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

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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.
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$_2$O) 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$_2$O 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.
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 m² 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 awakening 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 χ² 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 cTBWBIA and TBWBIA/TBWWatson 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 cTBWBIA, the TBWBIA/TBWWatson ratio, and the BMI. The cTBWBIA showed an independent positive association with male gender, BMI, and furosemide use and negative association with age. In contrast, the TBWBIA/TBWWatson 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 cTBWBIA and TBWBIA/TBWWatson ratio values were more likely to be significantly higher in patients with elevated ABP (cTBWBIA: 33.1 ± 5.5 L vs. 35.2 ± 5.1 L, p < 0.05, and TBWBIA/TBWWatson ratio: 0.952 ± 0.064 vs. 1.010 ± 0.050, p < 0.01). Further, the TBWBIA/TBWWatson 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 cTBWBIA 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 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 cTBWBIA, and Model 2 in Table 4 shows these values for variables concerning the TBWBIA/TBWWatson 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 TBWBIA/TBWWatson 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.

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 cTBWBIA and TBWBIA/TBWWatson ratio values, and patients with nocturnal non-dipping are more likely to...
have higher \( \text{TBW}_{\text{BIA}}/\text{TBW}_{\text{Watson}} \) 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 \( \text{TBW}_{\text{BIA}}/\text{TBW}_{\text{Watson}} \) ratio is an independent factor for average systolic 24-h ABP; and (3) BMI has a positive correlation with the \( c\text{TBW}_{\text{BIA}} \) and the TBW_{BIA}/TBW_{Watson} ratio.
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
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

### Table 4: Stepwise multivariate linear regression models for average 24-h blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Average 24-h SBP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria ≥ 1.0 g/g creatinine</td>
<td>0.626</td>
<td>2.220</td>
<td>&lt;0.001</td>
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<tr>
<td>Average 24-h DBP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>-0.449</td>
<td>0.122</td>
<td>0.003</td>
</tr>
<tr>
<td>Proteinuria ≥ 1.0 g/g creatinine</td>
<td>0.286</td>
<td>1.398</td>
<td>0.047</td>
</tr>
</tbody>
</table>

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.
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_{2}O, 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 D_{2}O value, and the reliability of the results did not vary enormously. Woodrow et al. reported more errors with BIA than with D_{2}O 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_{2}O and DEXA measurements. In this study, we did not assess D_{2}O 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_{2}O 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.

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