Significance of Apelin-13 for Inflammation and Cardiac Morphology in Peritoneal Dialysis Patients

Periton Diyaliz Hastalarında Serum Apelin-13'ün İnflamasyon ve Kardiyak Morfoloji İçin Önemi

İbrahim DOĞAN[1]
Serdar KAHVECİOĞLU[2]
Barış ESER[1]
Hüseyin KAYADİBİ[3]
Özlem YAYAR[4]
Tolga DOĞAN[5]
Ünal KURTOĞLU[6]
Sevda ÜNALLI ÖZMEN[7]
İsminur SAKA KARAGÖZ[7]

1 Hitit University, Erol Olçok Training and Research Hospital, Department of Nephrology, Çorum, Turkey
2 Bursa Yuksek Ihtisas Training and Research Hospital, Department of Nephrology, Bursa, Turkey
3 Hitit University, Erol Olçok Training and Research Hospital, Department of Biochemistry, Çorum, Turkey
4 Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Nephrology, Ankara, Turkey
5 Hitit University, Erol Olçok Training and Research Hospital, Department of Cardiology, Çorum, Turkey
6 Bursa Yuksek Ihtisas Training and Research Hospital, Department of Radiology, Bursa, Turkey
7 Uludağ University Faculty of Medicine, Department of Biochemistry, Bursa, Turkey

Received : 03.06.2017
Accepted : 24.07.2017

Correspondence Address:
İbrahim DOĞAN
Hitit Üniversitesi, Erol Olçok Eğitim ve Araştırma Hastanesi, Nefroloji Bölümü, Çorum, Turkey
Phone : + 90 364 223 03 00
E-mail : dr.ibrahimdogan@hotmail.com

ABSTRACT

OBJECTIVE: Apelin-13 is a biomarker that was shown to be related to cardiovascular disease risk in peritoneal dialysis patients. The aim of our study was to investigate the association of serum apelin-13 levels with inflammation, carotid artery intima media thickness (CIMT) and echocardiographic parameters in peritoneal dialysis patients.

MATERIAL and METHODS: 33 patient receiving peritoneal dialysis treatment (15 female) and 27 healthy controls (11 female) were enrolled. CIMT and echocardiographic measurements of all patients and controls were taken. Serum apelin-13 levels were measured by ELISA. Apelin-13, c-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), echocardiographic parameters and CIMT values were compared between patients and controls.

RESULTS: Apelin-13 was lower in the patient group [58 (12-131) ng/L] than in the control group [76 (18-130) ng/L] (p=0.083). CRP, NLR, CIMT were significantly higher in patients than controls (p<0.001). CIMT was 0.8 (0.4-1.5) mm and 0.60 (0.3-0.7) mm in the patients and the controls, respectively. Negative correlations were observed between Apelin-13 and age, ferritin, CRP, NLR and CIMT while positive correlations were found between calcium, ejection fraction (EF) and albumin. There was no correlation between apelin-13 and echocardiographic parameters except EF.

CONCLUSION: Apelin-13 levels tend to be lower in peritoneal dialysis patients, and may be important in the development of inflammation, endothelial dysfunction, and atherosclerosis.

KEY WORDS: Apelin-13, Carotid intima media thickness, Inflammation, Peritoneal dialysis

ÖZ

AMAÇ: Apelin-13, periton diyalizi hastalarında tanımlanmış kardiyovasküler hastalık riski ile ilişkili bir belirteçtir. Çalışmanın amacı periton diyalizi hastalarında serum apelin-13 düzeyleri ile inflamasyon, karotis arter intima-media kalınlığı (KİMK) ve ekokardiyografik parametreler arasındaki ilişkiyi araştırmaktır.

GEREÇ ve YÖNTEMLER: Çalışmaya 33 periton diyaliz tedavisi alan hasta (15'i kadın) ile 27 sağlıklı (11'i kadın) kontrol alındı. Hasta ve kontrol grubunun tümünün KİMK ve ekokardiyografik ölçümleri alındı. Serum apelin ölçümleri ELISA yöntemi ile çalışıldı. Gruplar arasında apelin-13, c-reaktif protein (CRP), nötrofil/lenfosit oranı (NLO), ekokardiyografik bulgular ve KİMK değerleri karşılaştırıldı.

BULGULAR: Apelin-13 hasta grubunda kontrol grubuna göre daha düşük saptandı. [58 ng/L (12-131)]'a karşın 76 ng/L [(18-130), p=0,083]. Hasta grubunda kontrol grubuna göre CRP, NLO, KİMK anlamlı olarak daha yüksekti (p<0,001). Hasta grubunda KİMK 0,8 mm (0,4-1,5), kontrol grubunda ise 0,6 mm (0,3-0,7) ölçüldü. Apelin-13 ile yaş, ferritin, CRP, NLO ve KİMK arasında negatif korelasyon, kalsiyum, ejeksiyon fraksiyonu ve albümin arasında pozitif korelasyon saptandı. Apelin-13 ile ejeksiyon fraksiyonu dışındaki ekokardiyografik bulgular arasında korelasyon saptanmadı.

SONUÇ: Periton diyalizi hastalarında apelin-13 düzeyi düşük olma eğilimindedir. Periton diyalizi hastalarında inflamasyon, endotel disfonksiyonu ve aterosklerozis gelişmesi sürecinde önemli olabilir.

ANAHTAR SÖZCÜKLER: Apelin-13, Karotis arter intima-media kalınlığı, İnflamasyon, Periton diyalizi

INTRODUCTION

Chronic renal disease (CRD) is an important risk factor for cardiovascular diseases (CVD), and CVD is the most important cause of mortality in CRD (1,2). Advanced age, hypertension (HT), diabetes mellitus (DM), chronic inflammation, malnutrition, hypervolemia and bone mineral disease are the risk factors for increased morbidity and mortality in patients with CRD (3). In peritoneal dialysis (PD) patients, left ventricular hypertrophy (LVH) is frequent due to the tendency to hypervolemia. Metabolic problems like obesity, hyperlipidemia and hyperglycemia are also more frequent in PD patients (4).

In dialysis patients, many adiponectin molecules related with the CVD risk are secreted from the adipose tissue. Apelin molecules that were firstly discovered as a peptide with 36 residues (apelin-36) and afterwards 13 residues (apelin-13) and 17 residues (apelin-17) are some of these adiponectines (5). However, the most abundant apelin in plasma is Apelin-13 (6).

Endogenous apelin receptor (APJ) is metabolized by angiotensin converting enzyme-2. The immune-reactivity of APJ has been determined in myocardial, renal, pulmonary, adrenal gland, and endocardial vascular endothelial cells (7). Apelin was shown to have protective effects on CVD such as heart failure, cardiac hypertrophy and myocardial ischemia-reperfusion injury and HT (8). Apelin may cause both endothelium dependent nitric oxide (NO) related vasodilatation and endothelium independent vasoconstriction (9). In the early periods of heart failure, myocardial apelin synthesis increases and results in increased myocardial contractility (9). However, decreased apelin levels have been found to be related to left ventricular systolic and diastolic dysfunction (10).

Serum apelin levels were significantly decreased in uremic cardiomyopathy compared to non-uremic cardiomyopathy (11). Moreover, in HD patients, serum apelin levels were inversely correlated with inflammatory markers (12). We therefore aimed to analyze the associations of serum apelin-13 levels with echocardiographic parameters, carotid artery intima-media thickness (CIMT) and inflammation in PD patients.

MATERIALS and METHODS

This study was designed as a cross-sectional study in the Nephrology Department of Bursa Sevket Yılmaz Training and Research Hospital. Ethics Committee approval was obtained from this institution. 33 patients who were on PD treatment for at least for three months, and 27 healthy controls were included in this study. Informed consent was obtained from each of these participants. Duration of dialysis treatment, recorded as months, was the period starting from the beginning of dialysis.

Age, sex, body mass index (BMI), systolic blood pressure, diastolic blood pressure, primary kidney disease, dialysis duration, dialysis modality [automated peritoneal dialysis (APD), continuous ambulatory peritoneal dialysis (CAPD)], Kt/V values, all medications, comorbidities and smoking habits were recorded.

The exclusion criteria were, peritonitis in the last 3 months of the PD period, presence of active infection and malignancy, New York Heart Association Class 3 or 4 heart failure, CVD in the last 6 weeks of the PD period, decompensated liver disease, surgical procedure in the last month, severe trauma history and presence of hypervolemia signs.

Blood pressures were measured from both arms in the last week for 12 times, and mean values were recorded as the blood pressure. The body mass index was calculated by the formula of weight (kg)/height^2 (m^2). After 12-hour of fasting, blood samples were taken in the morning. Complete blood count, sodium (Na), potassium (K), phosphorus (P), calcium (Ca), glucose, serum creatinine (Cr), blood urea nitrogen (BUN), uric acid, triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), albumin, protein, alkaline phosphatase (ALP), parathyroid hormone (PTH), ferritin, C- reactive protein (CRP) were analyzed. The ratio of absolute neutrophil count to absolute lymphocyte count (NLR) was calculated.

Blood samples for apelin-13 were centrifuged for 5 min in 4000 *g* and stored at - 80 °C until the study. Apelin-13 measurements were carried out by using the Human Apelin-13 ELISA Kit (Catalog No: CK-E11153, Eastbiopharm Inc. Zhejiang, China, Assay range: 0,5-200 ng/L).

Echocardiography was performed by using the GE Vivid 4 Cardiovascular ultrasound device with a 3.5 MHz transducer. Left ventricular ejection fraction measurements were carried out by the biplane Simpson's method and Teichols method. Left ventricular mass (LVM) was calculated by the Devereux formula, and left ventricular mass index (LVMI) was found by the division of LVM to BSA. Left ventricular hypertrophy was defined as more than 134 gr/m^2 and 110 gr/m^2 of LVMI for males and females, respectively (13). Inferior vena cava diameter was measured by the same device.

CIMT was measured with Logiq 5 Pro (GE Healthcare, Milwaukee, USA) Ultrasound by using a 7.5 MHz linear transducer. Three measurements were made from both common carotid arteries proximal to the bifurcation, and then the arithmetic mean was taken as the CIMT.

The SPSS for Windows 20.0 package program was used for statistical analysis. The Shapiro-Wilk test was selected for the detection of normality of the parameters. For the comparison of continuous parameters in two group, the Mann-Whitney U Test or student's *t* test was used as appropriate. Results were given as mean±standard deviation or median (25^{th}-75^{th} IQR) as appropriate. The chi square test was used for the analysis of categorical parameters. The Spearman or Pearson test was used for the analysis of correlation, as appropriate.

RESULTS

Thirty three PD patients (15 female, mean age 42±17 years) and 27 controls (11 female, mean age 43±8 years) were included in the study. 21 (63.7%), 11(33.3%) and 1 (3.0%) patients were taking APD, CAPD, and APD plus CAPD therapy, respectively. There were 11 patients with HT, 5 patients with DM, 5 patients with chronic glomerulonephritis, 3 patients with heart failure, 2 patients with post-renal causes, 2 patients with autosomal dominant polycystic renal disease, 1 patient with amyloidosis, 1 patient with Alport syndrome. The etiology was unknown in three patients. Mean treatment vintage was 34 months. There was no difference between the groups in terms of age, gender, smoking habit and BMI. Mean Kt/V was 2.23. Systolic and diastolic blood pressures were higher in patient group than in controls. The most frequent comorbidity was HT (66.7%), and the other demographical properties and comorbidities of the participants are listed in Table I.

Apelin-13 level was lower in the patient group compared to the control group. However, the difference was not statistically significant [58 (12-131) ng/L vs. 76 (18-130) ng/L, p= 0.083]. NLR, CRP and CIMT values were significantly higher in the patient group (p< 0.001 for all). Total protein and albumin levels were higher in the control group (p< 0.001 and p< 0.001, respectively). BUN, creatinine, Hb, Hct, ferritin, Ca, P, ALP and PTH levels were significantly different between groups (p<0.001 for all) (Table II).

In the patient group Apelin-13 was not different when compared in terms of gender (p=0.401), blood pressure (p=0.693), peritoneal membrane permeability type (p=0.118), and presence of LVH (p=1) (Table III).

When echocardiographic parameters were compared, there were no differences between the groups in terms of LAD, LVEDD, LVESD and LVM (p= 0.074, p= 0.522, p= 0.617, p= 0.137, respectively). IVST and PWT were significantly higher in the patient group (p< 0.05 and p< 0.05, respectively). However, EF and IVC diameter were significantly higher in the control group (p< 0.001 and p< 0.001, Table IV).

In correlation analysis apelin-13 was negatively correlated with age, BUN, ferritin, CRP, NLR and CIMT (p< 0.05, p< 0.05, p< 0.01, p< 0.01, p< 0.01, p< 0.05, respectively). Apelin-13 was positively correlated with Ca, albumin and EF as a cardiac function parameter level (p< 0.05 for all) (Table V).

DISCUSSION

In present study apelin-13 levels were lower in PD patients than in healthy controls, and they were negatively correlated with CIMT and positively correlated with EF.

Increased CVD incidence in patients with CKD cannot be fully explained by classical risk factors like HT, dyslipidaemia and DM. Therefore, non-traditional risk factors like oxidative stress, increased pro-inflammatory cytokines and endothelial dysfunction are emphasized. Apelin, related to atherosclerosis, HT, obesity and CV risk, acts via the NO pathway which is important in endothelial functions (14-16).

Studies of apelin in CKD are conflicting (17,18). In a study of Yavuz et al., apelin levels were not different with respect to

Table I: Demographic and clinical characteristics of patients and controls.

	Patients (n=33)	**Controls (n=27)**	***p***
Age (years)	42±17	43±8	0.917
Gender (F/M)	15/18	11/16	0.617
PD treatment duration (month)	34 (3-150)	-	
Kt/V	2.23±0.51	-	
Smoking (Y/N)	1/32	2/25	0.583
BMI (kg/m^2)	25.1±5.1	25.3±2.2	0.896
SBP (mm Hg)	127 (90-170)	113 (90-130)	<0.01
DBP (mm Hg)	78 (60-90)	72 (60-85)	<0.05
Hypertension (Y/N)	22/11		
Diabetes mellitus (Y/N)	5/28		
Coronary artery disease (Y/N)	4/29		
Peripheral arterial disease (Y/N)	1/32		
Chronic obstructive pulmonary disease (Y/N)	1/32		
Cerebrovascular disease (Y/N)	1/32		
Peritonitis history (Y/N)	8/25		

PD: Peritoneal dialysis, **BMI:** Body mass index, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure. **Y:** Yes, **N:** No.

Table II: Comparison of the variables between patients and controls.

	Patients (n= 33)	Controls (n= 27)	*p*
BUN (mg/dL)	45±11	14±4	<0.001
Creatinine (mg/dL)	9.6±3.3	0.91±0.1	<0.001
Glucose (mg/dL)	87 (53-255)	87 (72-104)	0.755
Uric Acid (mg/dL)	5.5±1.0	5.1±1.5	0.239
Hb (gr/dL)	10.8±1.2	13.9±1.5	<0.001
Hct (%)	33±3.7	42±3.9	<0.001
Na (mEq/L)	140±3	138±2	0.540
K (mEq/L)	4.1±0.6	4.3±0.3	0.112
Ca (mg/dL)	8.7±0.6	9.3±0.3	<0.001
Phosphorus (mg/dL)	4.9±1.3	3.3±0.6	<0.001
Total Cholesterol mg/dL)	178±29	188±26	0.154
HDL-C (mg/dL)	47±15	44±13	0.450
LDL-C (mg/dL)	111±26	116±28	0.410
TG (mg/dL)	87 (56-235)	120 (30-429)	0.291
Total Protein (gr/dL)	6.4±0.8	7.1±0.4	<0.001
Albumin (g/dL)	3.6 (2.8-4.1)	4.3 (3.9-4.7)	<0.001
Ferritin (ng/mL)	415 (70-1650)	48 (5-327)	<0.001
Transferrin saturation (%)	41 (5-200)	38 (10-133)	0.959
ALP (U/L)	102 (56-831)	65 (28-122)	<0.001
PTH (pg/mL)	321 (92-2138)	35 (7-77)	<0.001
CRP (mg/dL)	5.9 (2.6-53.7)	3.2 (3.2-8.7)	<0.001
NLR	3.1 (0.7-31.2)	1.6 (0.9-3.0)	<0.001
CIMT (mm)	0.8 (0.4-1.5)	0.6 (0.3-0.7)	<0.001
Apelin-13 (ng/L)	58 (12-131)	76 (18-130)	0.083

BUN: Blood urea nitrogen, **HDL-C:** High density lipoprotein, **LDL-C:** Low density lipoprotein, **TG:** Triglyceride, **PTH:** Parathyroid hormone, **CRP:** C-reactive protein, **NLR:** Neutrophil to lymphocyte ratio, **CIMT:** Carotid artery intima media thickness.

Table III: Relationship between Apelin-13 and gender, blood pressure, PET, and LVH.

	Apelin-13	*p*
Male (n=18)	59 (12-127)	0.401
Female (n=15)	56 (20-131)	
Hypertension (n=22)	56 (12-131)	0.693
Normotension (n=11)	61 (20-120)	
LA (n=12)	53 (20-127)	0.118
L (n=4)	59 (32-128)	
HA (n=13)	70 (12-131)	
H (n=4)	30 (18-43)	
With LVH (n=18)	59 (18-128)	1
Without LVH (n=15)	56 (12-131)	

PET: Peritoneal equilibration test, **LA:** Low average, **L:** Low, **HA:** High average, **H:** High, **LVH:** Left ventricular hypertrophy.

CKD stages, and there was no relationship between apelin-13 and the loss of renal function in one-year follow-up (19). In another study, apelin was found to be an effective reno-protective biomarker that prevents the progression of CKD (20). However, apelin levels increased while arginine vasopressin (AVP) levels and mean arterial blood pressure decreased during the HD. The AVP/apelin level was also found to be related to the blood pressure (21).

In the present study, apelin-13 levels were insignificantly decreased in PD patients compared to the control group. Moreover, apelin-13 levels were lower in patients with increased peritoneal permeability that supports the clearance of apelin-13 by big pores in the peritoneum. To evaluate this relationship clearly, studies including higher number of patients with low and high peritoneal permeability are needed.

Apelin-13 that has a protective role in ED and atherosclerosis by increasing the NO level is the most active fragment of apelin.

Table IV: Echocardiographic findings of the patients and controls.

	Patients (n= 33)	Controls (n= 27)	*p*
EF (%)	60 (40-68)	65 (59-80)	<0.001
LAD (cm)	3.5 (2.5-5.5)	3.3 (2.9-4.0)	0.074
LVEDD (cm)	4.67±0.46	4.74±0.41	0.522
LVESD (cm)	2.7 (2.0-4.8)	2.8 (2.1-3.4)	0.617
IVST (cm)	1.2 (0.9-1.8)	1.1 (0.8-1.3)	<0.05
PWT (cm)	1.2 (0.9-2.1)	1.0 (0.8-1.3)	<0.05
LVM (g)	210 (97-483)	182 (101-263)	0.137
LVMI (g/m^2)	122 (70-241)	98 (62-142)	<0.01
IVC (cm)	1.2 (0.9-1.8)	1.9 (1.1-2.2)	<0.001

EF: Ejection fraction, **LAD:** Left atrium diameter, **LVEDD:** Left ventricle end diastolic diameter, **LVESD:** Left ventricle end systolic diameter, **IVST:** Interventricular septum thickness, **PWT:** Left ventricle posterior wall thickness, **LVM:** Left ventricle mass, **LVMI:** Left ventricle mass index, **IVC:** Vena cava inferior diameter.

Apelin plays an important role in protection from myocardial ischemia-reperfusion injury. The Apelin/APJ system prevents mitochondrial oxygen damage and lipid peroxidation through nitric oxide formation (22). In newly diagnosed and untreated HT patients, apelin-13 levels were decreased with respect to the control group, and a negative correlation was detected between HT and apelin levels. In this study, apelin-13 was presumed to play a role in the etiology of HT (16). Apelin has been found to be decreased in HT with LVH, and is thought to be a marker of LVH (23). Treatment with apelin-13 after acute intramural MI induction decreased cardiac hypertrophy and myocardial remodeling parameters, and decreased apoptosis (24). In the present study, apelin-13 levels were decreased in the patient group, but apelin-13 levels were not different when the patients were grouped with respect to the presence of LVH.

Apelin-13 may be protective against vascular calcification via the inhibition of osteoblastic differentiation in vascular smooth muscle cells (25). In HD patients, apelin was negatively correlated with inflammatory parameters such as hsCRP and IL-6 (12). Moreover, in pediatric HD patients, apelin was thought to be a target molecule in slowing down the inflammation (26).

In the present study, there was a negative correlation between apelin-13 and CRP and CIMT as in the literature. NLR was higher in the patient group compared with the control group, and it was inversely correlated with apelin-13 levels. These data suggest that apelin-13 may be an effective marker in the inflammatory processes.

In the literature, the relationship of apelin with cardiac function, coronary artery disease and uremic cardiac disease has been much debated. Apelin increases contractility by increasing the calcium amount, and sensitivity in myocardial cells.

Table V: Correlation analyses of Apelin-13 with different variables.

	Apelin-13	
	r	*p*
Age (years)	-0.323	<0.05
BUN (mg/dL)	-0.294	<0.05
Ca (mg/dL)	0.298	<0.05
Albumin (g/dL)	0.297	<0.05
Ferritin (ng/mL)	-0.368	<0.01
CRP (mg/dL)	-0.331	<0.01
NLR	-0.328	<0.01
CIMT (mm)	-0.279	<0.05
LAD (cm)	-0.111	0.397
LVESD (cm)	0.008	0.951
LVEDD (cm)	0.154	0.239
IVST (cm)	-0.212	0.104
PWT (cm)	-0.208	0.111
LVM (g)	-0.077	0.559
LVMI (g/m^2)	-0.047	0.722
EF (%)	0.267	<0.05
IVC (cm)	0.192	0.141

LAD: Left atrium diameter, **LVESD:** Left ventricle end systolic diameter, **LVEDD:** Left ventricle end diastolic diameter, **IVST:** Interventricular septum thickness, **PWT:** Left ventricle posterior wall thickness, **LVM:** Left ventricle mass, **LVMI:** Left ventricle mass index, **EF:** Ejection fraction, **IVC:** Vena cava inferior diameter.

Some mechanisms like the caveolin-1-autophagy pathway mediate the cardiomyocyte hypertrophy induced by the apelin-13/APJ system (27).

Increased apelin levels have also been shown to reduce the systemic vascular resistance in early cardiac dysfunction (28). In experimental studies, myocardial vascularity increased and cardiomyopathy improved (29). Apelin also improved cardiac contractility, and reversed the fibrosis (30,31). Apelin ameliorates vascular calcification by suppressing osteoblastic differentiation (32). Moreover the Apelin/APJ axis may represent a new target for the treatment of HT and cardiovascular diseases (33).

In several studies, the relationship of apelin levels with cardiac functions in patients with renal failure were studied. In patients with uremic dilated cardiomyopathy, serum apelin levels were found to be decreased when compared to non-uremic dilated cardiomyopathy (11). In HD patients with ischemic heart disease, the apelin level was lower when compared to HD patients without ischemic heart disease, and the apelin level was found to be correlated with cardiac functions (17). Apelin was thought to be a marker for mortality and hospitalization in CKD patients with CVD (34). In our study, the interventricular septum, left ventricular posterior wall thickness and LVMI were increased in the patient group while EF was decreased when compared with the control group. However, there was a positive correlation between apelin levels and EF as in the literature, which may support the possible positive inotropic effect of apelin (11, 35). There was however no correlation between apelin and other cardiac parameters.

Some studies have focused on the association of apelin with volume status and CV functions (36). In PD patients without active cardiac disease and hypervolemic symptoms, apelin was negatively correlated with total body fluid (37). In addition, correlation of apelin levels with LVEDD, LVESD, PWT and aortic diameter, which are indirect indicators of volume status, supports this hypothesis (17). Unlike the literature, there was no difference between the patient and control groups in terms of LVEDD and LVESD in our study. IVC diameter, which is related to volume status in dialysis patients, was decreased in the patient group (38). These unexpected findings in our study may be related to strict volume control in our patients, as well as the difficulty in measuring the IVC diameter with ECHO and the user dependence of this technique.

Cardiovascular disease is the most important cause of mortality in patients with CKD. ED and atherosclerosis in CKD are caused by multiple factors. ED is thought to be the first step of CVD in uremic patients (39). In several studies, an increase in CIMT was accepted as an early sign of atherosclerosis, and it was shown to be increased with a decrease in renal function and dialysis vintage (40). In our study, inflammatory markers like NLR and CRP were increased while apelin-13 was decreased in the patient group. Apelin-13 levels were also negatively correlated with these inflammatory markers and CIMT. Thus, in accordance with the literature, we can comment that reduced apelin level is related to inflammatory markers and atherosclerotic processes.

In PD patients, there is an accelerated ED and atherosclerosis that progress with the additive effects of multiple adipocytokines like apelin-13. Multiple risk factors related to urea or not may take part in this process. Adipose tissue and many mediators released from adipose tissue appear as candidates to become future targets in ED treatment strategy.

There are some limitations of this study. First, patient number in this single centre study is low. Second, interpretation of data should be done more carefully due to the cross-sectional design. However, when taken together with the literature, the results of our study can shed light on a wide range of future studies involving more patients with homogeneous CKD etiology including the follow-up of inflammatory markers that evaluate the effect on mortality.

In conclusion, serum apelin-13 levels were higher in peritoneal dialysis patients as compared to the population with normal renal functions. Apelin-13 may play an important role in the atherosclerotic process and endothelial dysfunction in peritoneal dialysis patients.

REFERENCES

1. United States Renal Data System, Atlas of end-stage renal disease in United States, USRDS 2006 Annual Data Report, National Institute of Diabetes and digestive and Kidney Diseases, Bethesda, Md, USA, Washington:Minneapolis Medical Research Foundation, 2006
2. Walatek B, Sułowicz W: Cardiorenal syndrome-alternate challenge for nephrologist. Przegl Lek 2011;68:619-628
3. Collins AJ: Cardiovascular mortality in end-stage renal disease. Am J Med Sci 2003;325:163-167
4. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT; NECOSAD Study Group: Predictors of survival in anuric peritoneal dialysis patients. Kidney Int 2005;68:1199-1205
5. Ahima RS: Metabolic actions of adipocyte hormones: Focus on adiponectin. Obesity (Silver Spring) 2006;14 Suppl 1:9S-15S
6. Beltowski J: Apelin and visfatin: Unique "beneficial" adipokines upregulated in obesity. Med Sci Monit 2006;12:112-119
7. Ladeiras-Lopes R, Ferreira-Martins J, Leite-Moreira AF: The apelinergic system: The role played in human physiology and pathology and potential therapeutic applications. Arq Bras Cardiol 2008;90:343-349
8. Rastaldo R, Cappello S, Folino A, Losano G: Effect of apelin-apelin receptor system in postischaemic myocardial protection: A pharmacological postconditioning tool? Antioxid Redox Signal 2011;14:909-922
9. Foldes G, Harkay F, Szokodi I: Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. Biochem Biophys Res Commun 2003;308:480-485

10. Przewlocka-Kosmala M, Kotwica T, Mysiak A, Kosmala W: Reduced circulating apelin in essential hypertension and its association with cardiac dysfunction. J Hypertens 2011;29:971-979
11. Codognotto M, Piccoli A, Zaninotto M, Mion M, Vertolli U, Tona F, Boffa GM: Evidence of decreased circulating apelin beyond heart involvement in uremic cardiomyopathy. Am J Nephrol 2007;27:1-6
12. El-Shehaby AM, El-Khatib MM, Battah AA, Roshdy AR: Apelin: A potential link between inflammation and cardiovascular disease in end stage renal disease patients. Scand J Clin Lab Invest 2010;70:421-427
13. Sahn DJ, De Maria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978;58:1072-1083
14. Zoccali C, Mallamaci F, Tripepi G: Inflammatory proteins as predictors of cardiovascular disease in patients with end-stage renal disease. Nephrol Dial Transplant 2004;19:67-72
15. Zhang X, Ye Q, Gong D, Lv Y, Cheng H, Huang C, Chen L, Zhao Z, Li L, Wei X, Zhang M, Xia X, Yu X, Zheng X, Wang S, Wang Z, Tang C: Apelin 13 inhibits lipoprotein lipase expression via the APJ/PKCα/miR3615p signaling pathway in THP-1 macrophage-derived foam cells. Acta Biochim Biophys Sin (Shanghai) 2017;49:530-540
16. Sonmez A, Celebi G, Erdem G, Tapan S, Genc H, Tasci I, Ercin CN, Dogru T, Kilic S, Uckaya G, Yilmaz MI, Erbil MK, Kutlu M: Plasma apelin and ADMA levels in patients with essential hypertension. Clin Exp Hypertens 2010;32:179-183
17. Malyszko J, Mallyszko JS, Kozminski P, Mysliwiec M: Apelin and cardiac function in hemodialyzed patients: Possible relations? Am J Nephrol 2006;26:121-126
18. Büyükbakkal M, Canbakan B, Eser B, Yayar Ö, Ercan Z, Merhametsiz Ö, Haspulat A, Ayli MD: The relation between apelin levels, echocardiographic findings and carotid intima media thickness in peritoneal dialysis patients. Ren Fail 2015;37:433-438
19. Yavuz YC, Sevinc C, Deniz MS, Yavuz S, Altunoren O, Sayarlioglu H, Dogan E: The role of Apelin 13 in progression of chronic kidney disease. IJKD 2015;9:369-373
20. Wang LY, Diao ZL, Zhang DL, Zheng JF, Zhang QD, Ding JX, Liu WH: The regulatory peptide apelin: A novel inhibitor of renal interstitial fibrosis. Amino Acids 2014;46:2693-2704
21. Cernaro V, Lacquaniti A, Lorenzano G, Loddo S, Romeo A, Donato V, Lupica R, Buemi A, Buemi M: Apelin, plasmatic osmolality and hypotension in dialyzed patients. Blood Purif 2012;33:317-323
22. Chen Z, Wu D, Li L, Chen L: Apelin/APJ System: A novel therapeutic target for myocardial ischemia/reperfusion injury. DNA Cell Biol 2016 Dec;35:766-775
23. Ishida J, Hashimoto T, Hashimoto Y: Regulatory roles for APJ, a seven transmembrane receptor related to angiotensin type-1 receptor in blood pressure in vivo. J Biol Chem 2004;279:274-279
24. Azizi Y, Imani A, Fanaei H, Khamse S, Parvizi MR, Faghihi M: Post-infarct treatment with [Pyr1]apelin-13 exerts anti-remodeling and anti-apoptotic effects in rats heart. Kardiol Pol 2017;75:605-613
25. Shan PF, Lu Y, Cui RR, Jiang Y, Yuang LQ, Liao EY: Apelin attenuates the osteoblastic differentiation of vascular smooth muscle cells. PLoS One 2011;6:e17938
26. Yavuz S, Cetinkaya S, Anarat A, Bayazıt AK: Apelin and nutritional status in children on dialysis. Ren Fail 2014;36:1233-1238
27. Wu D, Xie F, Xiao L, Feng F, Huang S, He L, Liu M, Zhou Q, Li L, Chen L: Caveolin-1-Autophagy pathway mediated cardiomyocyte hypertrophy induced by Apelin-13. DNA Cell Biol 2017;36:611-618
28. Chen MM, Ashley EA, Deng DX: Novel role fort he potent endogenous inotrope apelin in human cardiac dysfunction. Circulation 2003;108:1432-1439
29. Zeng H, He X, Hou X, Li L, Chen JX: Apelin gene therapy increases myocardial vascular density and ameliorates diabetic cardiomyopathy via upregulation of sirtuin 3. Am J Physiol Heart Circ Physiol 2014;306:585-597
30. Ashley EA, Powers J, Chen M, Kundu R, Finsterbach T, Caffarelli A, Deng A, Eichhorn J, Mahajan R, Agrawal R, Greve J, Robbins R, Patterson AJ, Bernstein D, Quertermous T: The endogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. Cardiovasc Res 2005;65:73-82
31. Siddiquee K, Hampton J, Khan S, Zadory D, Gleaves L, Vaughan DE, Smith LH: Apelin protects against angiotensin II-induced cardiovascular fibrosis and decreases plasminogen activator inhibitor type-1 production. J Hypertens 2011;29:724-731
32. Han X, Wang LY, Diao ZL, Liu WH: Apelin: A novel inhibitor of vascular calcification in chronic kidney disease. Atherosclerosis 2016;244:1-8
33. Yamaleyeva LM, Shaltout HA, Varagic J: Apelin-13 in blood pressure regulation and cardiovascular disease. Curr Opin Nephrol Hypertens 2016;25:396-403
34. Silva AP, Fragoso A, Silva C, Viegas C, Tavares N, Guilherme P, Santos N, Rato F, Camacho A, Cavaco C, Pereira V, Faísca M, Ataíde J, Jesus I, Neves P: What is the role of Apelin regarding cardiovascular risk and progression of renal disease in type 2 diabetic patients with diabetic nephropathy? Biomed Res Int 2013;2013:247649
35. Japp AG, Cruden NL, Barnes G, van Gemeren N, Mathews J, Adamson J, Johnston NR, Denvir MA, Megson IL, Flapan AD, Newby DE: Acute cardiovascular effects of apelin in humans: Potential role in patients with chronic heart failure. Circulation 2010;121:1818-1827
36. Karadag S, Ozturk S, Gursu M, Gurdal A, Basinoglu F, Yigit S, Aydin Z, Uzun S, Sumnu A, Oflaz H, Kazancioglu R: The relationship between apelin and cardiac parameters in patients on peritoneal dialysis: Is there a new cardiac marker? BMC Nephrology 2014;15:18
37. Kazancioglu R, Gursu M, Karadag S, Tatli E, Aydin Z, Uzun S, Sumnu A, Cebeci E, Ozturk S: Volume status in patients on peritoneal dialysis: The role of apelin and bioimpedance spectroscopy. Ren Fail 2012;34:1068-1073
38. Mandelbaum A, Link G, Wambach G, Ritz E: Vena cava ultrasonography assessing the state of hydration of patients with renal failure. Dtsch Med Wschr 1993;118:1309-1315
39. Tatematsu S, Wakino S, Kanda T, Homma K, Yoshioka K, Hasegawa K, Sugano N, Kimoto M, Saruta T, Hayashi K: Role of nitric oxide-producing and degrading pathways in coronary endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol 2007;18:741-749
40. Tanaka M, Abe Y, Furukado S, Miwa K, Sakaguchi M, Sakoda S, Kitagawa K: Chronic kidney disease and carotid atherosclerosis. J Stroke Cerebrovasc Dis 2012;21:47-51