Total body water reduction in subjects with chronic kidney disease on peritoneal dialysis is associated with a better hypertension control

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Abstract

Introduction: Hypertension is highly prevalent in patients with chronic kidney disease and hypervolemia is one of the principal causes. **Objective:** To evaluate the influence of the reduction of volemia on blood pressure as well as on echocardiographic parameters in patients on continuous ambulatory peritoneal dialysis. **Methods:** Twelve patients with no clinical evidence of hypervolemia were submitted to an increase in the rate of the dialysis with the purpose of reducing body weight by 5%. The volemia was evaluated by electrical bioimpedance and by ultrasound of the inferior cava vena (ICV). Blood pressure was measured by ambulatory blood pressure monitoring and cardiac function was evaluated by echocardiography both at baseline and 5 weeks after the intervention period. **Results:** After the increase in the ultrafiltration, body weight, extracellular water and the inspiratory diameter of the ICV decreased significantly in parallel with a non-significant increase in the collapsing ICV index. Despite the reduction of anti-hypertensive drugs, systolic blood pressure during the sleep period decreased from 138.4 ± 18.6 to 126.7 ± 18.0 mmHg, the nocturnal blood pressure drop increased and the final systolic left ventricular diameter decreased significantly. **Conclusion:** Reduction of the volemia of patients on peritoneal dialysis, with no signs of hypervolemia, was associated with a better blood pressure control and with a decrease of the final systolic left ventricular diameter.

Keywords: blood pressure; body water; peritoneal dialysis.

Introduction

Systemic hypertension is a highly prevalent condition in patients with chronic kidney disease undergoing peritoneal dialysis (PD), in addition to increasing the risk of cardiovascular complications such as left ventricular hypertrophy (LVH), coronary artery disease (CAD) and stroke.[1] Hyperactivity of the sympathetic nervous system and the renin-angiotensin system (RAS), increased endothelin-1/nitric oxide ratio, use of recombinant erythropoietin, presence of secondary hyperparathyroidism, and increased extracellular volume are pathophysiological mechanisms of hypertension present in patients with chronic kidney disease (CKD).[2] A study carried out with 66 patients on continuous ambulatory peritoneal dialysis (CAPD) described a positive correlation between clinically detectable hypervolemia and systemic hypertension.[3] Similarly, a study carried at our institution found that a mean reduction of 1.5 kg in bodyweight of individuals on hemodialysis was associated with better blood pressure control and fewer prescriptions of antihypertensive medications.[4] Recent studies have shown that subclinical volume expansion - a finding correlated with poor blood pressure management[5] and unfavorable cardiovascular outcome[6,7] - is often observed in patients on PD. Therefore, assessing volume in patients with CKD on renal replacement therapy is a challenge faced daily in clinical practice.

Difficult-to-control hypertension, weight gain, peripheral edema, lung crepitations, jugular venous distension, increased heart size, and pulmonary edema seen on chest X-ray images are indicative of hypervolemia. However, assessment is subjective and subtle changes in fluid status may not always be detected.[8]

The gold standard for the assessment of fluid status is the tracer-based measurement of water spatial distribution. However, this is an expensive, poorly reproducible, and invasive method.[9] Other techniques have been proposed to overcome these hurdles. Levels of biochemical markers such as atrial natriuretic peptide and brain natriuretic peptide are good indicators of volume overload. However, these hormones do not allow volume quantification in the intracellular, extracellular and interstitial compartments, making it difficult to establish a patient's dry weight.[10]

In recent years, graphical methods such as bioelectrical impedance analysis (BIA) and inferior vena cava diameter measurement have been used as low cost alternatives for the assessment of volume levels and estimation of patient dry weight. BIA allows the measurement of extra and intracellular volume and offers a good correlation with hemodialysis ultrafiltration volume. Although it is an easy-to-perform method, BIA underestimates trunk volume and is affected by body composition and temperature.[10] On the other hand, the inferior vena cava diameter is an easy, low cost noninvasive method that correlates well with central venous pressure and total blood volume,[11] with the caveat of being operator-dependent.

This study looked into the impact of decreased total body water in the management of hypertension and cardiovascular parameters in patients with CKD undergoing peritoneal dialysis.

Materials and methods

Population

Seventeen patients of both genders with CKD and hypertension aged 18 and above on PD for at least three months with no episodes of peritonitis within the three months preceding the start of the study were enrolled. All patients were within their clinically estimated 'dry weight'. For the purposes of the study, dry weight was defined as the weight below which patients had symptoms of hypotension.[10] Patients with liver disease, lung disease, heart failure as per the Framingham[12] or echocardiographic criteria, valve disease with hemodynamic repercussions, or history of stroke within the six months preceding the study were excluded. The Ethics Committee of the institution approved this study; enrolled participants were asked to give informed consent.

Protocol

The study was carried out in two stages.

Stage 1 included the collection of patient demographic data, subject clinical evaluation and workup, and assessment of antihypertensive medications in use. After these procedures, patients underwent ambulatory blood pressure monitoring (ABPM), two-dimensional Doppler echocardiography (2DDE), ultrasound-based measurements of inferior vena cava diameter (IVCD), and BIA.

In Stage 2, patients underwent dialysis in order to reduce their bodyweights by at least 5% within four to five weeks. Solutions with concentrations of 1.5%, 2.5%, or 4.25% glucose (Dianeal®) were used to that end, based on the needs of each patient. Dialysis prescriptions were individualized based on peritoneal transport type and target weight. At the end of this stage, patients were submitted to the procedures described in Stage 1.

Assessments

Workup

Patient workup included serum hemoglobin, hematocrit, intact parathyroid hormone (iPTH), calcium, phosphorus, potassium, and albumin levels (data collected only at baseline).

The quality of dialysis was assessed weekly based on Kt/V values.

ABMP

Ambulatory blood pressure was monitored with a Spacelabs 90.200 device; blood pressure measurements were performed in 20-minute intervals during the day and every thirty minutes while the patients were asleep. Blood pressure was considered abnormal in ABPM when values were ≥ 130/80 mmHg for 24 hours, ≥ 135/85 mmHg for daytime, and ≥ 120/70 mmHg for nighttime. Nocturnal blood pressure dipping is considered normal if BP decreases by 10% to 20% when compared to the daytime period.[13]

Echocardiography and inferior vena cava diameter

Echocardiography was performed on a Hewlett-Packard Sonos 2500 device using 2 to 2.5 MHz probes. Studies were performed using the M-mode, two-dimensional, pulsed Doppler, continuous wave Doppler, and color flow mapping techniques. The following measurements were made as per the guidelines of the American Society of Echocardiography:[14] left atrium (LA) volume; interventricular septum (IVS) wall and posterior wall (PW) thickness in diastole; left ventricle end-diastolic diameter (LVEDD) and left ventricle end-systolic diameter (LVESD). The left ventricular mass (LVM) was computed using the equation proposed by Devereux[15] and indexed by height in meters to the 2.7 power. According to these criteria, a left ventricular mass index (LVMI) greater than 51 g/m^2 is indicative of left ventricular hypertrophy.[16] LV systolic function was assessed based on the ejection fraction calculated by the method described by Teichholz.[17] Mitral inflow velocities were recorded using the apical four-chamber view with the pulsed Doppler on. The probe was placed between the ends of the mitral valve cusps and the patients were asked to breathe in a calm, controlled fashion. After echocardiographic examination, the subcostal window was used to measure the individuals' inferior vena cava diameters and percent collapse (caval index). The diameter of a normal inferior vena cava is smaller than 1.7 cm and decreases during inspiration. When pressure in the right atrium is normal (0-5 mmHg), the IVCD is also normal and the caval index (CI) is greater than or equal to 0.5; when pressure in the right atrium ranges between 10-15 mmHg - a finding suggestive of hypervolemia - the IVCD is greater than 1.7 cm and the CI is lower than 0.5; and when pressure in the right atrium exceeds 15 mmHg, the IVCD is greater than 1.7 cm and caval collapse is not observed.[14]

Bioelectric impedance analysis

Measurements were performed using a multiple-frequency BIA device with a Biodynamics 310 version 8.01 body composition monitor. In this procedure, patients must remain in a supine position with their arms parallel to and not touching their torsos. Disposable electrodes are positioned on the dorsal aspect of the wrist and on the third metacarpal bone contralateral to the arteriovenous fistula, on the anterior aspect of the ankle, and on the third metacarpal bone ipsilateral to the upper ones. The proximal electrodes are positioned between the distal prominences of the ulna and the radius and between the malleoli of the ankle. An electric current of 800 mA at 50 kHz is applied via the distal electrodes and the voltage drop detected in the proximal electrodes generates the impedance. Measurements of total body resistance and reactance were used to calculate total body water (TBW), body cell mass, and extracellular water (ECW), reported as a percentage of TBW.

Statistical analysis

Continuous variables were expressed as mean values and their respective standard deviations, whereas categorical variables were expressed as percentages. The data sets collected before and after the intensification of dialysis were compared using Student's *t*-test or the Wilcoxon test. Categorical variables were compared using the chi-square test. Software package SPSS 13.0 was used in statistical calculations. Statistical significance was assigned to events with a $p < 0.05$.

Results

Demographic characteristics of the enrolled population

Seventeen individuals were originally selected. Three were excluded for having systolic heart failure, one due to renal transplantation, and one for being diagnosed with active lupus. Eight of the 12 patients who completed the protocol were women. The group had a mean age of 56.9 ± 13 years. The mean weekly Kt/V was 1.8 ± 0.2 (target Kt/V greater than or equal to 1.7), a level compatible with adequate dialysis. Mean calcium, phosphorus and iPTH levels were 9.4 ± 0.8 mg/dl, 5.3 ± 0.7 mg/dl, and 317.3 ± 302.1 pg/ml, respectively. The calcium-phosphorus product was 50.2 ± 8.5 mg^2/dl^2. Other demographic and clinical data can be seen in Table 1.

Total body water assessment

Bodyweight and bioelectrical impedance analysis

At baseline, patients had a mean body weight of 72.2 ± 12.7 kg. After the intensification of dialysis, the mean body weight dropped significantly to 70.9 ± 13.3 kg (p = 0.037) - a decrease of 5% in relation to the mean weight observed at baseline, indicating the effectiveness of dialysis in reducing bodyweight. The decrease in bodyweight was accompanied by a reduction in extracellular water (ECW) from 21.6% to 15.5% (p = 0.0001). The decrease in TBW - 49.6 ± 6.0% at baseline - to 49.6 ± 5.3% after the intensification of PD was not statistically significant (p = 0.9) (Graph 1).

Vena cava diameter

The inferior vena cava diameter during inspiration decreased from 10.19 ± 4.5 mm to 7.17 ± 2.2 mm (p = 0.042), while the caval index showed a non-significant increase. Patients had a CI between 0.5 and 0.75 at baseline, i.e., they were normovolemic according to this parameter.

Ventricular geometry - echocardiographic data

The reduction in dry weight was accompanied by a significant decrease in LVEDD from 30.8 ± 3.9 mm to 29.2 ± 2.22 mm (p = 0.04). No significant differences were seen in LVM, LVEDD, or left atrial volume (LAV) (Graph 2); ejection fractions and E/A ratios were not statistically different.

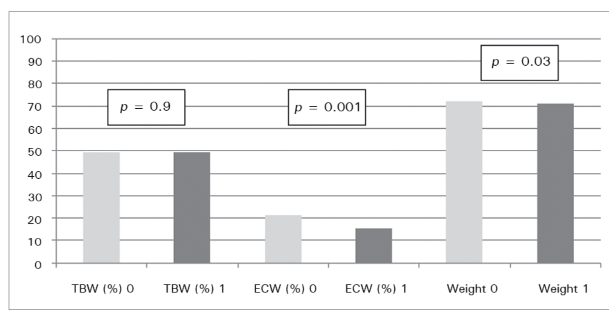
Blood pressure variation

The mean 24-hour systolic (SBP) and diastolic (DBP) blood pressure levels decreased from 140.2 ± 16.6 mmHg to 133.8 ± 18.9 mmHg (ns) and from 85.2 ± 9.8 mmHg to 81.2 ± 9.6 mmHg (ns), respectively. Although not significantly, the mean nighttime SBP decreased from 138.4 ± 18.6 to 126.7 ± 18 mmHg, while the mean DBP decreased from 82.6 ± 9.9 to 76.1 ± 7.8 mmHg. The dip in SBP increased from 1.8 ± 5.2% to 6.7 ± 4.9% (p = 0.02), while the dip in DBP increased from 4.1 ± 5.4% to 7.5 ± 3.9% (p = 0.08). Therefore, after the reduction in dry weight, patients experienced a significant reduction in SBP and an increase in the SBP dip during sleep. A

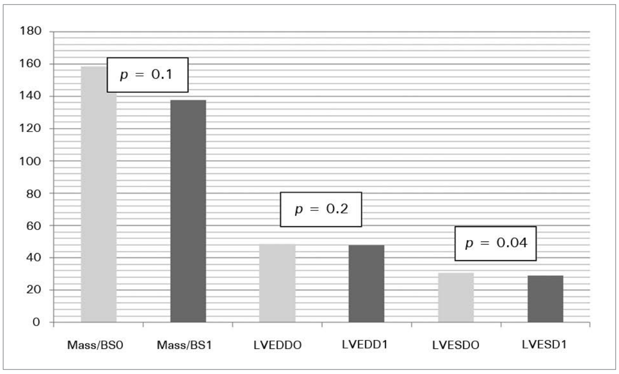
Table 1 Demographic and clinical data of 12 hypertensive patients on peritoneal dialysis

Data	
Age (years)	56.9 ± 13.1
Females	66.7%
Caucasian	83.3%
Etiology:	41.6%
Chronic glomerulonephritis	16.7%
Diabetic nephropathy	16.7%
Hypertensive nephropathy	25%
Undetermined	58.3%
Mean SBP	140.2 ± 16.6 mmHg
Mean DBP	85.2 ± 9.8 mmHg
Mean number of prescribed antihypertensive drugs	2.9 ± 1.08
Mode of dialysis:	41.7%
CAPD	
APD	
Mean time on dialysis (months)	35.1 ± 27.17

Graph 1. Weight, total body water (%), Extracellular water (%) assessed by bioelectric impedance on times 0 and 1 for the enrolled population. TBW (%): percent total body water Time 0; TBW 2 (%)percent total body water Time 1; ECW (%): Percent extracellular water Time 0; ECW (%): Percent extracellular water Time 1; Weight: Weight in kg on Time 0; Weight 2: Weight in kg on Time 1.



Graph 2. Ventricular Geometry (left ventricular mass, left ventricular end-diastolic diameter and left ventricular end-systolic diameter). Mass/BS: Left ventricular mass/body surface on time 0; Mass/BS2: Left ventricular mass/body surface on time 1; LVEDD: Left ventricular end-diastolic diameter on time 0; LVEDD 2: Left ventricular end-diastolic diameter on time 1; LVESD: Left ventricular end-systolic diameter on time 0; LVESD: Left ventricular end-systolic diameter on time 1.



clinically relevant reduction in 24-hour SBP was also observed (Graph 3).

The number of antihypertensive medications used to manage the patients' BP levels was reduced by 50%. At baseline, eight patients took three or more antihypertensive drugs; three took two antihypertensive drugs; and one took one antihypertensive drug. At the end of the study, seven patients ceased to require antihypertensive medication to manage their BP; one patient moved to taking only one antihypertensive drug; and four were taking two or three antihypertensive drugs (Graph 3).

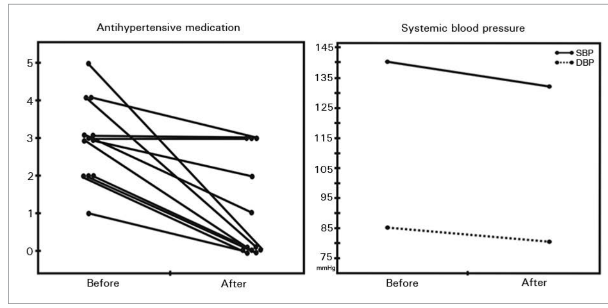
Discussion

In this study, the intensification of ultrafiltration offered to patients on PD without clinical evidence of fluid overload was associated with a significant reduction in bodyweight, ECW, and IVCD. These changes were accompanied by a significant reduction in BP, need for fewer antihypertensive drugs to manage BP, and decreased LVESD.

The assessment of fluid overload status of patients on peritoneal dialysis is required to calculate subject dry weight, adjust the prescription of dialysis, and optimize fluid balance.[18,19]

BIA and IVCD stand out as the most accessible methods used to assess TBW in daily clinical practice for their non-invasiveness, good reproducibility, and low cost when compared to tracers and natriuretic peptides.

Graph 3. Use of antihypertensive drugs and blood pressure levels on times 0 and 1.



Multiple-frequency BIA correlates well with tracer methods to assess TBW and body composition.[20] Several studies carried out with hemodialysis patients showed a positive correlation between decreased TBW, BP management, and improved cardiovascular parameters.[21-23] Passauer *et al.*[24] studied 370 subjects on hemodialysis and found that 63% of the patients had a mean of 1.1 liter of excess body water and 21% had fluid overload even after hemodialysis.

The literature contains few reports from interventional studies on the possible benefits of TBW decreases to the cardiovascular parameters of patients on PD. Woodrow *et al.*[18] used BIA to assess body composition and TBW in four patients on peritoneal dialysis. One female patient on four antihypertensive drugs and still hypertensive one month into dialysis lost 4.6 kg within seven weeks. Her weight loss was accompanied by TBW and ECW decreases and need for fewer antihypertensive drugs to keep her BP at an adequate level. In a recent study, Luo *et al.*[25] divided 160 patients on CAPD into two groups and used BIA to assess the fluid status of subjects in Group One and conventional methods such as estimated dry weight and clinical criteria to analyze the individuals in Group Two. After 12 weeks, the individuals in Group One had a mean decrease of 600 ml in fluid overload and a significant reduction in SBP; no decreases were seen on the number of antihypertensive drugs taken. Our study further supported these findings. BIA revealed that our patients had reductions in TBW in the order of two liters after a mean of four weeks of intensified ultrafiltration. As also described by Woodrow *et al.*,[18] our patients had improved BP control despite the reduction seen in the number of prescribed antihypertensive medications.

IVCD is an effective method to assess TBW. As previously mentioned, IVCD correlates well with intravascular volume and central venous pressure, and is a reliable technique for estimating fluid status. The data gathered in this study showed that, after PD intensification, the increase in CI was not significant. Considering that our patients had no signs of fluid overload at baseline and that after the increase in CI none of the subjects had subclinical hypovolemia, it may be stated that our patients had subclinical hypervolemia.

Recent studies have shown that subclinical hypervolemia is commonly seen in patients on peritoneal dialysis and is implicated in the maintenance of hypertension and cardiovascular alterations.[7,26-28] Koc *et al.*[29] looked into 74 patients and found that hypervolemia diagnosed by IVCD and CI contributed significantly to the maintenance of hypertension in patients undergoing PD. Likewise, Asci *et al.*[30] studied 38 patients with CKD on PD submitted to intensified ultrafiltration and given hypertonic solutions and dietary salt restriction. After this intervention, the authors found that eight patients with LVH at baseline had significant LVMI decreases. Similar findings were observed by other authors in studies with follow-up periods ranging from six months to three years, in which normovolemic patients on hemodialysis had significant LVH reductions.[22,23,31]

Monitoring cardiac morphological and functional changes through serial echocardiograms is of great importance in the assessment of the success rates of interventions devised to mitigate the cardiovascular risk of patients with CKD.[32] Studies on the effects of reduced preload induced by a single session of hemodialysis on Doppler echocardiographic parameters revealed decreased LVESD and LVEDD and suggested improved systolic function based on ejection fraction and tissue Doppler imaging.[33,34]

This paper presents some methodological differences when compared to the studies cited above. Firstly, our study included only patients on peritoneal dialysis submitted to gradual intensification of dialysis and reassessed after 4-5 weeks, which may have allowed slow TBW redistribution. Additionally, most of the patients (ten in 12) had normal LV systolic function. The effects of dialysis on LV systolic performance vary and seem to depend, in part, on the individuals' pre-dialysis ventricular volumes and contractile function. Evidence suggests that LV systolic function improves after dialysis only in patients with prior systolic dysfunction, and that it does not change significantly in individuals with normal LV systolic function.[35]

Such peculiarities may explain why no significant changes were found in parameters such as LVM, ejection fraction, and diastolic function in our population. Alternatively, the reduced size of our population may not have yielded enough statistical power to demonstrate subtler differences.

Conversely, decreased LVESD associated with reduced IVCD suggests the existence of an actual decrease in intravascular volume and in preload.

Another noteworthy finding was the relationship observed between TBW reduction and improved hypertension management, despite the 50% reduction in the number of prescribed antihypertensive drugs. Several mechanisms have been associated with hypertension in patients on PD. However, increased extracellular volume seems to play a central role in the elevation of BP in patients with CKD. Leypoldt *et al.*[36] showed that the absolute BP levels before and after hemodialysis were directly influenced by intradialytic decreases in body weight and plasma volume. Martinez-Maldonado[37] described a strong correlation between extracellular fluid volume and sodium balance in hypertensive patients with CKD on dialysis. The authors of a study carried out in Tassin with 712 patients with CKD on hemodialysis described an association between a reduction of 2 kg in dry weight with significant BP reductions within a period of up to one month, which allowed patients to stop taking antihypertensive medication.[9] These findings point to the role played by fluid overload in the genesis of hypertension in dialysis patients. As also observed in a study carried out in our department, a reduction of 1.5 kg in the bodyweight of patients on hemodialysis was accompanied by improved BP management and prescription of fewer antihypertensive drugs to patients.[4]

The limitations of this study include the size of the enrolled population, the short follow-up period, and the choice of not using the gold standard method for estimating TBW.

To sum up with, our findings have confirmed previous observations on the role of hypervolemia in the onset of hypertension in patients with CKD and pointed to the need to improve the assessment and management of fluid overload, particularly in patients on PD.

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