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# Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease

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**Volume overload is a predictor of mortality in dialysis patients. However, the fluid status of patients with chronic kidney disease (CKD) but not yet on dialysis has not been accurately characterized. We used the Body Composition Monitor, a multifrequency bioimpedance device, to measure the level of overhydration in CKD patients, focusing on the association between overhydration and cardiovascular disease risk factors. Overhydration was the difference between the amount of extracellular water measured by the Body Composition Monitor and the amount of water predicted under healthy euvolemic conditions. Volume overload was defined as an overhydration value at and above the 90th percentile for the normal population. Of the 338 patients with stages 3–5 CKD, only 48% were euvolemic. Patients with volume overload were found to use significantly more antihypertensive medications and diuretics but had higher systolic blood pressures and an increased arterial stiffness than patients without volume overload. In a multivariate analysis, male sex, diabetes, pre-existing cardiovascular disease, systolic blood pressure, serum albumin, TNF-α, and proteinuria were independently all associated with overhydration. Thus, volume overload is strongly associated with both traditional and novel risk factors for cardiovascular disease. Bioimpedance devices may aid in clinical assessment by helping to identify a high-risk group with volume overload among stages 3–5 CKD patients.**

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Chronic kidney disease (CKD) substantially increases the risks of death and cardiovascular disease (CVD) and the use of specialized health care.[1] Although traditional Framingham risk factors for CVD are more prevalent in patients with CKD than in the general population, these risk factors do not fully account for the accelerated progression of CVD in CKD patients.[2] Therefore, many recent studies have focused on the novel risk factors such as malnutrition, inflammation, and volume overload in the CKD population. Volume overload is related to CVD[3,4] and is a predictor of outcome in hemodialysis and peritoneal dialysis patients.[5,6] Although a large body of experimental evidence on fluid status has been collected for dialysis patients, only a limited number of studies have been conducted in CKD patients not yet on dialysis.[7] Furthermore, the fluid status of predialysis CKD patients has not been characterized using a valid method. The prevalence of volume overload during the earlier stages of CKD is unclear and its significance has not been elucidated.

The clinical assessment of fluid status is relatively difficult, because physical signs of edema are of limited value in diagnosing excess intravascular volume.[8] Ultrasonic evaluation of the diameter of the inferior vena cava can be used to assess intravascular volume (preload) but not tissue hydration.[9] Interpatient and interoperator variability and the presence of diastolic dysfunction or right-sided failure also limit the use of this technique.[10,11] Biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) can reflect changes in the fluid status but are also influenced by CVD, and they can be accumulated in CKD patients.[12] The most direct and accurate method involves isotope dilution, but the use of this method is limited to the research environment. Bioimpedance spectroscopy is a simple and effective approach for the assessment of fluid status.[13,14] The Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) is a bedside bioimpedance spectroscopy device for clinical use. The accuracy of fluid status and body composition measurements has been validated against available gold standard reference methods,[15,16] and the device has been used to monitor patients receiving hemodialysis[17,18] or peritoneal dialysis.[19,20]

We hypothesized that volume overload develops early during the course of CKD and may contribute significantly to the development of CVD.[21] The primary objectives of this study were to determine the fluid status in a representative sample of CKD patients using the BCM device, and the measured fluid status was compared with that of an age- and sex-matched healthy cohort.[22] We also sought to identify CVD risk factors associated with volume overload.

## RESULTS

### Patient characteristics

After the exclusion criteria were applied, 338 clinically stable patients (233 men and 105 women; mean age 65.7 ± 13.5 years) were enrolled in the study. All patients had moderate-to-severe CKD (mean estimated glomerular filtration rate (eGFR) 28.7 ml/min per 1.73 $m^2$; 151 in stage 3, 108 in stage 4, and 79 in stage 5). In this population, 45.3% were diabetic ($n = 153$) and 23.4% had CVD ($n = 79$) (coronary artery disease ($n = 38$), congestive heart failure ($n = 29$), and/or cerebrovascular accident ($n = 25$)). At least one type of antihypertensive drug was taken by 83.7% of the patients (calcium-channel blockers 51.2%, renin–angiotensin system (RAS) blockers 59.2%), with a mean of 2.0 ± 1.4 drugs prescribed per patient. A total of 113 (33.4%) patients were receiving diuretic treatment.

### Prevalence of volume overload

The baseline characteristics for the patient groups divided on the basis of the absence or presence of volume overload (defined as overhydration (OH) ⩾7%) are presented in Table 1. Overall, 52% ($n = 175$) of the study population showed evidence of volume overload (Figure 1). The patients in the two groups were similar with regard to age, sex, and smoking history, but there were greater numbers of patients with diabetes mellitus (DM) and CVD in the volume overload group. The proportion of patients with volume overload receiving antihypertensive agents and diuretics was higher. Patients with volume overload were found to have a similar body mass index and fat tissue index but a significantly lower lean tissue index compared with patients without volume overload. In addition, there were important differences in the blood pressure (BP), arterial stiffness, routine biochemical parameters, and inflammatory markers between the groups. Patients with volume overload had significantly higher systolic BP, brachial-ankle pulse wave velocity (baPWV), extracellular water (ECW), ECW to total body water ratio (ECW/TBW), NT-proBNP, urine protein-to-creatinine ratio (UPCR), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels and significantly lower intracellular water (ICW), eGFR, serum albumin, and hemoglobin levels. The results of the analysis were similar when volume overload was defined as absolute OH ⩾ 1.1 L (Supplementary Table S1 online).

### Factors associated with OH

Correlations between OH and other variables in the overall sample are presented in Figures 2–4. OH was positively and strongly correlated with ln NT-proBNP ($r^2 = 0.292$; Figure 2). A number of patients had high ln NT-proBNP levels despite normohydration or even underhydration. These patients were most likely patients with CVD or worse kidney function. Figure 2a illustrates the linear regression of OH on ln NT-proBNP and reveals that, for each value of OH, patients with CVD had a higher ln NT-proBNP than patients without CVD. Similar results were observed for stages 4 and 5 CKD compared with stage 3 CKD (Figure 2b).

OH also correlated positively with systolic BP ($r^2 = 0.097$; Figure 3a), baPWV ($r^2 = 0.021$; Figure 3b), and ln UPCR ($r^2 = 0.193$; Figure 3c) and correlated negatively with the eGFR ($r^2 = 0.023$; Figure 3d). With regard to malnutrition–inflammation complex syndrome in CKD patients, OH was positively correlated with ln IL-6 ($r^2 = 0.065$; Figure 4a) and ln TNF-α ($r^2 = 0.113$; Figure 4b) and was negatively correlated with serum albumin ($r^2 = 0.255$; Figure 4c) and lean tissue index ($r^2 = 0.038$; Figure 4d). No association was found with high-sensitivity C-reactive protein or the lipid profile.

Multivariate regression analysis included OH as the dependent variable and several relevant demographic (age and sex), clinical (DM, CVD, systolic BP, and diuretic use), and laboratory factors (eGFR, ln UPCR, serum albumin, and ln TNF-α) that were previously identified in univariate analyses as independent variables. As shown in Table 2, the

**Table 1 | Comparisons of CKD patients with and without volume overload according to the OH values**

| Variable | OH | | *P*-value |
|---|---|---|---|
| | <7% ($n = 163$) | ⩾7% ($n = 175$) | |
| Age (years) | 65.0 ± 14.2 | 66.4 ± 12.8 | 0.324 |
| Male sex, *n* (%) | 111 (68.1%) | 122 (69.7%) | 0.748 |
| Smoking history, *n* (%) | 32 (19.6%) | 39 (22.3%) | 0.550 |
| DM, *n* (%) | 45 (27.6%) | 108 (61.7%) | <0.001 |
| CVD, *n* (%) | 23 (14.1%) | 56 (32%) | <0.001 |
| Hypertension, *n* (%) | 132 (81%) | 156 (89.1%) | 0.035 |
| Systolic BP (mm Hg) | 133 ± 15 | 142 ± 18 | <0.001 |
| baPWV (m/s) | 15.1 ± 2.8 | 16.2 ± 2.8 | <0.001 |
| Total number of antihypertensives | 1.8 ± 1.4 | 2.3 ± 1.3 | 0.001 |
| Diuretics, *n* (%) | 42 (25.8%) | 71 (40.6%) | 0.004 |
| RAS blockers, *n* (%) | 95 (58.3%) | 105 (60%) | 0.748 |
| Statin, *n* (%) | 37 (22.7%) | 50 (28.6%) | 0.217 |
| ECW (l) | 15.8 ± 3.1 | 17.8 ± 3.8 | <0.001 |
| ICW (l) | 19.6 ± 4.6 | 18.4 ± 4.4 | 0.017 |
| TBW (l | 35.4 ± 7.5 | 36.2 ± 8.0 | 0.367 |
| ECW/TBW (%) | 44.9 ± 2.4 | 49.3 ± 2.7 | <0.001 |
| Body mass index (kg/$m^2$) | 25.7 ± 4.1 | 26.1 ± 4.3 | 0.455 |
| Lean tissue index (kg/$m^2$) | 16.0 ± 3.2 | 14.7 ± 3.1 | <0.001 |
| Fat tissue index (kg/$m^2$) | 9.5 ± 4.4 | 10.0 ± 4.3 | 0.285 |
| NT-proBNP (ng/l) | 112.0 (46.0–280.5) | 530.7 (177.4–1275.0) | <0.001 |
| eGFR (ml/min per 1.73 $m^2$) | 31.5 ± 14.8 | 26.1 ± 14.7 | 0.001 |
| UPCR (g/g) | 0.49 (0.22–1.26) | 1.67 (0.62–4.19) | <0.001 |
| Albumin (g/dl) | 3.8 ± 0.3 | 3.4 ± 0.4 | <0.001 |
| Fasting glucose (mg/dl) | 116 ± 35 | 124 ± 45 | 0.73 |
| Total cholesterol (mg/dl) | 173 ± 33 | 177 ± 46 | 0.35 |
| Triglyceride (mg/dl) | 164 ± 117 | 161 ± 109 | 0.803 |
| hs-CRP (mg/l) | 3.7 (1.6–8.4) | 4.4 (1.1–10.8) | 0.712 |
| IL-6 (pg/ml) | 2.87 (1.64–4.59) | 4.28 (2.62–8.33) | <0.001 |
| TNF-α (pg/ml) | 5.63 (4.13–8.07) | 7.96 (5.37–10.34) | <0.001 |
| Hemoglobin (g/dl) | 12.5 ± 2.0 | 10.9 ± 1.9 | <0.001 |

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ECW, extracellular water; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ICW, intracellular water; IL-6, interleukin-6; NT-proBNP, N-terminal pro-brain natriuretic peptide; OH, overhydration; RAS, renin–angiotensin system; TBW, total body water; TNF-α, tumor necrosis factor α; UPCR, urine protein-to-creatinine ratio.