Relationship Between Fetuin-A Level and Cardiovascular Risk Factors in Peritoneal Dialysis Patients

Periton Diyaliz Hastalarında Fetuin-A Düzeyi ile Kardiyovasküler Risk Faktörleri Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Vascular calcifications and chronic inflammation are the main reasons of the decreased life span and prevalent morbidity for patients on renal replacement therapy due to chronic renal failure. Scoring systems used to determine the chance of cardiovascular (CV) risk and traditional CV risk factors frequently fail to identify the risk in these patients. New markers to predict the risk of CV disease continues to be investigated. One of the most studied marker in recent years is a serum glycoprotein fetuin-A, which is major calcification inhibitor. We aimed to study the relation between fetuin-A subclinical inflammation and cardiovascular risk factors in Peritoneal Dialysis (PD) patients and healthy volunteers.

MATERIAL and METHODS: Forty-eight PD patients and 27 healthy volunteers were included in the study. Fetuin-A levels, body weight, body mass index, blood pressure, markers of inflammation (sedimentation, C-reactive protein, ferritin) and lipid profile tests were performed. The relationship between these parameters was compared with fetuin-A.

RESULTS: CRP and sedimentation levels were significantly higher in the group of PD patients. Fetuin-A levels were significantly lower in PD patients than the control group. There was a negative correlation between serum fetuin-A levels, average arterial blood pressure and CRP.

CONCLUSION: Fetuin-A can be used to predict subclinic inflammation, and cardiovascular mortality risk in PD patients.

KEY WORDS: Peritoneal dialysis, Cardiovascular risk factors, Fetuin-A, Inflammation

ÖZ

AMAÇ: Böbrek yerine koyma tedavisi gören, kronik renal yetmezlikli hastalarda subklinik inflamasyon ve vasküler kalsifikasyon, artmış kardiyovasküler ölüm riskinin başlıca sorumlularıdır. Kardiyovasküler riski belirlemek amacıyla kullanılan risk skorlamaları ve geleneksel risk faktörleri, bu hasta grubunda gerçek riski belirlemede yetersiz kalmaktadır. Bu nedenle yeni belirteçler üzerinde çalışılmaktadır. Son yıllarda çalışmaların üzerine yoğunlaştığı fetuin-A, serumda major kalsifikasyon inhibitörü olarak görev yapan bir glikoproteindir. Bu çalışmamızda periton diyaliz (PD) hastaları ve sağlıklı kontrol grubunda serum fetuin-A düzeyi ile subklinik inflamasyon ve kardiyovasküler risk parametreleri arasındaki ilişkiyi inceledik.

GEREÇ ve YÖNTEMLER: Çalışmaya 48 PD hastası ve sağlıklı gönüllülerden 27 erişkin kontrol grubu olarak alındı. Hastalar ve kontrol grubunun kilo, boy, beden kitle indeksleri, kan basınçları ölçüldü. İnflamasyon belirteçleri (ferritin, C-reaktif protein (CRP), sedimantasyon, fibrinojen, albumin), lipid profilleri ve fetuin-A düzeyleri çalışıldı. Çalışılan parametreler ile fetuin-A arasındaki ilişki değerlendirildi.

BULGULAR: CRP düzeyi PD grubunda, kontrol grubuna göre yüksek, fetuin-A düzeyi ise anlamlı düzeyde düşük saptandı. PD grubunda serum fetuin-A düzeyi ile CRP düzeyi ve ortalama arteryel kan basıncı arasında negatif korelasyon olduğu gösterildi.

SONUÇ: Serum fetuin-A düzeyi, periton diyaliz hastalarında subklinik inflamasyonu, ve kardiyovasküler riski ön görmek amacıyla kullanılabilecek risk faktörlerindendir.

ANAHTAR SÖZCÜKLER: Periton diyalizi, Kardiyovasküler risk faktörleri, Fetuin-A, İnflamasyon

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INTRODUCTION

According to data from the United States renal data system (USRDS), the cardiovascular mortality rate in end-stage renal disease (ESRD) patients is at least 10-20 times higher than age- and gender-matched healthy controls (1). The lifespan of patients with ESRD is reduced and cardiovascular disease (CVD) accounts for premature death in more than 50% of patients from Western Europe and North America undergoing regular dialysis (1). Actually, the risk for CVD in a 30-yr-old ESRD patient is similar to the calculated risk of a 70 to 80-yr-old person from the non-renal population (2). Death due to cardiovascular causes in patients receiving renal replacement therapy is the leading cause of mortality (rate among all deaths 53%) in Turkey (3).

This increased risk can only be partially explained by a higher prevalence of CVD and traditional CV (cardiovascular) risk factors (Table I) at the initiation of dialysis (4,5,6,7). The extent and severity of CV complications is clearly disproportionate to the underlying risk factor profile (8).Therefore, recent interest has focused on non-traditional CV risk factors (Table I) such as inflammation, malnutrition, vascular calcification and oxidative stress, all common phenomena of ESRD that may promote atherosclerosis (9,10).

From experimental culture of vascular smooth muscle and endothelial cells, it has been reported that tumor necrosis factor (TNF)-alfa, fibroblast growth factor, osteocalcin, osteonectin, core binding factor, alkaline phosphatase and bone matrix 2a are involved in vascular calcification (13,14,15,16). Fetuin-A, matrix GIa protein, osteoprotegerin and osteopontin have been reported to reduce vascular calcification. Fetuin-A (α2-Heremans-Schmid glycoprotein; AHSG) is a circulating calcium-regulatory glycoprotein that inhibits vascular calcification in dialysis patients, and is also a prognostic factor in dialysis patients (17,18). Excessive vascular calcification is observed in the majority of patients with ESRD and on dialysis. It is also known that some patients do not have severe calcification despite the same uremic conditions. There are many factors that effect this phenomenon of vascular calcification, including the primary renal disease, dietary habit, the calcium-phosphorus product and natural inhibitors of calcification (19).

Table I: Classic and non-classic cardiovascular risk factors in chronic renal failure.

Classic risk factors	Nontraditional risk factors
Advanced age	Albuminuria
Male sex	Hyperhomocysteinemia
Hypertension	Advanced dialysis time
High LDL, Low HDL	Anemia
Diabetes	Oxidative stress
Cigarette smoking	Inflammation
Immobility	Malnutrition
Family history of CAD	Impaired Ca/P metabolism
Menopause	Thrombogenic factors
	Extracellular volume overload
	Impaired Nitric oxide/Endothelin balance
	Low Fetuin-A levels

One of the non- traditional CV risk factors is inflammation. In recent years, several reports have suggested that inflammation, alone or in combination with a low protein intake, plays a significant role in atherosclerosis and CVD pathogenesis in ESRD. It has been established that moderately elevated plasma concentrations of CRP are associated with an increased risk of CVD in ESRD and healthy subjects (20).

In this study, we evaluated the contribution of fetuin-A as a prognostic factor for the inhibition of vascular calcification and its relation to various parameters in peritoneal dialysis (PD) patients and healthy subjects.

MATERIAL and METHODS

The prospective study was performed in Uludağ University Medical Faculty hospital between February 2011 and November 2011. The study population consisted of 48 PD patients and 27 healthy volunteers. The local ethics committee approved the study, and informed consent was obtained from each patient and healthy volunteer. Fetuin-A, calcium, phosphorus, urea, uric acid, hemoglobin, creatinine, alkaline phosphatase levels, hemogram, inflammation markers (sedimentation, CRP, ferritin), lipid profile were checked and dialysis adequacy tests were performed. The quantitative CRP technique was used and a reference value <0,5 mg/dl were considered normal. Length, weight, body mass index and blood pressure were measured. Blood samples were stored at – 80°C until analysis. The enzyme-linked immünosorbent assay (ELISA) kit (BioVendor Laboratorni Medicina - Czech Republic) was used for fetuin-A determination. All biochemical analyses were performed at the Uludağ University Biochemistry laboratory. The relationship between these parameters was compared with the fetuin-A level.

Statistical analysis

The SPSS 15.0 statistical software was used for the statistical analysis. The Shapiro-Wilk test was used to determine normality of variable distribution. Continuous variables with normal distribution were presented as mean ± standard deviation. The median value was used for variables without normal distribution. The categorized variables were given as percentages. Student's t-test was used to determine the significance of differences between the groups. Non-numerical variables were compared by Fischer's exact test. A value of $P< 0.05$ was considered to be statistically significant.

RESULTS

The mean age in PD patients and healthy volunteers was 47 ± 13 and 37 ± 2 years respectively. Sex distribution, mean

Table II: Peritoneal dialysis and control group patients demographic characteristics and cigarette smoking.

	PD patients (n: 48)	Control group patients (n: 27)
Sex (M/F)	28/20	10/17
Age (years)	47 ± 13	37 ± 2
HT (n, %)	4 (8%)	0 (0%)
DM (n, %)	4 (8%)	0 (0%)
CAD (n, %)	5 (10%)	0 (0%)
Obesity (n, %)	6 (9%)	1 (3%)
COPD (n, %)	1(2%)	0 (0%)
Cigarette (n, %)	6 (9%)	5 (18%)

M: Male; **F:** Female; **HT:** Hypertension; **DM:** Diabetes mellitus; **PD:** Peritoneal dialysis; **COPD:** Chronic Obstructive Pulmonary Disease; **CAD:** Coronary artery disease

Table III: Comparison of biochemical parameters and fetuin–A levels for PD patients and control group.

	PD (n: 48)	Control (n: 27)
Hb (g/dL)	**11.2 ± 1.5**	**13.4 ± 2.4*****
Sedimentation (mm/h)	**75 ± 34**	**34 ± 14***
CRP (mg/L)	**2.33 ± 1.53**	**1.24 ± 1.06***
Glucose (mg/dL)	97.23 ± 25.8	89.3 ± 10.1
Urea (mg/dL)	**106 ± 26**	**25 ± 9*****
Uric acid (mg/dL)	**4.9 ± 0.9**	**3.7 ± 1.2*****
Creatinine (mg/dL)	**10.1 ± 2.8**	**0.8 ± 0.1*****
Calcium (mg/dL)	9.6 ± 0.9	9.5 ± 0.4
Phosphate (mg/dL)	**4.9 ± 1.6**	**3.1 ± 0.7*****
Ca x P	**47.3 ± 16.0**	**30.0 ± 7.1*****
Fetuin-A (μg/mL)	**230 ± 50.7**	**282 ± 43.4*****
T-Chol (mg/dL)	**193 ± 59**	**185 ± 46.4*****
HDL (mg/dL)	**37.7 ± 9.7**	**51.9 ± 133.4*****
LDL (mg/dL)	120.4 ± 40	111.06 ± 36
Triglyceride (mg/dL)	175.8 ± 110	113.8 ± 65.2

Values are expressed as mean and standard deviation
HDL: High density Lipoprotein; **LDL:** Low density lipoprotein; **T-Chol:** Total cholesterol
*: p<0.05, **: p<0.01, ***: p<0.001.

age, smoking history, family history of hypertension (HT), diabetes (DM), coronary artery disease (CAD) and obesity were similar in the two groups (Table II). 26 PD patients were on a continuous ambulatory peritoneal dialysis (CAPD) program and 22 patients were on an automatic peritoneal dialysis (APD) program. Average PD time was 81 ± 43 months.

CRP and sedimentation levels were significantly higher in PD patients than in the control group (P<0.05). The average fetuin-A level of the PD group was found to be 230 ± 50 μg/mL and the control group fetuin–A level was found to be 282 ± 43 μg/ml. The difference between the two groups was significant (P<0.001). Uric acid, phosphorus (P), and Ca x P levels were significantly higher in the PD group (Table III).

Total cholesterol, low density lipoprotein (LDL) and triglyceride levels were higher in the PD group but only cholesterol level differences was significant (P<0.001). High density lipoprotein (HDL) level was lower in PD group than healthy controls (P<0.001). Other differences were not significant (Table IV).

A significant negative correlation (P<0.01; r= -0.85) was found between the serum fetuin-A level and average arterial blood pressure in the PD group but this correlation was not significant in healthy controls.

A negative correlation was found between serum fetuin-A and CRP levels (P<0,05; r= -0,4) in the PD group and a positive correlation was present between serum fetuin-A levels and age, fasting blood glucose, HDL levels in healthy volunteers. Correlation of other parameters with fetuin-A is shown in Table IV.

DISCUSSION

Fetuin-A, a 62-kD glycoprotein, is synthesized by liver cells and exerts strong inhibition of ectopic calcification by inhibiting hydroxyapatite formation. Stenvinkel et al. reported that low fetuin–A levels are associated with malnutrition, inflammation and atherosclerosis as well as with increased cardiovascular and other mortality causes (21). The relationship between serum fetuin-A level and various parameters in the group of PD patients were compared with healthy control subjects. In our study as well, it was observed that the levels of serum fetuin-A in the group of PD patients were significantly lower than in healthy control group, and inflammatory markers (sedimentation rate and CRP) were significantly higher in the PD group. Furthermore, fetuin-A levels in PD patients showed a significant negative correlation with CRP levels. Previous studies reported an inverse relationship between serum fetuin-A level and CRP in chronic hemodialysis patients (22). We observed the same relation in PD patients. As shown by studies, serum fetuin-A is regulated as a negative acute phase protein and its serum concentration falls during the acute inflammatory response and normalizes when the infection is successfully treated (23). The anti-inflammatory

Table IV: Correlation analysis of biochemical parameters and Fetuin –A levels in PD and control group.

	Control (n: 27)	PD Patients (n:48)
Age	P<0.05; r=0.4	NS
BMI	NS	NS
SBP	NS	NS
DBP	NS	NS
AABP	NS	P<0.01; r= - 0.8
CRP	NS	P<0.05; r= - 0.4
Sedimentation	NS	NS
Hemoglobin	NS	NS
Fasting glucose	P<0.05; r=0.4	NS
Urea	NS	NS
Uric acid	NS	NS
Creatin	NS	NS
Calcium	NS	NS
Phosphate	NS	NS
Ca x P	NS	NS
PTH	-	NS
Total cholesterol	NS	NS
HDL	P<0.01; r=0.5	NS
LDL	NS	NS
Triglyceride	NS	P<0.01; r = - 0.7
PET	-	NS
NpCR	-	NS
Creatinine clearance	-	NS

BMI: Body mass index; **SBP:** Systolic Blood pressure; **DBP:** Diastolic blood pressure **AABP:** Average arterial blood pressure; **PTH:** Parathyroid hormone; **PET:** Peritoneal equilibrium test **NpCR:** Normalized Protein Catabolic Rate **NS:** Not significant.

property of fetuin–A was evidenced further by the suppression of the tumor necrosis factor release from stimulated macrophages in an in vitro study (24). Another hypothesis is that fetuin-A may influence the resolution of inflammation by modulating the phagocytosis of apoptotic cells by macrophages (25).

Growing evidence suggests that increased risk of CV mortality in PD patients may be partly explained by the predisposition of this population to vascular calcification. Hyperphosphatemia and elevated Ca x P product promote vascular calcification, and are significantly linked to all causes of CV mortality in patients with ESRD (26). Apart from occlusive arterial disease as seen in atherosclerosis, arterial stiffening as a feature of predominant medial calcification is a hallmark of vascular pathology in dialysis patients (29-30). Increased aortic stiffening, reflected for example by an increased pulse wave velocity (PWV) or aortic augmentation index is an important determinant of all cause and CV mortality in ESRD patients (31-32). In our study we observed a negative correlation between average arterial blood pressure and fetuin-A level. As a sign of arterial stiffness, average arterial blood pressure could be high in this group and can be an indirect sign of vascular calcification. Further studies with bigger study groups are necessary to confirm this data. Hermans et al. studied the relationship between serum fetuin-A concentration and aortic stiffness in patients on dialysis (33 on peritoneal dialysis and 98 on haemodialysis). Univariate analysis in dialysis patients showed that fetuin-A levels were inversely related to pulse wave velocity (PWV). However, after correction for age, gender, main arterial pressure and diabetes mellitus, this relation lost its statistical significance (27). In contrast, another study with PD patients found serum fetuin–A to be an independent determinant of aortic stiffness (28).

It is believed that low fetuin-A levels are associated with atherosclerosis, inflammation and cardiovascular risk. Our study showed other cardiovascular risk factors, such as anemia, atherogenic lipid profile, hyperuricemia and impaired Ca X P levels in PD group, but could not show correlation of these parameters with fetuin-A.

Cardiovascular death is the most frequent cause of death in patients on peritoneal dialysis. Traditional risk factors may explain some, but probably not all of the increased atherosclerotic cardiovascular disease. Subclinical inflammation and atherosclerosis play a key role in pathogenesis of cardiovascular disease. Our results demonstrate the usefulness of a single random CRP and fetuin-A determination in predicting subclinical inflammation, cardiovascular mortality and vascular calcification in PD patients. In the early stages of atherosclerotic cardiovascular disease, CV disease risk can be reduced and necessary measures can be taken by using markers of subclinical chronic inflammation. These data need to be supported by large study groups.

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