributable to an impairment of vascular nitric oxide. J Am Soc Nephrol 2005;16:959–965.

6 Buckalew VM Jr, Berg RL, Wang SR, Porush JG, Rauch S, Schulman G: Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. Modification of Diet in Renal Disease Study Group. Am J Kidney Dis 1996;28:811–821.

7 Portaluppi F, Montanari L, Massari M, Di Chiara V, Capanna M: Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. Am J Hypertens 1991;4:20–26.

8 Schmieder RE, Messerli FH: Does obesity influence early target organ damage in hypertensive patients? Circulation 1993;87:1482–1488.

9 Nyamdorj R, Qiao Q, Söderberg S, Pitkäniemi J, Zimmet P, Shaw J, Alberti G, Nan H, Uusitalo U, Pauvaday V, Chitson P, Tuomilehto J: Comparison of body mass index with waist circumference, waist-to-hip ratio, and waist-to-stature ratio as a predictor of hypertension incidence in Mauritius. J Hypertens 2008;26:866–870.

10 Sarzani R, Salvi F, Dessì-Fulgheri P, Rappelli A: Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. J Hypertens 2008;26:831–843.

11 Ferris M, Hogan SL, Chin H, Shoham DA, Gipson DS, Gibson K, Yilmaz S, Falk RJ, Jennette JC: Obesity, albuminuria, and urinalysis findings in US young adults from the Add Health Wave III study. Clin J Am Soc Nephrol 2007;2:1207–1214.

12 Elsayed EF, Sarnak MJ, Tighiouart H, Griffith JL, Kurth T, Salem DN, Levey AS, Weiner DE: Waist-to-hip ratio, body mass index, and subsequent kidney disease and death. Am J Kidney Dis 2008;52:29–38.

13 Foster MC, Hwang SJ, Larson MG, Lichtman JH, Parikh NI, Vasan RS, Levy D, Fox CS: Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. Am J Kidney Dis 2008;52:39–48.

14 Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2001;38:1251–1263.

15 Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int 2002;62:2238–2245.

16 Agarwal R: Body mass index-mortality paradox in hemodialysis: can it be explained by blood pressure? Hypertension 2011;58:1014–1020.

17 Woodrow G, Oldroyd B, Turney JH, Davies PS, Day JM, Smith MA: Four-component model of body composition in chronic renal failure comprising dual-energy X-ray absorptiometry and measurement of total body water by deuterium oxide dilution. Clin Sci (Lond) 1996;91:763–769.

18 Cha K, Brown EF, Wilmore DW: A new bioelectrical impedance method for measurement of the erythrocyte sedimentation rate. Physiol Meas 1994;15:499–508.

19 Bellizzi V, Scalfi L, Terracciano V, De Nicola L, Minutolo R, Marra M, Guida B, Cianciaruso B, Conte G, Di Iorio BR: Early changes in bioelectrical estimates of body composition in chronic kidney disease. J Am Soc Nephrol 2006;17:1481–1487.

20 Paniagua R, Ventura MD, Avila-Díaz M, Hinojosa-Heredia H, Méndez-Durán A, Cueto-Manzano A, Cisneros A, Ramos A, Madonia-Juseino C, Belio-Caro F, García-Contreras F, Trinidad-Ramos P, Vázquez R, Ilabaca B, Alcántara G, Amato D: NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. Nephrol Dial Transplant 2010;25:551–557.

21 Chamney PW, Wabel P, Moissl UM, Müller MJ, Bosy-Westphal A, Korth O, Fuller NJ: A whole-body model to distinguish excess fluid from the hydration of major body tissues. Am J Clin Nutr 2007;85:80–89.

22 Ohashi Y, Otani T, Tai R, Tanaka Y, Sakai K, Aikawa A: Assessment of body composition using dry mass index and ratio of total body water to estimated volume based on bioelectrical impedance analysis in chronic kidney disease patients. J Ren Nutr DOI: 10.1053/j.jrn.2011.12.006

23 Wabel P, Moissl U, Chamney P, Jirka T, Machek P, Ponce P, Taborsky P, Tetta C, Velasco N, Vlasak J, Zaluska W, Wizemann V: Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. Nephrol Dial Transplant 2008;23:2965–2971.

24 Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am J Clin Nutr 1980;33:27–39.

25 Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–2100.

26 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–992.

27 Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D: American Heart Association; American Society of Hypertension; Preventive Cardiovascular Nurses Association: Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension 2008;52:1–9.

28 Pickering TG: Should we be evaluating blood pressure dipping status in clinical practice? J Clin Hypertens (Greenwich) 2005;7:178–182.

29 Nicholl DD, Hemmelgarn BR, Turin TC, MacRae JM, Muruve DA, Sola DY, Ahmed SB: Increased urinary protein excretion in the "normal" range is associated with increased renin-angiotensin system activity. Am J Physiol Renal Physiol. 2012;302:F526-F532.

30 Kimura G, Dohi Y, Fukuda M: Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. Hypertens Res 2010;33:515–520.

31 Davenport A, Hussain Sayed R, Fan S: The effect of racial origin on total body water volume in peritoneal dialysis patient. Clin J Am Soc Nephrol 2011;6:2492–2498.

32 Cooper BA, Aslani A, Ryan M, Zhu FY, Ibels LS, Allen BJ, Pollock CA: Comparing different methods of assessing body composition in end-stage renal failure. Kidney Int 2000;58:408–416.

33 Basile C, Vernaglione L, Bellizzi V, Lomonte C, Rubino A, D'Ambrosio N, Di Iorio B: Total body water in health and disease: have anthropometric equations any meaning? Nephrol Dial Transplant 2008;23:1997–2002.

34 Woodrow G, Oldroyd B, Turney JH, Tompkins L, Brownjohn AM, Smith MA: Whole body and regional body composition in patients with chronic renal failure. Nephrol Dial Transplant 1996;11:1613–1618.

35 Woodrow G, Oldroyd B, Turney JH, Davies PS, Day JM, Smith MA: Measurement of total body water by bioelectrical impedance in chronic renal failure. Eur J Clin Nutr 1996;50:676–681.