THE ASSOCIATION OF RELATIVE HYDRATION STATUS WITH NT-PROBNP, IVC INDEX AND BLOOD PRESSURE IN NEWLY DIAGNOSED STAGE 5 CHRONIC KIDNEY DISEASE

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ABSTRACT

Introduction*: Accurate and sensitive methods are very important for the assessment of volume status in chronic kidney disease (CKD). Bioelectrical impedance analysis (BIA) is a simple, non-invasive and promising method to assess volume status in patients with CKD.*

Objective*: The aim of this study was to evaluate the association between BIA derived relative hydration status (RHS) and clinical findings and other markers of volume status in patients who were newly diagnosed with stage 5 CKD.*

Patients and method: Totally 85 patients who were newly diagnosed with stage 5 CKD and have not received any renal replacement therapy were enrolled in this study. Hydration status was assessed by multi-frequency BIA device (Body Composition Monitor, Fresenius). Relative hydration status was defined as the overhydration (OH) to extracellular water (ECW) ratio and clinical overhydration was considered as an overhydration-to-extracellular water ratio of >% 15. The patient population was divided into 2 groups; group 1: RHS >% 15, group 2: RHS ≤ %15. Inferior vena cava (IVC) diameter was measured by echocardiography and indexed for body surface area as IVC index (mm/m2). NT-proBNP was measured by immunoassay.

Results*: Among subjects, 57.6% of the patients had RHS >% 15. Systolic blood pressure (SBP), diastolic blood pressure (DBP), proteinuria, OH, ECW, IVC index, and NT-proBNP were significantly higher, while serum albumin and residual urine were significantly lower in group 1 than group 2 (p<0.05). There was a significant positive correlation between RHS and SBP, DBP, proteinuria, OH, ECW, NT-proBNP and IVC index and a negative correlation with albumin and residual urine (p<0.05).*

Conclusions*: RHS may be an important measuring parameter of volume overload in patients with CKD. RHS is correlated with NT-proBNP, blood pressure and IVC index.*

Key words*: Bioelectrical impedance analysis, relative hydration status, IVC index, NT-proBNP, blood pressure.*

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Introduction

Chronic Kidney Disease (CKD) is progressive, irreversible loss of kidney function, which results with in end stage renal disease (ESRD) in general, despite improvements in current treatment. Water clearance is usually maintained until the late stages of CKD. Volume overload occurs due to not removable of excess fluid volume in intact nephrons at these late stages of chronic kidney disease. Early detection and management of hypervolemia associated with morbidity and mortality is extremely important in patients with CKD.

Although physical examination findings are still an important role in determining of the volume status, it may be insufficient, especially in early stages of volume overload. Thus, more accurate and sensitive methods seem to be needed for the assessment of volume status in chronic kidney disease.

It is known that volume overload is primarily compensated in venous system and leads to increase the diameter of large veins. In this regard, inferior vena cava (IVC) diameter can be used to assess intravascular volume status[1,2] and is an effective non-invasive tool for volume management[2].

Natriuretic peptides are other markers of volume status. Since the disease progresses through the stages of CKD, sodium retention typically occurs, leading to expansion of the extracellular fluid volume with the compensatory release of natriuretic peptides due to cardiac wall stretch[3]. NT-pro-BNP has been found to be elevated in patients with CKD[4,5] and has also been found to be associated with volume overload in haemodialysis patients[3,6].

The other tool, bioelectrical impedance analysis (BIA) is a simple, inexpensive, reproducible, non-invasive and easy method to assess changes in hydration status and is based on the human body's resistance to alternating electrical currents. BIA assesses not only hydration status but also intracellular and extracellular water, the extracellular and intracellular ratio, the total water volume, as well as nutritional parameters[7]. Several parameters of BIA such as OH, ECW/TBW and OH/ECW (Relative hydration status) were used as markers of the volume status in patients with CKD. BIA has been used in HD[8,9] as well as in peritoneal dialysis (PD) and chronic kidney disease patients (CKD)[10,11].

We evaluated the association of relative hydration status between clinical findings and other markers of volume status in patients with newly diagnosed stage 5 CKD in our study.

Materials and methods

From January, 2012 to December 2012, 85 patients whose age ranged between 18-70 years with stage 5 CKD and who have not undergone renal replacement therapy and also fluid management were enrolled in this study. The Local Human Research Ethics Committee approved the study protocol and informed consents were obtained from all patients at the time of study enrollment. The exclusion criteria were as follows; patients who had received renal replacement therapy; patients with EF <55%, limb amputation, pacemakers or metallic intravascular devices, any malignant disease, severe obesity (BMI ≥35 kg/m2), pregnancy and use of diuretics.

Demographic characteristics of patient's were provided from patient's registries. Systolic and diastolic blood pressures of patients were measured from the right arm after at least 5 minutes resting. Glomerular filtration rate (GFR) was estimated by modification of diet in renal disease (MDRD) formula. Stage 5 CKD (estimated GFR < 15 mL/min/1.73 m2) was defined according to Kidney Disease Outcomes Quality Initiative (K/DOQI) classification[12]. 24-hour urine samples were collected to assess the level of proteinuria and residual urine.

A multi-frequency BIA device (Body Composition Monitor, BCM, Fresenius Medical Care D GmbH) that measures 50 different frequencies from 5 to 1000kHz was used to assess hydration status. Measurements were performed after 20 minute resting in the supine position at the bedside. Electrodes of BCM device were placed on the wrist and ankle of the patients. The following parameters were collected; overhydration (OH), extracellular water (ECW), intracellular water (ICW), total body water (TBW) in liters (l) and OH/ECW ratio (%) as a percentage in the study. Relative hydration status (RHS) was defined as the OH to ECW ratio and clinical overhydration was defined as an overhydration-to-extracellular water ratio of >% 15 (13,14). Patients were divided into 2 groups according to RHS value; group 1:RHS >% 15, group 2: RHS ≤ % 15.

IVC diameter was measured during expiration in the supine position after 10 min of rest at the level just below the diaphragm in the hepatic segment by 2D-guided M-mode echocardiography (Vivid S5 System, GE Healthcare, USA). IVC diameter was indexed for body surface area (BSA) as IVC index (mm/m2).

Blood samples were taken from all patients for the biochemical (urea, creatinine, albumin) analysis after overnight fasting and on the same day as the BIS examination. NT-proBNP was measured in serum using Elecsys proBNP sandwich immunoassay (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

The data were analyzed using SPSS software version 16.0. Results are expressed as mean, standard deviation for data with normal distribution; and as median (maximum and minimum) for data that did not have normal distribution. Comparisons between groups were performed using the Student's t-test and the Mann-Witney U-test according to the distribution of the variables. The Pearson or Spearman correlations were used for the univariate analysis, depending on the nature of the variable. P values below 0.05 were considered statistically significant.

Results

The demographic, clinical and laboratory characteristics of the patients were presented in Table 1. Underlying renal diseases were hypertension (29.4%), diabetic nephropathy (28.2%), obstructive nephropathy (17.6 %), unknown conditions (9.5%), glomerular disease (4.7%), polycystic kidney disease (7%) and interstitial nephritis (2.6%).

Parameter	
Patients (male/female) (n)	49/36
Age (years)	51.99±16.80
SBP (mm Hg)	133±19.13
DBP (mm Hg)	83.41±10.21
Estimated glomerular filtration rate (ml/min/1.73m2)	9.16 ±3.45
Residual urine (l/day)	1.66±0.78
Proteinuria(gr/day)	2.96±2.20
Serum albumin (g/dl)	2.84±0.77
Urea(mg/dl)	177.64±80.35
Creatinine(mg/dl)	6.80±2.95
NT-proBNP (pg/ml)	319 (43-2401)
IVC index (mm/m2)	11.32±2.14
OH (l)	3,8±3.29
ECW (l)	17.86±4.46
ICW (l)	17.82±4.12
TBW (l)	35.59±7.58
Relative hydration status (OH/ECW) %	19.78±12.74

Table 1: Demographic, clinical and laboratory characteristics of patients.
SBP: systolic blood pressure; DBP: diastolic blood pressure; OH: overhydration; ECW: extracellular water; ICW: intracellular water; TBW: total body water; IVC index: inferior vena cava index.

Group 1 included 49/85 (57.6%) patients and 36/85 (42.4%) of the patients were in Group 2. SBP (p=0.004), DBP (p<0.010), proteinuria (p=0,019), OH (p<0,001), ECW (p=0,006), IVC index (p<0,001), and NT-proBNP (p=0,001) were significantly higher, while serum albumin (p<0,001) and residual urine (p=0,042) were significantly lower in Group1 than Group 2. There was no significant difference in age, gender, GFR, urea, creatinine, TBW and ICW between these groups (p>0.05) (Table 2).

There was a significant positive correlation between RHS and SBP (r= 0.391, p<0,001), DBP (r=0.306, p= 0.004), proteinuria (r= 0.356, p=0.001),OH (r=0.939, p<0,001), ECW (r=0.532, p<0.001, Figure 1), NT-proBNP (r = 0.490, p < 0.001, Figure 2) and IVC index (r = 0.437, p < 0.001, Figure 3) and a negative correlation with albumin (r=-0.448, p<0,001) and residual urine (r=-0.286, p=0.008) (Table 3).

Parameter	Group 1 (n=49)	Group 2 (n=36)	p
Age (years)	51,34± 17,40	52,86±16,14	0,684
Gender (M/F)	25/24	19/17	0,873
GFR(ml/min/1.73m2)	8,54±3,56	10,00±3,22	0,056
SBP(mmHg)	138,06±19,44	126,11±16,60	0,004
DBP(mmHg)	85,81±10,27	80,13±9,29	0,010
Urea(mg/dl)	192±93,59	157±52,83	0,052
Creatinine(mg/dl)	7,21±3,41	6,25±2,10	0,143
Albumin(g/dl)	2,59±0,75	3,18±0,66	<0,001
Proteinuria(gr/day)	3,43±2,44	2,31±1,64	0,019
Residual urine (l/day)	1,51±0,76	1,86±0,77	0,042
OH(l)	5,60±3,19	1,35±1,14	<0,001
TBW(l)	35,85±7,10	35,23±8,28	0,710
ECW(l)	18,98±4,46	16,33±4,04	0,006
ICW(l)	17,05±3,64	18,87±4,55	0,052
IVC index (mm/m2)	12,01±2,08	10,37±1,86	<0,001
NT-proBNP (pg/mlt)	425.00 (43.00-2401.00)	192.50 (47.00-2190.00)	0,001

Table 2: Demographic, clinical and laboratory characteristics of the groups .

Parameter	r	p
RHS&Albumin	-0.448	<0,001
RHS &Proteinuria	0.356	0.001
RHS & Residual urine	-0.286	0.008
RHS & SBP	0.391	<0,001
RHS & DBP	0.306	0.004
RHS & OH	0.939	<0,001
RHS & ECW	0.532	<0,001
RHS & ICW	-0.191	0.080
RHS & TBW	0.198	0.069
RHS & NT-proBNP	0.490	<0,001
RHS & IVC index	0.437	<0,001

Table 3: Correlation (Pearson) between RHS and study parameters.

Discussion

Hydration and volume status are known to be significant predictors of outcome in patients with end stage renal disease on renal replacement therapy[15]. Therefore, early diagnosis of volume overload is so important in CKD.

Several methods such as natriuretic peptides, measurement of inferior vena cava diameter and BIA have been used to evaluate the volume status in clinical practice. In recent years, BIA has been reliable and widely used technique for assessment of body composition. Several parameters of BIA such as OH, ECW/TBW and OH/ECW (Relative hydration status) were used as markers of the volume status in patients with CKD. Lopot et al assessed the optimal dry weight in HD patients using ECW/TBW ratio[16]. Passauer et al determined hydration status by means of OH[9]. Devolder et al, compared volume status in peritoneal dialysis (PD) and hemodialysis patients by using OH/ECW (overhydrated OH/ECW>15%)[15]. In a study of 269 dialysis patients conducted in three European centres by Wizemann et al, found that OH/ECW ratio > %15, as measured by the BCM, is associated with increased cardiovascular mortality[14]. Overhydration was assesed by OH/ECW in the present study.

BIA has still not been used extensively in patients with chronic kidney disease (CKD) who are not undergoing dialysis[17]. To the best of our knowledge, this is the first study that investigated overhydration, which can be assesed by relative hydration status in newly diagnosed patients with stage 5 CKD and its association with the other clinical markers of hydration status.

Dumler et al, in a prospective study including 40 patients with a mean GFR 36±12 ml/min/1.72 m2, reported that overhydration was developed in 62% of patients over a 9-month period[18]. A recent study by Caravaca et al, reported that among 175 patients with eGFR < 40 ml/min, overhydration was found in 19 patients (10.8%)[17]. 49 of 85 newly diagnosed patients with stage 5 CKD had overhydration (57.6%) in the present study. Our results indicate that high percentage of patients with stage 5 CKD had overhydration. As kidney failure progresses, fluid and electrolyte homeostasis disturbed and may lead to volume overload even in early stages of chronic kidney disease.

Dialysis patients often have expanded TBW, and they can accumulate excess fluid in their ECW compartment[19]. In a study by Kyle et al, reported that ECW changes do not corrupt the ICW[20]. Dumler et al, suggested that the greater total body water reflected an increase in extracellular volume[18]. In the present study overhydrated patients were found to have significantly higher ECW, whereas ICW was not significantly different in these patients. In addition, we found a positive correlation between RHS and ECW (Figure 1).

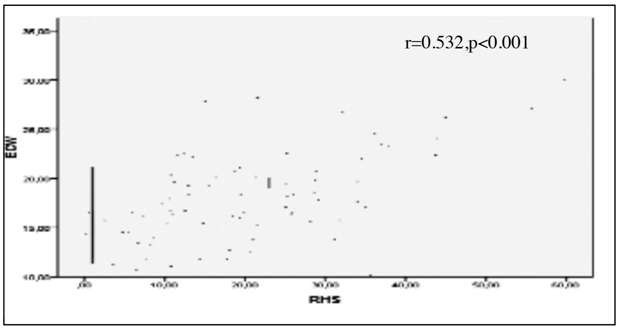

Figure 1: Correlation between RHS and ECW.

It seems that overhydration reflects an increase in ECW.

Overhydrated patients group with a lower serum albumin levels in our study could be explained by these patients had higher levels of proteinuria and hemodilution secondary to expansion of the ECW compartment.

Hypertension is quite common among patients with chronic kidney disease. Although several factors contribute to the pathogenesis of hypertension, increased volume load seems to be major cause of hypertension in advanced stages of chronic kidney disease. Several studies have shown the association between volume overload and hypertension in dialysis patients. Chen et al. found that hypertensive patients had significantly higher ECW than normotensive patients and reduction of ECW in hypertensive HD patients accompanied with decrease in BP[21]. In another study of 32 dialysis patients with CKD by Alvarez et al, also observed that hypertensive patients had significantly greater ECW and total body water volume than the normotensive patients[22]. Fagugli et al. found a correlation between ECW and SBP[23]. Compatible with the findings of previous studies, in the present study we found that SBP and DBP were both significantly higher in overhydrated patients group. Besides, we found a positive correlation between RHS with SBP and DBP (Table 3). As volume overload is closely associated with hypertension, we suggest that BIA may be useful tool in the management and control of hypertension in patients with CKD.

Natriuretic peptides such as NT-proBNP are known to be elevated in chronic kidney disease. However, it has been debated that whether increased level of NT-proBNP in patients with CKD is result of decreased renal clearance of NT-proBNP or volume overload. In a multinational, observational study of 177 nondiabetic patients with mild-to-moderate renal insufficiency from 3 countries, both BNP and NT-proBNP plasma concentrations were progressively higher in patients with progressively more advanced stages of CKD[24]. Anwaruddin et al. showed that NT-proBNP and GFR are inversely corelated[25]. Jacobs et al, in a prospective study including 44 HD patients, observed that the extracellular water (ECW)/TBW ratio (reflecting overhydration) had a positive effect on BNP and NT-proBNP concentrations[6]. In another study by Booth et al, a strong association was found between NTproBNP and the predialysis ratio of extracellular water/total body water[3]. In line with the findings of Jacobs et al. and Booth et al., our study revealed that NT-proBNP levels were significantly higher in overhydrated patients compared patients without ovehydration and RHS was significantly correlated with NT-proBNP (Figure 2).

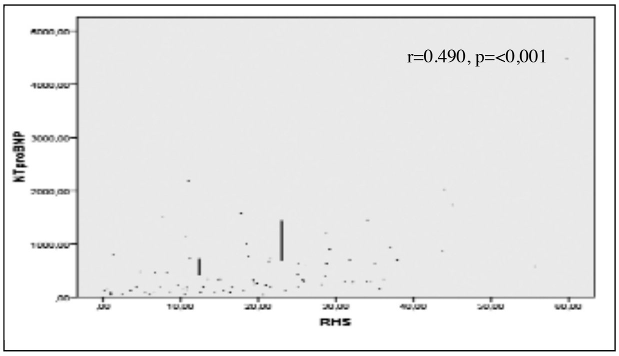

Figure 2: Correlation between RHS and NT-proBNP.

Echocardiographic examination of IVC diamater is a simple, quick, and non-invasive method for the assessment of intravascular volume status[26]. An increase in the intravascular volume leads to an increase in venous filling and IVC diamater[27]. However, the measurement of IVC diamater is also operator-dependent and can be influenced by the cardiovascular diseases. Cheriex et al. defined overhydration as a IVC index >11.5mm/m2[1]. Ando et al. observed that expiration IVC diameter decreased proportionally to the amount of ultrafiltration[28]. Oe et al. found a correlation between IVC diameter with ECW/TBW and ICW/ECW in a study conducted with 19 PD patients[29]. In the present study, overhydrated patients were found to have significantly higher IVC index compared patients without ovehydration and mean IVC index was 12,01±2,08 mm/m2 in overhydrated patients group. Also, RHS was significantly correlated with IVC index in our study (Figure 3).

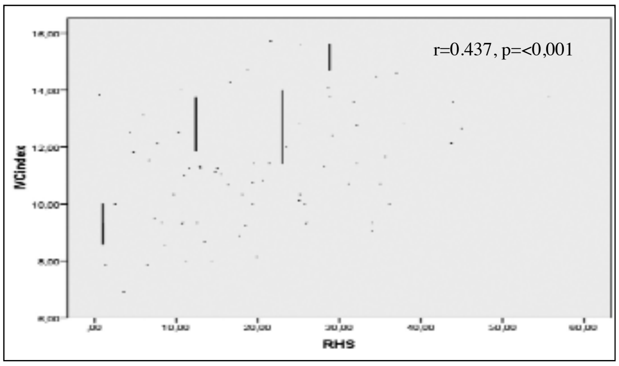

Figure 3: Correlation between RHS and IVC index.

In conclusion, RHS may be an important measuring parameter of volume overload in patients with CKD. RHS is correlated with NT-proBNP, blood pressure and IVC index.

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