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CLINICAL STUDY

Volume Status in Patients on Peritoneal Dialysis: The Role of Apelin and Bio-Impedance Spectroscopy

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Abstract

One of the main factors determining the survival of peritoneal dialysis (PD) patients is volume status. We aimed to investigate hydration status of PD patients by bio-impedance spectroscopy (BIS) and echocardiography and to study the relation of them with apelin, which has effects related with volume status like vasodilation, positive inotropism, and inhibition of ADH release and RAS antagonism. Chronic PD patients without active cardiac disease or clinically prominent hypervolemia were included. Besides the demographic, clinical, and laboratory data, BIS and echocardiographic findings together with apelin levels were recorded. The study included 21 patients. Of them, eight patients were euvolemic, one patient was hypovolemic, and others have some degree of overhydration (1.1–6.8 L) with BIS, although all were euvolemic clinically. Mean apelin level was 1.49 ± 0.49 ng/mL. Apelin level was positively correlated with ejection fraction and negatively with total body water (TBW), intracellular and extracellular water, lean tissue mass, and left atrium diameter. On linear regression model, TBW was the major determinant of apelin. Although apelin is expected to increase in hypervolemic patients, the negative correlation with body water in this study may be related with yet unknown role of apelin in dialyzed patients. They may have important roles in volume status in future.

Keywords: apelin, bio-impedance spectroscopy, echocardiography, hypervolemia, peritoneal dialysis

INTRODUCTION

Fluid status has prime importance for the survival of patients on both hemodialysis (HD) and peritoneal dialysis (PD) program. For both the treatment modalities, international guidelines underline volume status for dialysis adequacy.[1] One of the main factors determining the morbidity and mortality in PD patients is volume status[2–7] and may even be more important than solute clearance.[8] Besides clinical findings (blood pressure, presence of edema, and weight gain), echocardiography, Dual Energy X-ray Absorptiometry (DEXA), direct measurement of extracellular and total body water (TBW), brain natriuretic peptide (BNP) has been used for the determination of hydration status.[9] None of these methods are perfect, each having either clinical or financial limitations. Clinical findings may be misleading as vascular stiffness and cardiac dysfunction may confuse the status by affecting blood pressure.

Bio-impedance spectroscopy (BIS) is a bio-impedance approach in which body composition is determined in a noninvasive way by measuring the opposition to the flow of electrical current through tissues. With BIS, TBW, intracellular water (ICW), and extracellular water (ECW) are measured from which body cell mass can be estimated.[10] Although BIS is not a perfect method, because of the variable results about absolute volumes and wide variation in limits besides being expensive;[11] it has been claimed to be a reliable method for the assessment of fluid status in PD patients.[12]

Apelin is a marker recently related with volume status. O'dowd et al.[13] described a gene very close to angiotensin-1 (AT-1) receptor, in 1933, which was found later to code a G protein-coupled membrane receptor called Apelin G-protein coupled receptor (APJ). Apelin is the selective endogenous ligand of that receptor.[14] Although APJ and AT-1 receptors have high degree of homology, neither shares the receptor of the other.[15]

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APJ receptors have been detected in endothelial cells of small intramyocardial, renal, pulmonary, and bronchial vessels as well as coronary arteries, endocardial cells, and vascular smooth muscle cells.[16] Apelin is thought to have actions effective on cardiovascular and renal functions and fluid status like stimulation of nitric oxide (NO) related vasodilation;[17] vasoconstriction in the presence of dysfunctional endothelium,[18] positive inotropic effects;[19] inhibition of antidiuretic hormone (ADH) release,[20] and antagonistic effects to renin–angiotensin-system (RAS).[21] Apelinergic system has also been reported to have roles in the pathogenesis of coronary disease secondary to chronic renal failure,[22] systemic inflammatory response, and cardiovascular functions[23] and renal physiology like vasodilatation of afferent and efferent arterioles; inhibition of angiotensin-2 (AT2) induced increase in intracellular calcium (Ca) via NO release.[24]

In our study, we primarily aimed to investigate the hydration status of PD patients by BIS and echocardiography. At the same time, the relationship of the results of these methods with apelin levels was also investigated.

SUBJECTS AND METHODS

PD patients aged 18–80 years, who gave written informed consent, were included in this study. Those younger than 18 years and older than 80 years, those having PD treatment less than 3 months, patients with valvular heart disease and arrhythmias, active infectious or inflammatory disease, patients with clinically prominent hypervolemia, and those with malignancy were excluded from the study.

The age, gender, body mass index (BMI), body surface area (BSA), systolic and diastolic blood pressures, the mean duration of PD treatment, the modality of PD, primary kidney disease, comorbidities, and the drugs used by the patients were recorded. Hypertension, diabetes mellitus, and hyperlipidemia were accepted as comorbidities if clinical or laboratory criteria are present according to the international guidelines; or if the patient takes medications for the mentioned diseases. Ischemic heart disease or peripheral vascular disease were recorded if they were diagnosed angiographically—not only with clinical suspicion.

Blood samples obtained after 12 h of fasting were examined for serum glucose, urea, creatinine, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, Ca, phosphorus (P), parathyroid hormone (PTH), total protein, albumin, hemoglobin (Hb), hematocrit (Hct), ferritin, and high-sensitive C-reactive protein (hsCRP) levels. Apelin levels were studied from plasma by enzyme immune assay method using Phoenix Pharmaceuticals, Inc., Human Apelin-36 Enzyme Immunoassay kit (Burlingame, CA, USA). Standard peritoneal equilibration test was performed for the calculation of peritoneal and residual Kt/V, weekly urea and creatinine clearance, and ultrafiltration volume (UFV).

BIS was evaluated by Body Composition Monitor H02.201.1® Fresenius Medical Care Deutschland GmbH (Bad Homburg, Germany). The device used 50 different frequencies between 5 and 1000 kHz through four electrodes attached to one upper and one lower extremity. The parameters recorded by this analysis included overhydration (OH), TBW, ECW, ICW, extracellular/intracellular ratio (ES/IS), lean tissue mass (LTM), fat ratio, and body cell mass (BCM).

Echocardiographic examination was performed using a General Electric VIVID-4 machine by the same physician. Diameters of cardiac chambers were measured by M-mode ultrasonography. Ejection fraction (EF) was calculated by modified Simpson method. Left ventricular mass (LVM) was calculated by Devereux formula and left ventricular mass index (LVMI) was found by dividing LVM by BSA.[25]

Statistical analysis was conducted by SPSS (Statistical Package for Social Sciences) for Windows 14.0 program (Chicago, IL, USA). Numerical values were defined as mean ± standard deviation (SD). Correlation analysis of numeric and non-numeric parameters was performed by Pearson and Spearman's rho correlation tests, respectively. Parameters found to be correlated with apelin levels were analyzed by linear regression analysis. Student's *t*-test was used for intergroup comparisons. *p*-Values 0.05 were considered as statistically significant.

RESULTS

Twenty-one patients (13 females and 8 males) were included in this study. Mean age was 51.38 ± 11.95 years. Mean BMI and BSA were 28.07 ± 6.09 kg/m^2 and 1.79 ± 0.20 m^2, respectively. The mean duration of PD treatment was 45.05 ± 25.59 months. Treatment modality was continuous ambulatory PD (CAPD) in 13 patients, automated PD (APD) in five patients, and continuous cyclic PD (CCPD) in three patients. Primary renal disease was diabetic nephropathy in eight patients, chronic glomerulonephritis in two patients, autosomal dominant polycystic kidney disease in two patients, chronic pyelonephritis in two patients, nephrosclerosis in two patients, and unknown in five patients. Hypertension ($n = 10$), hyperlipidemia ($n = 9$), diabetes mellitus ($n = 8$), ischemic heart disease ($n = 2$), and peripheral vascular disease ($n = 1$) were recorded as comorbidities. The biochemical parameters are shown in Table 1. Mean apelin level was measured as 1.49 ± 0.49 ng/mL.

All patients were found to have Kt/V and urea and creatinine clearance values above limits suggested by international guidelines (mean total $Kt/V = 2.35 \pm 0.69$, weekly urea clearance = 85.00 ± 24.60, and weekly creatinine clearance = 76.16 ± 33.26). Mean UFV was 919 ± 482 mL/day with systolic and diastolic blood pressures of 136 ± 24 mmHg and 79 ± 11 mmHg, respectively.

Table 1. Biochemical results.

Parameter	Mean ± SD	Parameter	Mean ± SD
Glucose (mg/dL)	153 ± 94	Total cholesterol (mg/dL)	199
Urea (mg/dL)	104 ± 33	LDL cholesterol (mg/dL)	118
Creatinine (mg/dL)	8.04 ± 2.27	HDL cholesterol (mg/dL)	45.67 ± 16.79
Uric acid (mg/dL)	6.07 ± 1.07	Triglyceride (mg/dL)	182 ± 93
Ca (mg/dL)	9.15 ± 0.69	Hb (g/dL)	10.47 ± 1.46
P (mg/dL)	5.06 ± 1.06	Hct (%)	32.4 ± 3.4
PTH (pg/mL)	529 ± 483	TSAT (%)	27.67 ± 9.35
Total protein (g/dL)	6.45 ± 0.75	Ferritin (ng/mL)	301 ± 189
Albumin (g/dL)	3.7 ± 0.44	hsCRP	1.138 ± 1.491

Major findings with BIS and echocardiography are presented in Table 2. Eight patients were euvolemic, one was hypovolemic, and others have some degree of OH (min: 1.1 L, max: 6.8 L); although all the patients in the study group were euvolemic clinically.

Patients with (>200 mL/day, $n = 13$) or without (<200 mL/day, $n = 8$) significant amounts of urine had similar TBW (34.8 ± 6.28 L vs. 33.45 ± 6.42 L, $p = 0.645$), ECW (17.22 ± 3.24 L vs. 16.27 ± 3.72 L, $p = 0.50$), ICW (17.58 ± 3.49 L vs. 17.15 ± 3.31 L, $p = 0.916$), EF (65 ± 4% vs. 58 ± 12%, $p = 0.185$), LA (3.54 ± 0.56 cm vs. 3.6 ± 0.69 cm, $p = 0.645$), and LVMI (148 ± 40 g/m^2 vs. 145 ± 39 g/m^2, $p = 1$). Apelin levels in these groups of patients were similar too (1.54 ± 0.48 ng/mL vs. 1.43 ± 0.54 ng/mL, $p = 0.860$).

Table 2. Findings of BIS and echocardiography.

Parameter	Mean ± SD	Parameter	Mean ± SD
OH (L)	1.87 ± 2.06	ECW/ICW	0.98 ± 0.13
TBW (L)	34.28 ± 6.22	LTM (kg)	33.98 ± 8.43
ICW (L)	17.42 ± 3.34	Fat ratio (%)	36.24 ± 11.23
ECW (L)	16.86 ± 3.37	BCM (kg)	18.46 ± 5.57
EF (%)	62.5 ± 8.5	LA (cm)	3.56 ± 0.59
AD (cm)	3.17 ± 0.30	LVMI (g/m^2)	147 ± 38

Notes: OH, overhydration; TBW, total body water; ICW, intracellular water; ECW, extracellular water; EF, ejection fraction; AD, aorta diameter; LTM, lean tissue mass; BCM, body cell mass; LA, left atrium diameter; LVMI, left ventricular mass index.

Because of the small number of patients with different primary kidney diseases, it was not convenient to study the effect of these factors on apelin levels and BIS findings.

In correlation analysis, apelin was positively correlated with PTH ($r = 0.542$, $p = 0.011$), total cholesterol ($r = 0.482$, $p = 0.027$), LDL cholesterol ($r = 0.571$, $p = 0.007$), TSAT ($r = 0.576$, $p = 0.006$), ferritin ($r = 0.532$, $p = 0.013$), and EF ($r = 0.500$, $p = 0.021$) and negatively with BSA ($r = -0.474$, $p = 0.03$), TBW ($r = -0.637$, $p = 0.002$), ICW ($r = -0.611$, $p = 0.003$), ECW ($r = -0.564$, $p = 0.008$), LTM ($r = -0.526$, $p = 0.014$), BCM ($r = -0.514$, $p = 0.017$), and LA ($r = -0.589$, $p = 0.005$). The negative correlation of apelin with TBW, ICW, and ECW is presented graphically in Figure 1.

Echocardiographically, EF was negatively correlated with TBW ($r = -0.566$, $p = 0.008$), ECW ($r = -0.583$, $p = 0.006$), ICW ($r = -0.461$, $p = 0.035$), LA

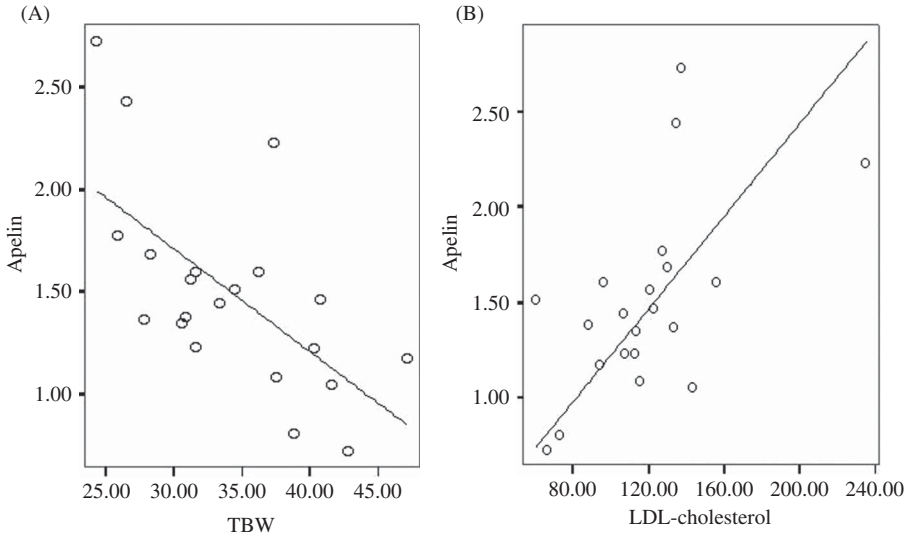

Figure 1. The scatter plots showing the relation of apelin with TBW (total body water) (A) and LDL-cholesterol (B).

($r = -0.591$, $p = 0.005$), LTM ($r = -0.448$, $p = 0.042$), and OH ($r = -0.521$, $p = 0.015$). Left atrium diameter has been found to be positively correlated with ECW ($r = 0.752$, $p < 0.001$), TBW ($r = 0.625$, $p = 0.002$), and OH ($r = 0.547$, $p = 0.01$), besides its negative correlation with apelin levels.

Linear regression model was applied to determine the factors acting on apelin level using the parameters found to be correlated with apelin in univariate analysis. It was found that TBW ($B = -0.044$, Beta $= -0.561$, $p = 0.001$) and LDL cholesterol ($B = 0.006$, Beta $= 0.483$, $p = 0.004$) were the major determinants of apelin levels (Figure 1A and B).

DISCUSSION

One of the main factors determining the survival of PD patients is the volume status affecting the cardiovascular functions.[2–8] But there are no clear-cut criteria for the diagnosis of hypovolemia or hypervolemia. Some patients have elevated systolic blood pressure, despite being euvolemic which is thought to be due to vascular stiffness. On the other hand, there are patients with heart failure who might be normotensive, although they are hypervolemic. So blood pressure is not sufficient when used alone to assess the hydration status. Additionally, confounding is the more common presence of hypoalbuminemia in patients on PD than on HD. In hypoalbuminemic subjects, increase in TBW is not always together with increased plasma volume and rigid measures to normalize ECW/TBW may lead to hypovolemia and loss of residual renal functions.[26]

BIS has been shown to be a reliable tool for the assessment of fluid status in patients on PD.[11] BIS has been recently reported to be comparable to clinical findings and NT-proBNP levels for determining dry weight in HD patients.[27,28] Sipahi et al.[29] found BIS findings to be related with echocardiographic findings of OH in PD patients.

Apelin is thought to be related with cardiovascular function and fluid status. Angiotensin converting enzyme-2 (ACE2) converts apelinergic peptides to more active forms.[15,30] Studies have shown that apelin levels increase in mildly symptomatic heart failure but decrease in more symptomatic patients without statistically significant difference between functional classes or correlation with EF.[31,32] El-Shehaby et al.[23] reported that apelin is positively correlated with echocardiographic measurements and negatively correlated with hsCRP and IL-6 levels in HD patients showing its role in systemic inflammatory response and cardiovascular functions. With all these data from the literature, it may be speculated that hypervolemia and the resulting hypertension provokes increased levels of apelin to provide diuresis, vasodilation, and increased cardiac contractility. But current literature is poor for the proof of this hypothesis. There is a need for broad-based studies about the effect of apelin on volume status in both uremic and nonuremic population.

Due to the lack of enough knowledge about apelin in dialysis population, there is no cut-off value for its level. So it is difficult to say that apelin level is elevated or decreased in our study group. We think that the more important thing is its correlation with clinical signs of volemia and findings on BIS. We saw that apelin is not related with residual renal function as patients with or without significant daily urine volume have similar apelin levels. Another important finding of our study is that clinical assessment has limited value in determining the fluid status of PD patients considering that only 8 of 21 patients were found to be euvolemic with BIS; and BIS findings were not correlated with systolic and diastolic blood pressures. So it is wise to use BIS for this assessment as it is more definite, relatively cheap, and easy to perform.

Apelin was found to be negatively correlated with TBW, ECW, and ICW measured by BIS. According to the literature, hypervolemia should stimulate apelin release as a compensatory mechanism. But, the reverse was true in our study. This could be related with renal failure as one of the sites of apelin production is kidneys. Also, a prior study showed downregulation of apelinergic system in increasing degrees of heart failure.[20] This mechanism may be operating in dialysis population too. The small number of patients may be responsible for the results inconsistent with the current literature. It is imperative to compare levels in predialysis population with those in dialysis patients with broad-based studies.

Apelin is known to be produced in many tissues including adipose tissue. Malyszko et al.[22] found apelin to be correlated negatively with triglyceride, total cholesterol, and LDL cholesterol. In two studies by Tasci et al.[33,34] apelin levels were lower in nonuremic patients with elevated LDL cholesterol levels; and the levels increased with life-style changes and statin treatment. In our study, we detected positive correlation of apelin with total and LDL cholesterol as LDL cholesterol was one of the determinants of apelin levels in multivariate analysis. These different results may be related with changes in the lipid profile in nonuremic, HD, and PD populations. Nevertheless, many studies showed the effects of statin treatment to be different in uremic population than the nonuremic one.[35]

We did not detect any relation of apelin with residual renal functions and dialysis adequacy. Although a relation with urine volume may be expected due to the known effect of apelin on ADH; lack of such a finding may be related with inability of kidneys to respond to the effects of ADH.

The concordance between echocardiographic and BIS findings may allow the use of both in determining volume status. BIS may be advantageous being not operator dependent and readily repeatable. Additionally, this may be performed by the staff of the PD unit without

requiring any specialist. The major disadvantage of this method is the financial burden caused by it.

Major limitations of this study are the lack of a control group with normal renal functions and the low number of patients included. But apelin level is already known to be different in uremic patients than nonuremic population; so it is not logical to compare our patient group with such a control group. Otherwise the main objective of this study is to measure the reliability of apelin levels in detecting volume status measured by other methods, namely BIS and echocardiography. Although the number of patients included is not much; it adds additional information to the literature as being the first study to compare apelin levels with other methods of determining volume status. Moreover, it would be significantly more expensive with large number of patients.

CONCLUSION

Although apelin is known to have vasodilator, natriuretic, and diuretic effects and logically expected to increase in dialysis patients who have hypervolemia frequently; we found a negative correlation with body water. This may be related with yet unknown role of apelin in physiopathology of volume regulation in dialyzed patients. Still, BMC and apelin levels may take the place of other methods for determining volume status in the future.

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