# Early Detection of Subclinical Edema in Chronic Kidney Disease Patients by Bioelectrical Impedance Analysis

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**Background:** Abnormalities in body water distribution are common in chronic kidney disease (CKD) patients. Volume expansion, even in the absence of overt edema, contributes to high blood pressure, and progressive volume expansion eventually leads to clinical edema and fluid overload. Total body water (TBW) can be accurately estimated by multifrequency bioelectrical impedance analysis (MF-BIA) which has been proposed for earlier detection of subclinical edema in CKD patients.

**Objective:** To study body fluid distribution and edematous states in CKD patients measured by MF-BIA, compared with clinical edema assessed by physical examination. In addition, to evaluate the correlation of MF-BIA estimated TBW and anthropometry-derived TBW calculated by Watson formula.

**Material and Method:** CKD patients at Rajavithi Hospital together with healthy adults were prospectively enrolled during a 12-month period. The body fluid compositions assessed by bioelectrical impedance analyzer (InBody® S20, Republic of Korea) were taken immediately after physical examination for edema detection. The patients were categorized into stages 1 to 5 according to CKD staging in the NKF-K/DOQI guidelines, and reclassified into 3 groups of stages1-2, stages 3-4, and stage 5.

**Results:** Sixty-nine CKD patients were compared with 48 healthy volunteers. The estimated glomerular filtration rate (GFR) in CKD patients and normal controls were $53.5\pm41.1$ and $113.9\pm0.8$ ml/min/1.73 $m^2$ respectively. The extracellular water (ECW) to TBW ratio, which represents edematous state if higher than 0.4, was significantly higher in patients with CKD stages 3-4 ($0.400\pm0.008$) and stage 5 ($0.404\pm0.011$), than in those in CKD stages 1-2 ($0.393\pm0.009$) and controls ($0.385\pm0.007$) ($p<0.001$). The prevalence of edematous state detected by BIA (edema-BIA) in CKD patients was significantly greater than in normal controls (78.3% vs. 25.0%, $p<0.001$). The number of CKD patients with edema-BIA was also significantly higher than the number of patients with clinical edema (36.2%), which represented a significant proportion of patients (42.1%) with subclinical edema. The sensitivity and specificity of edema detected by physical examination in all CKD patients compared to the assessment by MF-BIA were 44.4% and 93.3% respectively. There was a significant correlation between the TBW calculated by the Watson formula and TBW estimated by MF-BIA ($r^2 = 0.848$, $p<0.001$).

**Conclusion:** The present study demonstrated that assessment of body fluid distribution by MF-BIA was a reliable measure. Subclinical edema actually occurred in early stages of CKD before detection of overt edema by physical examination. TBW calculated by Watson formula can alternatively be used for evaluation of hydration status and can assist physicians in prescribing appropriate management for CKD patients.

**Keywords:** Body fluid distribution, Subclinical edema, Chronic kidney disease, Multifrequency bioimpedance analysis

Chronic kidney disease (CKD) often goes unrecognized until the disease is well advanced and renal failure is threatening. Sodium and intravascular volume balances are usually maintained via homeostatic mechanisms until the estimated glomerular filtration rate (eGFR) falls below 10 to 15 ml/min/1.73 $m^2$. In the early stages of CKD, patients may be asymptomatic; however, symptoms will progressively appear as renal function deteriorates. Patients with mild to moderate CKD are less able to respond to rapid intake of water and are therefore prone to fluid overload and edematous states, and acute pulmonary edema can eventually occur in more advanced stages of CKD. Furthermore, volume expansion, often in the absence of overt edema, contributes to high blood pressure in most forms of CKD. Therefore, early detection of subclinical edema

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will improve the quality of care in the management of CKD patients by assisting in controlling hypertension and body fluid balances and edematous states.

Measurement of total body water (TBW) is frequently performed to evaluate body composition and hydration status in both normal subjects and renal failure patients. Accurate measurement of TBW requires the isotopic dilution technique which is considered as the gold standard method but is not easily applicable to the clinical setting. Therefore, several indirect methods of estimating TBW with other noninvasive devices or anthropometric-derived TBW calculations are commonly employed. It has been shown that body composition, TBW and body fluid distribution can be accurately and reliably estimated by bioelectrical impedance analysis (BIA)[1-3], and this is currently the most popular and practical method due to its safety, noninvasiveness, ease of use, and low cost[4,5]. Multifrequency BIA (MF-BIA) has been used in the evaluation of body water distribution in end-stage renal disease and other clinical disorders of fluid volume and distribution[6] and has been validated for assessment of body water in hemodialysis patients[7]; as a result, the MF-BIA technique has been introduced to measure body fluid volume more precisely[8,9]. Currently, BIA is utilized extensively in monitoring lean body mass and hydration status in dialysis patients; however, it has still not been used widely in predialysis CKD patients.

The purpose of the present study was to investigate the efficacy of the BIA method in early detection of subclinical edema or changes of body water distribution in various stages of predialysis CKD patients by using the MF-BIA[7,8]. In addition, the correlation between the anthropometry-derived TBW calculated by the Watson formula and the TBW measured by MF-BIA was also evaluated.

## Material and Method
### Patients
A cross-sectional, comparative study was conducted over a period of 12 months with predialysis CKD patients and normal healthy volunteers who had no self-reported history of any kidney disease, diabetes or hypertension. Stable CKD adult patients were consecutively enrolled using the following inclusion criteria: (1) age $\geq$18 years; (2) predialysis CKD patients, categorized into 5 stages according to the NKF-K/DOQI classification[10]: CKD stage 1, GFR 90-75 ml/min/1.73 m$^2$; CKD stage 2, 75-60 ml/min/1.73 m$^2$; CKD stage 3, 60-30 ml/min/1.73 m$^2$; CKD stage 4, 30-15 ml/min/1.73

m$^2$; and CKD stage 5, <15 ml/min/1.73 m$^2$. Then they were reclassified into 3 groups of stages 1-2, stages 3-4 and stage 5. Patients were excluded when any of the following criteria was met: (1) dialysis treatment; (2) pregnancy; (3) any intercurrent illness that could potentially have had an effect on hydration status or nutrition within the preceding 3 months; (4) use of medication that could have influenced body water balance within 4 weeks of the beginning of the study; (5) patients with pacemakers, metallic intravascular devices or prosthesis; (6) amputees; (7) clinical conditions with extreme alterations of body composition such as cancer or severe liver disease; and (8) post-kidney transplant patients.

Written informed consent was obtained from all patients and normal volunteers. They were scheduled for their testing appointment after receiving verbal and written descriptions of the study protocol. Subjects were instructed to abstain from physical activity and food for at least 2 hours before testing. The present study protocol was reviewed and approved by the Ethical Committee of Rajavithi Hospital.

### Methods
The clinical data were obtained from the patients' history and medical records. Each subject enrolled in the present study was weighed with a digital scale, and standing height was also measured using a linear height scale. Body mass index (BMI) was calculated using the conventional Quetelet formula (kg/m$^2$). Blood pressure at rest was measured in all patients and normal volunteers, and systolic or diastolic blood pressure over 140/90 mmHg was defined as hypertension. The presence of edema in the patients' legs was investigated before the results of the MF-BIA assessment were known.

### Laboratory analysis
Blood was taken from each patient for assessment of complete blood count (CBC), fasting plasma glucose, blood urea nitrogen (BUN), serum creatinine, electrolytes, albumin, calcium and phosphorus, and spot urine protein: creatinine index. For normal controls, the laboratory assessment included only the CBC, fasting plasma glucose, BUN, serum creatinine and urinalysis in order to exclude any underlying disease.

### Estimated GFR calculation
The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to

estimate the GFR of both patients and normal controls. The CKD-EPI formula is currently accepted as the most accurate measurement, more precise and reliable than the MDRD formula[11], and can be reported throughout the GFR range[12] as shown in the following equation:

Female:

Scr $\leq 0.7$ mg/dl, GFR = 144 x (Scr/0.7)$^{-0.329}$ x (0.993)$^{Age}$

Scr >0.7 mg/dl, GFR = 144 x (Scr/0.7)$^{-1.209}$ x (0.993)$^{Age}$

Male:

Scr $\leq 0.9$ mg/dl, GFR = 141 x (Scr/0.9)$^{-0.411}$ x (0.993)$^{Age}$

Scr >0.9 mg/dl, GFR = 141 x (Scr/0.9)$^{-1.209}$ x (0.993)$^{Age}$

### TBW measurement by BIA (TBW-BIA)

For determination of TBW-BIA by MF-BIA, a body composition analyzer (InBody S20®, Biospace Co. Ltd, Seoul, Republic of Korea) was used, with tetrapolar 8-point tactile/detachable electrode system and operated at emission frequencies pre-set by the manufacturer of 1 KHz, 5 KHz, 50 KHz, 250 KHz, 500 KHz and 1 MHz. The TBW, intracellular and extracellular fluid spaces, and body compositions were analyzed using equations in the BIA software[9,13]. The efficacy and accuracy of this MF-BIA device in determining the body fluid status and body compositions in human has been previously validated[14,15].

In both healthy controls and CKD patients, the study was performed in the fasting state and after urination. The measurements were carried out in the recumbent posture, and subjects' arms and legs were fully extended and abducted approximately 20 degrees laterally. Electrodes were applied to the fingers, heels and ankles in accordance with the device manual instructions. TBW was calculated from the sum of each body segment using equations in the built-in BIA software.

The body fluid compositions of interest in the present study were the following: ratios of TBW/Wt, ECW/Wt, ICW/Wt and ECW/TBW which determine the edematous state. The normal range of ECW/TBW is 0.36 to 0.40, and any value above 0.40 was considered to be edema.

### Anthropometry-derived TBW calculations

The anthropometric-derived TBW calculations include: a constant fraction of body weight[16], the Watson formula[17], the Hume formula[18], and the Chertow formula[19]. All the anthropometry-based equations overestimated the TBW in both control and hemodialysis subjects[20,21]; however, the best prediction of TBW was obtained with the Watson formula (TBW-W)[20,22] which was therefore used in the present study as given below

Male:

TBW-W = 2.447 - (0.09516 x age) + (0.1074 x height in cm) + (0.3362 x weight in kg)

Female:

TBW-W = -2.097 + (0.1069 x height in cm) + (0.2466 x weight in kg).

### Statistical analysis

Using a 2-sided type 1 error, 90% power[23], sample of 40 normal controls and 20 subjects for each CKD group would be adequate to test the difference in mean $\pm$ SD of TBW between the CKD patients (61.3$\pm$6.1%) and normal controls (56.5$\pm$3.6%) as reported by Jha et al[1].

Continuous variables were expressed as mean values $\pm$ standard deviation. One-way ANOVA was employed to compare quantitative variables among 4 groups of subjects. For multiple comparisons, Tukey method was used due to unequal sample size in each group. Chi-square test or Fisher's exact test was used to test the difference in qualitative variables among 4 groups. The sensitivity and specificity of clinical edema compared to edema-BIA were also determined. Pearson correlation coefficients (r) and their significance were calculated between two related variables. The intraclass correlation coefficient (ICC) was also used for testing agreement between two related variables. A $p$-value of less than or equal to 0.05 was considered statistical significance. SPSS 17 was used for all statistical analyses.

### Results
### Patient characteristics

During a 12-month cross-sectional study, 69 CKD patients in the Department of Medicine, Rajavithi Hospital with a mean age of 52.5$\pm$18.1 years (44.9% male) and 48 normal controls with a mean age of 34.2$\pm$7.0 years (22.9% male) met the enrollment criteria and agreed to participate in the present study. The CKD patients were classified into 3 groups: stages 1-2 (n = 25), stages 3-4 (n = 29) and stage 5 (n = 15). The demographic characteristics of normal controls and CKD patients are presented in Table 1. The most common comorbid disease in CKD patients was hypertension (75.4%), followed by dyslipidemia (62.3%), diabetes

(30.4%), systemic lupus erythematosus (17.4%) and ischemic heart disease (13%).

The number of patients with hypertension in CKD stages 3-4 (86.2%) and stage 5 (86.7%) was significantly higher than in CKD stages 1-2 (56%) ($p<0.001$). The number of patients with diabetes in CKD stages 3-4 (44.8%) and stage 5 (33.3%) was also significantly higher than in CKD stages 1-2 (12%) ($p<0.001$), and the number of patients with ischemic heart disease in CKD stages 3-4 and stage 5 was also significantly higher than in stages 1-2. The systolic and diastolic blood pressures in all CKD patients ($130.0\pm16.0/77.8\pm11.4$ mmHg) were significantly higher than in normal controls ($114.2\pm14.4/71.3\pm10.3$ mmHg) ($p<0.001$ and $p = 0.002$, respectively), but there were no significant differences in blood pressure among the various groups of CKD patients. Clinical edema in all patients with CKD was 36.2%, with CKD stages 1-2, stages 3-4 and stage 5 at 24.0%, 48.3% and 33.3%, respectively.

Table 2 shows the basic laboratory findings in normal controls and CKD patients. The hemoglobin, hematocrit, and eGFR levels in CKD patients were significantly lower than those of normal controls ($p<0.001$) whereas fasting plasma glucose, BUN and serum creatinine levels in CKD patients were significantly higher than in normal controls ($p<0.001$). Among the various groups of CKD, the hemoglobin and hematocrit, serum bicarbonate, and albumin levels in patients with CKD stage 5 were significantly lower than in other stages of CKD. Conversely, BUN, serum creatinine, phosphate levels, and urine protein: creatinine index (UPCI) in patients with CKD stage 5 were significantly higher than in other stages of CKD.

***Body composition analysis***

Comparison of body composition and body fluid distributions assessed by MF-BIA among normal controls and CKD patients at various stages are presented in Table 3. The ICW/ECW ratio in normal controls was significantly higher than that of CKD patients ($1.60\pm0.04$ vs. $1.52\pm0.07$, $p<0.001$). The TBW-BIA/Wt ratios in normal controls and CKD patients were not significantly different; however, the TBW-BIA/Wt of patients in CKD stage 5 was significantly higher than that of those in CKD stages 3-4 ($0.56\pm0.10$ vs. $0.50\pm0.07$, $p = 0.039$). The ECW/Wt ratio in CKD stage 5 patients was also significantly higher than that of patients in CKD stages 3-4 and controls ($0.23\pm0.04$ vs. $0.20\pm0.03$ vs. $0.20\pm0.02$, $p = 0.009$).

**Table 1.** Baseline demographic characteristics in normal controls and various groups of CKD patients, depicted as mean $\pm$ SD or n (%)

| | | CKD (n = 69) | | | All CKD (n = 69) | *p*-value |
|---|---|---|---|---|---|---|
| | Controls (n = 48) | Stages 1-2 (n = 25) | Stages 3-4 (n = 29) | Stage 5 (n = 15) | | |
| Age (years) | $34.2\pm7.1^a$ | $38.6\pm15.5^a$ | $62.9\pm12.3^b$ | $55.6\pm17.5^{bc}$ | $52.5\pm18.1^{**}$ | - |
| Gender | | | | | | |
|     Male | 11 (22.9) | 8 (32.0) | 16 (55.2) | 7 (46.7) | 31 (44.9) | - |
|     Female | 37 (77.1) | 17 (68.0) | 13 (44.8) | 8 (53.3) | 38 (55.1) | - |
| Weight (kg) | $59.6\pm10.3^{ab}$ | $62.7\pm16.4^{ab}$ | $66.7\pm14.4^b$ | $55.6\pm11.4^{ac}$ | $62.8\pm15.0$ | - |
| Height (cm) | $159.8\pm7.3$ | $159.1\pm9.3$ | $160.3\pm10.3$ | $156.7\pm8.3$ | $159.1\pm9.5$ | 0.587 |
| BMI (kg/m²) | $23.3\pm3.0^a$ | $24.5\pm5.4^{ab}$ | $25.9\pm4.5^b$ | $22.6\pm3.7^{ab}$ | $24.7\pm4.8$ | 0.022 |
| Systolic BP (mmHg) | $114.2\pm14.4^a$ | $130.5\pm13.0^b$ | $130.8\pm18.5^b$ | $127.6\pm17.7^b$ | $130.0\pm16.0^{**}$ | <0.001 |
| Diastolic BP (mmHg) | $71.3\pm10.3^a$ | $76.2\pm11.9^{ab}$ | $79.6\pm11.5^b$ | $76.7\pm10.8^{ab}$ | $77.8\pm11.4^*$ | 0.012 |
| D M | $0 (0.0)^a$ | $3 (12.0)^b$ | $13 (44.8)^c$ | $5 (33.3)^{cd}$ | $21 (30.4)^{**}$ | <0.001 |
| Hypertension | $0 (0.0)^a$ | $14 (56.0)^b$ | $25 (86.2)^c$ | $13 (86.7)^{cd}$ | $52 (75.4)^{**}$ | <0.001 |
| Dyslipidemia | $2 (4.2)^a$ | $14 (56.0)^b$ | $20 (69.0)^{bc}$ | $9 (60.0)^{bd}$ | $43 (62.3)^{**}$ | <0.001 |
| Ischemic heart disease | $0 (0.0)^a$ | $0 (0.0)^a$ | $6 (20.7)^b$ | $3 (20.0)^{bc}$ | $9 (13.0)^*$ | <0.001 |
| SLE | $0 (0.0)^a$ | $8 (32.0)^b$ | $1 (3.4)^{ac}$ | $3 (20.0)^{bc}$ | $12 (17.4)^{**}$ | <0.001 |
| Edema (clinical) | $0 (0.0)^a$ | $6 (24.0)^b$ | $14 (48.3)^{bc}$ | $5 (33.3)^{bd}$ | $25 (36.2)^{**}$ | <0.001 |

Values were represented as mean $\pm$ SD and number (percent)
[a,b,c,d] different characters mean significant difference between groups in multiple comparisons
*$p = 0.002$ vs. control, **$p<0.001$ vs. control

**Table 2.** Comparison of basic laboratory data among normal controls and various groups of CKD patients

| | CKD patients (n = 69) | | | | All CKD patients (n = 69) | *p*-value |
|---|---|---|---|---|---|---|
| | Controls (n = 48) | Stages 1-2 (n = 25) | Stages 3-4 (n = 29) | Stage 5 (n = 15) | | |
| eGFR | $113.9 \pm 10.8^a$ | $101.3 \pm 22.1^b$ | $35.8 \pm 14.5^c$ | $7.9 \pm 3.5^d$ | $53.5 \pm 41.1*$ | <0.001 |
| Hemoglobin (g/dl) | $13.1 \pm 1.5^a$ | $12.7 \pm 1.6^a$ | $12.3 \pm 1.8^a$ | $9.4 \pm 2.0^b$ | $11.8 \pm 2.2*$ | <0.001 |
| Hematocrit (%) | $39.7 \pm 4.2^a$ | $38.3 \pm 4.3^a$ | $37.2 \pm 5.3^a$ | $29.2 \pm 6.9^b$ | $35.9 \pm 6.4*$ | <0.001 |
| BUN (mg/dl) | $11.9 \pm 3.0^a$ | $13.2 \pm 5.2^a$ | $27.6 \pm 12.3^b$ | $76.3 \pm 32.3^c$ | $33.0 \pm 29.2*$ | <0.001 |
| Creatinine (mg/dl) | $0.7 \pm 0.16^a$ | $0.80 \pm 0.21^{ab}$ | $2.00 \pm 0.72^b$ | $8.00 \pm 5.50^c$ | $2.87 \pm 3.76*$ | <0.001 |
| Fasting plasma | | | | | | |
| Glucose (mg/dl) | $82.5 \pm 11.0^a$ | $105.8 \pm 58.5^{ab}$ | $120.2 \pm 53.3^b$ | $103.5 \pm 29.5^a$ | $111.4 \pm 51.1*$ | 0.001 |
| Sodium (mEq/L) | - | $137.2 \pm 3.2$ | $137.3 \pm 3.3$ | $138.6 \pm 3.5$ | $137.6 \pm 3.3$ | 0.402 |
| Potassiu (mEq/L) | - | $4.3 \pm 0.6$ | $4.5 \pm 0.5$ | $4.6 \pm 0.7$ | $4.4 \pm 0.6$ | 0.190 |
| Bicarbonate (mEq/L) | - | $26.1 \pm 2.2$ | $24.5 \pm 2.7$ | $20.4 \pm 3.1$ | $24.2 \pm 3.4$ | <0.001 |
| Calcium (mg/dl) | - | $9.1 \pm 0.6$ | $9.3 \pm 0.6$ | $9.0 \pm 0.7$ | $9.2 \pm 0.6$ | 0.219 |
| Phosphorus (mg/dl) | - | $3.9 \pm 0.7$ | $3.6 \pm 0.5$ | $4.7 \pm 1.0$ | $4.0 \pm 0.8$ | <0.001 |
| Albumin (g/dl) | - | $3.7 \pm 0.7$ | $4.1 \pm 0.4$ | $3.8 \pm 0.4$ | $3.9 \pm 0.6$ | 0.020 |
| UPCI | - | $1.8 \pm 2.5$ | $1.0 \pm 1.2$ | $2.8 \pm 3.0$ | $1.6 \pm 2.2$ | 0.055 |

UPCI = urine protein: creatinine ratio. Values were represented as mean $\pm$ SD
[a,b,c,d] different characters mean significant difference between groups in multiple comparisons, *$p$<0.001 vs. control


**Table 3.** Comparison of body composition and body fluid distribution among normal controls and various groups of CKD patients, depicted as mean $\pm$ SD or n (%)

| | Controls | Stages 1-2 | Stages 3-4 | Stages 5 | All CKD (n = 69) | *p*-value |
|---|---|---|---|---|---|---|
| Body composition analysis | | | | | | |
| ICW (L) | $19.0 \pm 3.9$ | $19.3 \pm 5.0$ | $19.9 \pm 5.1$ | $20.4 \pm 8.9$ | $22.8 \pm 5.0$ | 0.798 |
| ECW (L) | $11.9 \pm 2.2$ | $12.5 \pm 2.9$ | $13.2 \pm 3.2$ | $12.5 \pm 3.2$ | $15.0 \pm 3.0$ | 0.251 |
| TBW-BIA (L) | $30.9 \pm 6.1$ | $31.8 \pm 7.9$ | $33.1 \pm 8.3$ | $30.9 \pm 7.6$ | $37.8 \pm 8.0$ | 0.622 |
| Fat mass (kg) | $17.5 \pm 5.6^{ab}$ | $19.4 \pm 9.1^{ab}$ | $21.9 \pm 8.1^a$ | $13.9 \pm 8.8^b$ | $19.1 \pm 10.3$ | 0.006 |
| Fat free mass (kg) | $42.1 \pm 8.3$ | $43.1 \pm 10.7$ | $44.8 \pm 11.2$ | $41.8 \pm 10.2$ | $51.2 \pm 10.9$ | 0.666 |
| Soft lean mass (kg) | $39.7 \pm 7.9$ | $40.7 \pm 10.2$ | $41.2 \pm 9.3$ | $39.4 \pm 9.6$ | $47.3 \pm 9.7$ | 0.864 |
| Skeletal muscle mass (kg) | $22.8 \pm 5.1$ | $23.2 \pm 6.5$ | $25.6 \pm 12.6$ | $23.7 \pm 7.9$ | $30.2 \pm 11.7$ | 0.517 |
| Body cell mass (kg) | $26.3 \pm 7.5$ | $27.7 \pm 7.1$ | $28.5 \pm 7.3$ | $26.4 \pm 6.4$ | $32.7 \pm 7.2$ | 0.579 |
| Body fluid composition analysis (ratio) | | | | | | |
| ICW/ECW | $1.60 \pm 0.04$ | $1.54 \pm 0.06$ | $1.50 \pm 0.05$ | $1.64 \pm 0.62$ | $1.52 \pm 0.07**$ | 0.171 |
| TBW-BIA/weight | $0.52 \pm 0.05^{ab}$ | $0.51 \pm 0.06^{ab}$ | $0.50 \pm 0.07^a$ | $0.56 \pm 0.10^b$ | $0.55 \pm 0.08$ | 0.039 |
| ICW/weight | $0.32 \pm 0.03^a$ | $0.31 \pm 0.04^a$ | $0.30 \pm 0.04^a$ | $0.36 \pm 0.10^b$ | $0.33 \pm 0.05*$ | 0.002 |
| ECW/weight | $0.20 \pm 0.02^a$ | $0.20 \pm 0.03^a$ | $0.20 \pm 0.03^a$ | $0.23 \pm 0.04^b$ | $0.22 \pm 0.04$ | 0.009 |
| Edema | | | | | | |
| ECW/TBW | $0.385 \pm 0.007^a$ | $0.393 \pm 0.009^b$ | $0.400 \pm 0.008^c$ | $0.404 \pm 0.011^c$ | $0.400 \pm 0.010**$ | <0.001 |
| Edema (BIA) | $12 (25.0)^a$ | $17 (68.0)^b$ | $24 (82.8)^c$ | $13 (86.7)^{cd}$ | $54 (78.3)**$ | <0.001 |

Values were represented as mean $\pm$ SD and number (percent)
[a,b,c,d] different characters mean significant difference between groups in multiple comparisons, *$p$<0.05 vs. control, **$p$<0.001 vs. control

The ECW/TBW ratio in all CKD patients was significantly higher than in normal controls (0.400±0.010 vs. 0.385±0.007, $p<0.001$). In addition, the ECW/TBW ratio in all stages of CKD was also significantly higher than that of normal controls (Table 3). When comparing patients at various stages of CKD, the ECW/TBW in CKD stages 3-4 and stage 5 were significantly higher than in CKD stages 1-2 ($p = 0.032$ and $p = 0.004$, respectively). The edematous state detected by BIA (edema-BIA) in CKD patients was also significantly higher than in normal controls (78.3 vs. 25.0%, $p<0.001$). There were no differences in edema-BIA between patients with CKD stages 3-4 (82.8%) and stage 5 (86.7%), but both of these groups had significantly higher edema-BIA than patients in stages 1-2 (68.0%). Fig. 1 depicts the comparison of clinically apparent edema, edema-BIA and subclinical edema in controls and CKD patients at various stages. The sensitivity and specificity of detecting edematous state by physical examination in all CKD patients, compared to the assessment by MF-BIA, were 44.4% and 93.3% respectively (Table 4). Therefore, the false negative for detection of edema by physical examination was 70.6% in stages 1-2, decreasing to 41.7% and 61.5% in stages 3-4 and stage 5 respectively.

### Correlation of TBW-W and TBW-BIA

The correlation value obtained between the TBW calculated by the Watson formula (TBW-W) and the TBW assessed by MF-BIA (TBW-BIA) was statistically significant ($r^2 = 0.848$, $p<0.001$). The intraclass correlation coefficient (ICC) of the two methods was 0.92 ($p<0.001$). A linear regression model for the correlation between the TBW-W and TBW-BIA is shown in Fig. 2.

### Discussion

Body composition assessment by BIA is being increasingly used to evaluate clinical interventions, and has the potential to improve patient care. TBW is constantly maintained in normal subjects, with minor fluctuations of ±5% daily because of food consumption and metabolic processes. A normal adult's body consists of about 60% water by weight, and this is found in 2 major fluid compartments: the intracellular (ICW) and extracellular (ECW) compartments. The latter is further divided into intravascular plasma (25.0%) and interstitial fluid (75.0%)[25]. The TBW and body fluid distribution, together with other body compositions, can be accurately and reliably estimated using BIA. Measurement of TBW is important in many pathologic processes; for example, it is useful in evaluation of diuretic therapy and also in measuring the amount of excess fluid gained in hemodialysis patients in order to determine how much fluid should be removed during a dialysis session.

Edematous states in CKD patients are due to accumulation of ECW. In the present study, using the MF-BIA technique, it was found that the ECW/TBW, which indicates edematous state, was significantly higher in patients with CKD stages 3-4 and stage 5 than in normal controls ($p<0.001$) and in patients in
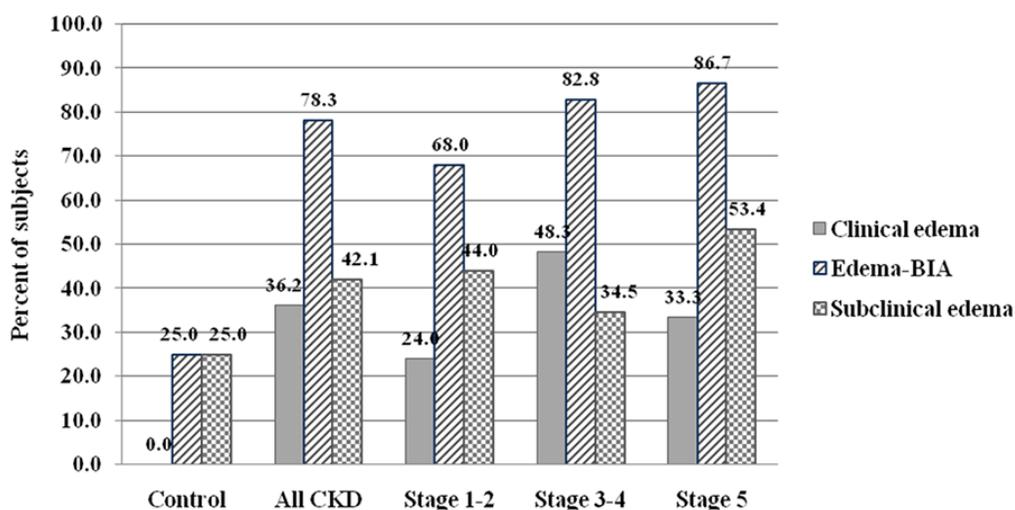


**Fig. 1** Comparison of clinically apparent edema, edema-BIA, and subclinical edema in controls and patients at various stages of CKD.

**Table 4.** Sensitivity and specificity of clinical edema compared to edema-BIA

| Clinical edema | Edema-BIA | | Sensitivity | Specificity |
|---|---|---|---|---|
| | Yes | No | | |
| All CKD | | | | |
|    Yes | 24 | 1 | 44.4 | 93.3 |
|    No | 30 | 14 | | |
| Stages 1-2 | | | | |
|    Yes | 5 | 1 | 29.4 | 87.5 |
|    No | 12 | 7 | | |
| Stages 3-4 | | | | |
|    Yes | 14 | 0 | 58.3 | 100 |
|    No | 10 | 5 | | |
| Stage 5 | | | | |
|    Yes | 5 | 0 | 38.5 | 100 |
|    No | 8 | 2 | | |
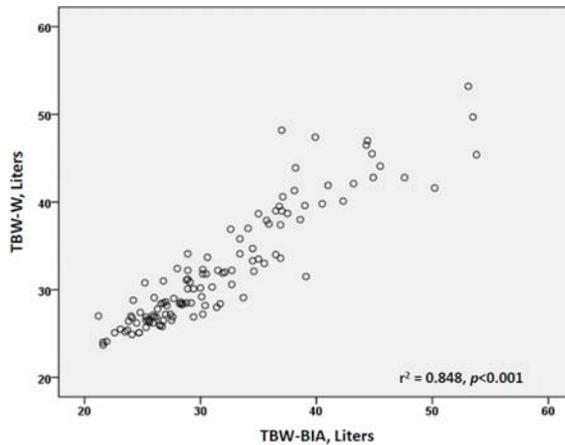


**Fig. 2** Correlation of Watson formula-derived TBW (TBW-W) and TBW determined by MF-BIA (TBW-BIA).

earlier stages of CKD ($p<0.05$). Comparing the detection of edematous state by physical examination with detection using the MF-BIA technique, it was found that physical examination had lower sensitivity, but higher specificity. Furthermore, the sensitivity of physical examination-detected edema was even higher in patients at more advanced stages of CKD with 100% specificity.

Importantly, although edematous state in a significant number of CKD patients went undetected by physical examination in the present study, it was successfully identified by the MF-BIA technique, and this demonstrated that subclinical edema was present at earlier stages of CKD, and could actually be found in every stage of CKD. The authors were able to demonstrate that false negative for edema detection by physical examination was 70.6% in CKD stage 1-2, 41.7% in stage 3-4, and 61.5% in stage 5.

Although the TBW-BIA/Wt ratios in normal controls and in CKD patients were not significantly different, the TBW-BIA/Wt in CKD stage 5 was significantly higher than in CKD stages 3-4 ($0.56\pm0.10$ vs. $0.50\pm0.07$, $p = 0.039$) and the ECW/Wt ratio in CKD stage 5 was also significantly higher than in CKD stages 3-4 ($0.23\pm0.04$ vs. $0.20\pm0.03$, $p = 0.009$). These findings are accounted for by the fact that excess water usually accumulates firstly in the interstitial space which is a part of ECW space. Furthermore, it confirms that patients with advanced stages of CKD usually have excess ECW volume and are prone to have fluid overload; in addition, acute pulmonary edema could develop eventually.

A variety of factors that could be related to the occurrence of edema in CKD patients, besides the progressive loss of renal function, include hypertension, diabetes, heart failure, proteinuria, and high salt and water intake. Patients with diabetes are prone to develop coronary heart disease and heart failure, which can cause edema; furthermore, proteinuria is usually a hallmark of overt diabetic nephropathy which can cause hypoalbuminemia and edema. In the present study, although diabetes and ischemic heart disease were more prevalent in advanced stages of CKD, serum albumin levels were comparable in all groups of CKD patients.

Hypertension was present in approximately

80.0 to 85.0% of CKD patients[25] and its prevalence increased progressively from 65.0 to 95.0% as the GFR fell from 85 to 15 ml/min/1.73 m²[26]. Sodium retention and volume expansion are generally of primary importance in contributing to the increased prevalence of hypertension in patients with CKD, even though the degree of extracellular volume expansion may be insufficient to induce edema. As a result, the absence of overt edema does not exclude hypervolemia.

In the present study, the authors were able to demonstrate the superiority of the MF-BIA technique over physical examination in early detection of alterations in body fluid distribution and subclinical edema in patients at various stages of CKD. However, MF-BIA devices are available only in a few tertiary hospitals, and there is still insufficient availability in most general practice institutes. The assessment of TBW by the anthropometry-derived TBW calculated by the Watson formula has been found to be significantly correlated with MF-BIA derived TBW ($r^2$ = 0.848, $p$<0.001), in addition, a good agreement (ICC = 0.92) of the 2 methods were also demonstrated. Therefore, the authors propose that the alteration of TBW in CKD patients assessed by the Watson formula will serve as an alternative assessment method which will be able to guide physicians in evaluating hydration status and prescribing appropriate management of CKD patients.

## Conclusion

Edematous states in CKD patients are due to accumulation of ECW. Detection of clinically apparent edema by physical examination may not be sensitive enough whereas assessment of hydration status by MF-BIA provides useful information for early detection of alteration of body fluid distribution and subclinical edema in patients in various stages of CKD. Due to its significant correlation with TBW assessed by MF-BIA, TBW calculated by the Watson formula can be a suitable alternative method of evaluating hydration status and guiding physicians in prescribing appropriate management of CKD patients

## Acknowledgement

## Potential conflicts of interest

## References

1. Jha V, Jairam A, Sharma MC, Sakhuja V, Piccoli A, Parthasarathy S. Body composition analysis with bioelectric impedance in adult Indians with ESRD: comparison with healthy population. Kidney Int 2006; 69: 1649-53.
2. Bellizzi V, Scalfi L, Terracciano V, De Nicola L, Minutolo R, Marra M, et al. Early changes in bioelectrical estimates of body composition in chronic kidney disease. J Am Soc Nephrol 2006; 17: 1481-7.
3. Donadio C, Consani C, Ardini M, Bernabini G, Caprio F, Grassi G, et al. Estimate of body water compartments and of body composition in maintenance hemodialysis patients: comparison of single and multifrequency bioimpedance analysis. J Ren Nutr 2005; 15: 332-44.
4. Jaffrin MY. Body composition determination by bioimpedance: an update. Curr Opin Clin Nutr Metab Care 2009; 12: 482-6.
5. Caravaca F, Martinez del Viejo C, Villa J, Martinez Gallardo R, Ferreira F. Hydration status assessment by multi-frequency bioimpedance in patients with advanced chronic kidney disease. Nefrologia 2011; 31: 537-44.
6. Cha K, Chertow GM, Gonzalez J, Lazarus JM, Wilmore DW. Multifrequency bioelectrical impedance estimates the distribution of body water. J Appl Physiol 1995; 79: 1316-9.
7. Ho LT, Kushner RF, Schoeller DA, Gudivaka R, Spiegel DM. Bioimpedance analysis of total body water in hemodialysis patients. Kidney Int 1994; 46: 1438-42.
8. Earthman C, Traughber D, Dobratz J, Howell W. Bioimpedance spectroscopy for clinical assessment of fluid distribution and body cell mass. Nutr Clin Pract 2007; 22: 389-405.
9. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body composition spectroscopy in health and disease. Physiol Meas 2006; 27: 921-33.
10. National Kidney Foundation . K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (2 Suppl 1): S1-266.
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to

estimate glomerular filtration rate. Ann Intern Med 2009, 150: 604-12.

12. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, et al. Comparative Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010, 56: 486-95.

13. De Lorenzo A, Andreoli A, Matthie J, Withers P. Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. J Appl Physiol 1997; 82: 1542-58.

14. Chan C, McIntyre C, Smith D, Spanel P, Davies SJ. Combining near-subject absolute and relative measures of longitudinal hydration in hemodialysis. Clin J Am Soc Nephrol 2009; 4: 1791-8.

15. Shafer KJ, Siders WA, Johnson LK, Lukaski HC. Validity of segmental multiple-frequency bioelectrical impedance analysis to estimate body composition of adults across a range of body mass indexes. Nutrition 2009; 25: 25-32.

16. Keshaviah PR. Quantitative approaches to prescribing peritoneal dialysis. In: La Greca G, Ronco C, Feriani M. Chairamonte S, Conz P, editors. Peritoneal Dialysis: Proceedings of the fourth international course on peritoneal dialysis. Milano: Wichtig Editore, 1991: 53-60.

17. 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.

18. Hume R, Weyers E. Relationship between total body water and surface area in normal and obese subjects. J Clin Pathol 1971; 24: 234-8.

19. Chertow GM, Lazarus JM, Lew NL, Ma L, Lowrie EG. Development of a population-specific regression equation to estimate total body water

in hemodialysis patients. Kidney Int 1997; 51: 1578-82.

20. Lee SW, Song JH, Kim GA, Lee KJ, Kim MJ. Assessment of total body water from anthropometry-based equations using bioelectrical impedance as reference in Korean adult control and haemodialysis subjects. Nephrol Dial Transplant 2001; 16: 91-7.

21. Borgonha S, Petracchi C, Ferro Luzzi A, Shetty PS, Kurpad AV. Prediction of total body water in Indian men from anthropometry and bioelectrical impedance using deuterium dilution as reference. Ann Hum Biol 1997; 24: 355-61.

22. Arkouche W, Fouque D, Pachiaudi C, Normand S, Laville M, Delawari E, et al. Total body water and body composition in chronic peritoneal dialysis patients. J Am Soc Nephrol 1997; 8: 1906-14.

23. Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of sample size in health studies. England: World Health Organization ; John Wiley & Sons, 1990.

24. Verbalis JG, Disorders of water balance. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, editors. Brenner and Rector's the kidney. 9th ed. Philadelphia: Elsevier/ Saunders, 2012: 540-94.

25. Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, et al. 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 (Suppl 2): S13-20.

26. 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: 811-21.

# การตรวจพบระยะแรกของภาวะบวมซ่อนเร้นในผู้ป่วยโรคไตเรื้อรังโดยเครื่อง *multifrequency bioimpedance analysis*

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*ภูมิหลัง: ความผิดปกติในการกระจายของสารน้ำในร่างกายพบได้บ่อยในผู้ป่วยโรคไตเรื้อรัง การมีปริมาณน้ำเพิ่มขึ้นในร่างกายเป็นสาเหตุของความดันโลหิตสูงได้แม้ในระยะที่ยังไม่เกิดอาการบวมชัดเจน และหากปล่อยให้มีปริมาณน้ำในร่างกายสะสมเพิ่มขึ้นไปอีกจะทำให้เกิดอาการบวมชัดเจนและเกิดภาวะน้ำเกินในร่างกายได้ การประเมินปริมาตรน้ำในร่างกายในปัจจุบันสามารถวัดได้ด้วยเครื่อง multifrequency bioimpedance analysis (MF-BIA) ซึ่งเชื่อว่าจะทำให้สามารถตรวจพบภาวะบวมซ่อนเร้นได้ตั้งแต่ระยะแรกๆ ของโรคไตเรื้อรัง*

*วัตถุประสงค์: เพื่อศึกษาการกระจายของสารน้ำในร่างกายและอาการบวมในระยะต่างๆ ของผู้ป่วยโรคไตเรื้อรังด้วยเครื่อง MF-BIA เปรียบเทียบการตรวจร่างกายพบอาการบวมและเพื่อเปรียบเทียบความสัมพันธ์ ระหว่างการประเมินปริมาตรน้ำในร่างกายโดยการตรวจด้วยเครื่อง MF-BIA และการคำนวณด้วยสูตรของ Watson*

*วัสดุและวิธีการ: เป็นการศึกษาไปข้างหน้าในผู้ป่วยโรคไตเรื้อรังและอาสาสมัคร โดยประเมินการกระจายของสารน้ำในร่างกายด้วยเครื่อง bioelectrical impedance analyzer (InBody® S20, สาธารณรัฐเกาหลี) พร้อมกับการตรวจร่างกาย โดยแบ่งโรคไตเรื้อรังออกเป็นระยะที่ 1-5 ตามแนวทางเวชปฏิบัติ NKF-K/DOQI ปี 2002 และจัดแบ่งเป็น 3 กลุ่มใหม่คือ โรคไตเรื้อรังระยะที่ 1-2 ระยะที่ 3-4 และระยะที่ 5*

*ผลการศึกษา: ผู้ป่วยโรคไตเรื้อรังจำนวน 69 ราย เปรียบเทียบอาสาสมัคร 48 ราย มีระดับ GFR 53.5±41.1 และ 113.9±10.8 มล./นาที/1.73 ม.$^2$ ตามลำดับ อัตราส่วนระหว่าง extracellular water (ECW) ต่อ total body water (TBW) ซึ่งแสดงถึงการบวมในผู้ป่วยโรคไตเรื้อรัง ระยะที่ 3-4 (0.400±0.008) และระยะที่ 5 (0.404±0.011) มีค่าสูงกว่าในระยะที่ 1-2 (0.393±0.009) และอาสาสมัคร (0.385±0.007) อย่างมีนัยสำคัญทางสถิติ (p<0.001) อาการบวมที่ตรวจพบด้วยเครื่อง MF-BIA ในผู้ป่วยโรคไตเรื้อรังพบว่ามีจำนวนสูงกว่าในอาสาสมัครอย่างมีนัยสำคัญทางสถิติ (78.3% เทียบกับ 25.0%, p<0.001) และยังสูงกว่าอาการบวมที่ตรวจพบโดยการตรวจร่างกาย (36.2%) ซึ่งแสดงถึงการมีผู้ป่วยจำนวนไม่น้อย (42.1%) ที่มีภาวะบวมซ่อนเร้น การตรวจร่างกายพบอาการบวมเมื่อเปรียบเทียบกับการตรวจด้วยเครื่อง MF-BIA นั้นมี sensitivity 44.4% และ specificity 93.3% การประเมินสารน้ำในร่างกายโดยการคำนวณด้วยสูตรของ Watson มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติเมื่อเทียบการประเมินด้วย MF-BIA (r$^2$ = 0.848, p<0.001)*

*สรุป: การประเมินสารน้ำในร่างกายด้วยเครื่อง MF-BIA เป็นวิธีที่น่าเชื่อถือทำให้สามารถตรวจพบภาวะบวมซ่อนเร้น ได้ตั้งแต่ระยะแรกๆ ของโรคไตเรื้อรังก่อนที่จะตรวจพบโดยการตรวจร่างกาย นอกจากนี้การประเมินสารน้ำในร่างกายโดยการคำนวณด้วยสูตรของ Watson เป็นอีกวิธีหนึ่งที่สามารถนำมาใช้ให้เกิดประโยชน์ในการประเมินปริมาณสารน้ำ เพื่อพิจารณาให้การรักษาที่เหมาะสมในผู้ป่วยโรคไตเรื้อรัง*