DETERMINATION OF VOLUME OVERLOAD BY BIOELECTRICAL IMPEDANCE ANALYSIS AND NT-PROBNP IN DIABETIC PRE-DIALYSIS PATIENTS

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Abstract

Introduction. Diabetic chronic kidney disease has more fatal clinical progresses and this situation can be related to volume overload, which is seen more commonly in diabetic chronic kidney disease patients than in non-diabetic chronic kidney disease patients. Therefore, we examined the effect of diabetes mellitus on volume overload in newly diagnosed stage 5 chronic kidney disease patients whose volume overloads were not showing signs of improvement from renal replacement therapy.

Method. One hundred and five patients (46 diabetic, 59 non-diabetic) with end-stage chronic kidney disease, who had glomerular filtration rate (GFR) under 15 mL/min for at least three months were enrolled in this prospective study. We determined the body volume overload and configuration using a bioimpedance device. NT-proBNP levels were recorded.

Results. There was a statistically significant difference between diabetic and non-diabetic groups according to overhydration (OH, $p=0.003$), extracellular water (ECW, $p=0.045$), intracellular water (ICW, $p<0.001$) and OH/ECW ($p=0.003$). In addition, there was a statistically significant difference between groups in terms of N-terminal Pro-brain Natriuretic Peptide (NT-proBNP levels, $p=0.008$).

Discussion. We compared diabetic and non-diabetic end-stage chronic kidney disease patients who were not in renal replacement therapy yet. We found more volume overload and extracellular fluid volume in the diabetic group.

Key words: Diabetic nephropathy, NT-pro BNP, Pre-dialysis chronic kidney disease patients, bioimpedance analysis.

INTRODUCTION

Today, diabetes mellitus is the most common cause of chronic kidney disease; it constitutes approximately 45% of the newly diagnosed end-stage renal disease patients in the United States (1) and about one-third of newly diagnosed patients in Europe (2). In Turkey, this ratio is close to that in Europe and

has been increasing over the past few years (3). The situation is becoming more complex in diabetic chronic kidney disease because of complications with diabetes mellitus (diabetic nephropathy) and complications associated with the progression of chronic kidney disease. Volume overload is one of the considerable causes of this complexity and one of the most common clinical problems encountered by nephrologists in newly diagnosed end-stage renal disease patients.

If the amount of salt taken into the body is greater than the sum of renal and extrarenal losses, volume overload occurs, which causes hypertension in the early (4) and later stages (5) of chronic kidney disease. Therefore, the determination of volume overload is critical, yet difficult. Determination of volume overload can be done by showing an increase in the diameter of the inferior vena cava (6) and left atrium (7) via echocardiography. It can also be discovered via an increase in hormone levels of the natriuretic peptide family, and in relation to other clinical findings such as hypertension and peripheral oedema. However, it is difficult to reach a conclusion due to diseases affecting the measurements, especially cardiovascular diseases. A bioimpedance analysis is an alternative way to determine volume overload. It is a valid, low-cost, commonly used and non-invasive method (9) that can determine the configuration of the body water in addition to the amount of total body water.

There are many studies showing that volume overload is more often seen in diabetic haemodialysis and peritoneal dialysis patients than in non-diabetic patients. According to Gan *et al.* (10), who studied 58 peritoneal dialysis (PD) patients with water and salt restrictions, at a three-month follow-up, there were no differences between diabetic and non-diabetic patients regarding urine volume. However, they discovered that the extra-cellular water (ECW) in diabetic patients had increased (10). In a study by Davenport *et al.* (11), diabetic and nondiabetic patients who had similar PET

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findings were compared. Volume overload, determined by ECW/TBW (total body water) ratio, was found to be higher in diabetic patients. If we examine the mortality rate of patients starting haemodialysis, we find that the mortality rate of diabetic patients is higher. Chantrel *et al.* (12) showed that 32% of diabetic patients that started haemodialysis in France died after about seven months. As we know, diabetic chronic kidney disease has more fatal clinical progresses and this situation can be related to volume overload, which is seen more commonly in diabetic chronic kidney disease patients than in non-diabetic chronic kidney disease patients.

There are many studies on chronic kidney disease, renal replacement therapy and volume overload. However, there are very few publications relevant to the predialytic period. What are the different characteristics between the diabetic and non-diabetic population in this period? Is there more volume overload in the diabetic population than the non-diabetic population? What are the clinical consequences of this

situation? To answer these questions, we examined the effect of diabetes mellitus on volume overload in newly diagnosed stage 5 chronic kidney disease patients whose volume overloads were not showing signs of improvement from renal replacement therapy.

MATERIALS AND METHODS

One hundred and five diabetic and nondiabetic newly diagnosed stage 5 chronic kidney disease patients, who were patients at the Nephrology Clinic of Dicle University Faculty of Medicine Research Hospital, but who were not in renal replacement therapy yet, were included in this study. Disease staging was performed using the Kidney Disease Outcomes Quality Initiative (KDOQI) (13). Glomerular filtration rate (GFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD). Patients with stage 5 chronic kidney disease who had GFR under 15 mL/min for at least three months were enrolled (14). Exclusion criteria

Figure 1. The box plots shows (a) OH/ECW, (b) SBP, (c) DBP, (d) log NT-proBNP values in patients with DM and non-DM.

for this study were: hemodynamically unstable patients, patients who underwent diuretic therapy, patients in a haemodialysis or peritoneal dialysis programme and patients who refused to give informed consent. Seventeen of the 46 patients in the diabetic group, and 20 of the 59 patients in the non-diabetic group were using antihypertensive medication. Patients in both groups were mainly taking ACE inhibitor therapy.

Fresenius Body Composition Monitoring (BCM), which can make measurements with 50 different frequencies between 5 and 1000 kHz, was used to detect the volume overload of patients. In an effort to minimise disruption, measurements were performed in the absence of metal and electronic devices on patients. Patients were not allowed to eat heavy meal at least 4–5 hours before measurement, did not exercise 12 hours prior to measurement and did not consume drinks containing alcohol or caffeine 24 hours prior to measurement. During the application, measurements were made by electrodes placed on wrists and ankles on the same side while patients were in a supine position. A quality value above 90% was our goal when we evaluated the measurement results.

The total body fluid volume, volume overload and extracellular fluid volume measurements were obtained by bioelectrical impedance analysis (BIA). Relative hydration status (RHS) was calculated as the ratio of overhydration (OH) to ECW. RHS values over 15% are associated with mortality (15), so we divided our patients into groups according to this knowledge. It has been validated intensively against all available gold-standard methods in the general population and patients on dialysis therapy (16). BIA can also be used to determine body fat percentage and metabolic consequences of such, in addition to determining body fluid configuration (17).

After fasting for 12 hours, blood samples were taken to evaluate biochemical and haematological parameters. The samples were immediately studied in the haematology laboratory. N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) levels were determined in all subjects using the Elecys ProBNP sandwich immunoassay in the central laboratory in Dicle University. Reference ranges of ProBNP are 0–125 pg/mL in healthy individuals under the age of 75. Systolic and diastolic blood pressure of patients, at least 15 minutes after rest, were measured using an air pressure gauge. Twenty-four-hour urine was collected from all patients in the clinic, and the amount of protein in the urine was analysed.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 16 was used to carry out the analyses. A Student's t-test was performed for comparisons of independent variables of groups, which were determined according to volume overload. Correlation between OH/ECW and variables were analysed with Pearson's correlation coefficients. A multiple linear regression test was used for independent determinants of OH/ECW. Data were expressed as mean group $\pm$ and p values <0.05 were considered statistically significant using a 95% confidence interval.

Ethics committee approval

Ethical approval was obtained from the Dicle University Ethics Commission. The informed consent form, which was determined by the Helsinki Declaration, was read to the patients, and written consent was requested. Deception was not used.

RESULTS

One hundred and five end-stage renal failure patients (determined by the MDRD formula) were enrolled in the study. Forty-six had diabetic aetiology and 59 had non-diabetic aetiology. Ultrafiltration had not been yet made by haemodialysis or peritoneal dialysis in any subjects. Diabetic patients were defined as group 1, and non-diabetic patients were defined as group 2. In group 1, 18 patients (39.13%) were male, 26 (60.87%) were female, and the mean age was 58.02 ± 5.80 years. In group 2, 33 patients (55.9%) were male, 26 patients (44.1%) were female, and the mean age was 53.47 ± 13.52 . There was no statistically significant difference between the two groups in terms of gender ($p=0.116$) or mean age ($p=0.060$). The demographics of the subjects are shown in Table 1.

There were statistically significant differences between the two groups in terms of GFR ($p=0.001$), BMI ($p=0.021$), systolic blood pressure ($p=0.017$) and diastolic blood pressure ($p=0.020$). The non-diabetic group had lower GFR than the diabetic group, although patients in the two groups had stage 5 chronic kidney disease (CKD, $p=0.001$). The bioimpedance analysis of subjects is given in Table 1.

There were statistically significant differences between groups in terms of volume overload ($p=0.003$), ECW ($p=0.045$) and OH/ECW ($p=0.003$). Volume overload was detected in group 1 (Table 2).

There were statistically significant differences between the two groups in terms of creatinine

Table 1. Demographic, clinical and laboratory parameters of the groups

Parameters	Group 1 Diabetic stage 5 CKD (n = 46)	Group 2 Non diabetic stage 5 CKD (n = 59)	p
Age (years)	58.02±5.80	53.47±17.04	0.060
Gender (M/F)	18/28	33/26	0.116
GFR(ml/min)	11.56±4.83	8.7±3.48	0.001
Proteinuria(gr/day)	4.85±2.58	3.34±2.64	0.004
BMI (kg/m ²)	25.19±5.54	22.94±4.26	0.021
SBP(mmHg)	144.34±12	137.96±13.86	0.017
DBP(mmHg)	90.00±7.60	86.61±7.09	0.020

GFR: Glomerular filtration rate, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 2. BIA characteristics of the groups

Parameters	Group 1 Diabetic stage 5 CKD (n = 46)	Group 2 Non diabetic stage 5 CKD (n = 59)	p
OH(l)	4.98±3.16	3.31±2.41	0.003
ECW (l)	19.32±4.16	17.63±4.29	0.045
TBW (l)	35.16±6.34	35.68±7.94	0.714
RHS (OH/ECW %)	24.57±11.58	17.72±10.80	0.003

OH: Overhydration, ECW: Extracellular water, TBW: Total body water, RHS: Relative hydration status.

Table 3. Laboratory parameters of the groups

Parameters	Group 1 Diabetic stage 5 CKD (n = 46)	Group 2 Non diabetic stage 5 CKD (n = 59)	p
Urea(mg/dL)	159.28±53.55	184.55±96.60	0.114
Creatinine (mg/dL)	4.89±1.59	6.49±2.03	<0.001
Na (mEq/l)	135.76±4.97	137.06±3.73	0.127
Albumin (gr/dL)	2.68±0.58	2.88±0.81	0.150
NT-ProBNP (pg/mL)	270±41	247±42	0.008

NT-ProBNP: N-terminal Pro-brain Natriuretic Peptide.

Table 4. Correlations between OH/ECW with study parameters

Variable	r	p
SBP	0.684	<0.001
Albumin	-0.404	<0.001
NT-ProBNP	0.461	<0.001
Proteinuria	0.287	<0.003
OH	0.926	<0.001

($p<0.001$), proteinuria ($p=0.004$) and NT-proBNP ($p=0.008$) values. The relationship between OH/ECW and the other study parameters was studied by Pearson's correlation test and the results were given in Table 3.

There were significant positive correlations between OH/ECW and systolic blood pressure ($p<0.001$), NT-Pro BNP ($p<0.001$), proteinuria ($p<0.003$), over hydration ($p<0.001$), and extracellular fluid ($p<0.001$), and a negative correlation between OH/ECW and albumin ($p<0.001$) (Table 4).

Further, we modelled a multiple regression

analysis to define the independent determinants of SBP. Sex, albumin, proteinuria, OH/ECW ratio, and NT-proBNP were included into the model. OH/ECW ratio was found to be independent predictors of SBP ($R^2 = 0.497$; $p<0.001$; Table 5).

DISCUSSION

Volume overload increases along with the progression of chronic kidney disease. In a study by Bellizi *et al.* (18), authors compared volume overload between healthy individuals and patients with chronic kidney disease whose mean creatinine clearance value was 27.8 ± 13.8 ; they found an increased volume overload in chronic kidney disease patients. A study by Caravaca *et al.* (19) was conducted in a similar population. The authors also found volume overload in 15% of patients. However, volume overload is becoming a more serious problem in later stages of the disease and more patients are affected.

Table 5. Covariables associated with SBP by multiple linear regression

Independent variables	Beta coefficient	95% CI B coefficient	Standardized Beta coefficient	p
Sex (0=female. 1=male)	1.48	-2.46 to 5.44	0.05	0.457
Albumin	0.93	-2.21 to 4.07	1.58	0.559
Proteinuria	0.60	-0.19 to 1.40	0.12	0.135
OH/ECW	0.72	0.51 to 0.92	0.60	<0.001
NT-proBNP	0.03	-0.01 to 0.06	0.12	0.133
Constant	7.013			

CI: Confidence interval; Model: $p < 0.001$; $R^2 = 0.497$.

Van Biesen *et al.* (20) and Dumler *et al.* (21) found that a high percentage of people suffered from volume overload (53% and 62%, respectively). This variability can cause hypertension or difficulties in controlling hypertension. In addition, consequences of hypertension, such as left ventricular hypertrophy, congestive heart failure, pulmonary edema and peripheral edema, are seen more frequently in this patient group.

In our patient groups, volume overload in the diabetic group 1 was 4.98 ± 3.16 L and volume overload in the non-diabetic group 2 was 3.31 ± 2.41 L ($p=0.003$). Mortality related volume overload was 3.5L by Machek *et al.* (22). We can see that patients in the diabetic group are at a high risk for volume overload based on this value. It is suggested that volume overload in chronic kidney disease occurs mostly in extracellular compartment (23, 24). Extracellular fluid in the diabetic group 1 was significantly higher than in the non-diabetic group 2 ($p=0.045$). Tsai *et al.* (25) compared diabetic and nondiabetic groups with and without volume overload. They discovered a statistically significant difference between groups ($p<0.001$) in a study which relative tissue fluid was accepted 7% (25). Further, they found a statistically significant relationship between volume overload and extracellular fluid volume, which was also found in our study. Volume overload and extracellular fluid volume are more frequent in patients with diabetic chronic kidney disease than in others.

An important result from this study is that diabetic group 1 patients had higher GFR levels at the time of application. There were statistically significant differences between the two groups in terms of GFR ($p<0.001$) and creatinine ($p<0.001$). We believe that higher GFR levels in the diabetic group at the time of application is associated with volume overload. Volume overload is an important cause of high blood pressure in end-stage renal failure patients. Many studies show a correlation between blood pressure and volume overload. Alvarez *et al.* (5) found a statistically significant increase in total body water ($p<0.05$) and ECW ($p<0.01$) in hypertensive groups in

a bioimpedence study, where end-stage renal disease patients were divided into two groups (hypertensive and normotensive). In a study by Zucchelli *et al.* (26), a positive correlation between volume overload and hypertension was determined by 24-hour blood pressure holter monitoring. In our study, we found a statistically significant difference between the diabetic group 1 and the non-diabetic group 2 according to blood pressure. In stage 5 chronic kidney disease, the diabetic population has higher blood pressure levels; we believe that this situation is related to volume overload.

An important question relates to what influences the presence of diabetes mellitus in terms of volume overload. The answer to this question is in the endothelium. The endothelial structure plays an important role in hypertension pathogenesis by synthesising vasoactive substances (27). The endothelial structure is impaired in diabetic patients, even in the early stages (28). In addition, volume overload causes impairment in endothelial functions (29). Perhaps, for this reason, blood pressure is found to be higher in all stages of diabetic chronic kidney disease compared to non-diabetic chronic kidney disease (30). In our study, we found a statistically significant increase in systolic ($p=0.017$) and diastolic ($p=0.020$) blood pressure in diabetic group 1 patients. In addition, there was a stronger relationship between systolic blood pressure increase and volume overload using further statistical measures (Pearson's correlation test; $r=0.684$, $p<0.001$). There was a statistically significant relationship between SBP and OH/ECW (beta coefficient: 0.497 $p<0.001$). SBP was significantly higher in diabetic group 1 due to association with volume overload.

As a result, high volume overload increased glomerular capillary pressure by raising systemic blood pressure. This increase is especially prominent in efferent renal arterioles, which may contribute to the decline in GFR by decreasing renal blood flow (31). An increase in NT-proBNP is a good marker for major cardiac events, even in asymptomatic type 2 diabetes mellitus patients (32). In addition, it is a good indicator of volume overload, although an increase in

NT-proBNP values is correlated with a GFR decline. Booth *et al.* (8) found a positive statistical correlation ($p=0.009$) between volume overload and NT-proBNP levels in a study containing 72 end-stage renal failure patients. In our study, there was a statistically significant difference between the diabetic group 1 and the nondiabetic group 2 according to NT-proBNP values ($p=0.008$). This difference was also found in Desai *et al.* (33), in which they detected higher NT-proBNP levels in diabetic haemodialysis patients than non-diabetic patients. There was a strong relationship between volume overload and NT-proBNP in Pearson's correlation test ($r=0.461$, $p<0.001$).

Apart from these results, another important consequence of volume overload is its contribution to the progression of chronic kidney disease. Tsai *et al.* (24) showed that the relationship between the decline in GFR and volume overload was independent of other variables. In their study, starting to the renal replacement therapy was found three times faster in volume overload group than in another group (24). Chen *et al.* (34) showed a more rapid decline in eGFR in a non-dialysis patient group with volume overload determined using the left atrium LA diameter. We know that there is an increase in cardiovascular risk in the predialysis period (35), but in diabetic patients, intolerance to volume overload is more prominent because of an increased cardiovascular risk of diabetes mellitus itself, in addition to cardiovascular risk of chronic kidney disease (36). For this reason, diabetic patients need earlier renal replacement therapy than others (37).

In conclusion, the presence of diabetes mellitus in stage 5 chronic kidney disease patients who are not in renal replacement therapy yet is associated with higher systolic and diastolic blood pressures and increased volume overload, which is related to mortality.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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