Association of Fetuin-A Levels with Carotid Intima Media Thickness and Valvular Calcification in Hemodialysis and Peritoneal Dialysis Patients

Hemodiyaliz ve Periton Diyaliz Hastalarında Fetuin-A Seviyeleri ile Karotis İntima Media Kalınlığı ve Valvuler Kalsifikasyon Arasındaki İlişki

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ABSTRACT

BACKGROUND: Fetuin-A is a negative acute-phase reactant which prevents vascular calcification. Coronary artery disease (CAD) is the most important cause of mortality in patients undergoing renal replacement therapy (RRT). The key element of cardiovascular disease (CVD) seen in end-stage renal disease patients who are on dialysis treatment is accelerated calcific atherosclerosis. There are a limited number of studies in which HD and PD is compared in terms of fetuin-A level.

OBJECTIVE: We aimed to investigate the association of serum fetuin-A level with valvular calcification and predictors of CAD in hemodialysis (HD) and peritoneal dialysis (PD) patients.

MATERIAL and METHODS: 39 HD (24 males, 15 females) and 39 PD (25 males, 14 females) patients were included in the study. We determined carotid artery intima media thickness (CIMT) and evaluated heart valve calcification via echocardiography. We also measured serum fetuin-A level, CRP, ferritin, fibrinogen and serum albumin level. According to fetuin-A level, patients were stratified into quartiles.

RESULTS: Fetuin-A level was significantly lower in HD patients when compared with that of PD patients (28.6±5.934 ng/ml, 32±4.8 ng/ml respectively p<0.001). There was a significant negative correlation between CIMT and fetuin-A level. CIMT was found to be lower in PD patients than in HD patients. We found a positive correlation between fetuin-A and dialysis adequacy and albumin level. There was a negative correlation of fetuin-A with age, fibrinogen, ferritin and CRP. Fetuin-A level was lower in patients with aortic calcification.

CONCLUSION: Fetuin-A level was found to be lower in HD patients. Fetuin-A may be a novel marker for CVD in patients undergoing RRT.

KEY WORDS: Calcification, Fetuin-A, Hemodialysis, Intima media thickness, Peritoneal dialysis

ÖZ

GİRİŞ: Fetuin A vasküler kalsifikasyonu önleyen bir negatif akut faz reaktanıdır. Koroner arter hastalığı (KAH) renal replasman tedavisi almakta olan hastalarda en önemli ölüm sebebidir. Diyalize giren son dönem böbrek yetmezliği hastalarında görülen kardiyovasküler hastalığın ana elementi hızlanmış kalsifik aterosklerozdur. Fetuin A seviyeleri açısından hemodiyaliz (HD) ve periton diyalizini(PD) karşılaştıran sınırlı sayıda çalışma mevcuttur.

AMAÇ: HD ve PD hastalarında KAH prediktörleri ve valvüler kalsifikasyon ile serum fetuin A düzeyleri arasındaki ilişkiyi araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: 39 HD (24 erkek, 15 kadın) ve 39 PD (25 erkek, 14 kadın) hastası çalışmaya alındı. Karotis intima media kalınlığı (KIMK) ultrason ile ölçüldü ve kalp kapağı kalsifikasyonları ekokardiyografi ile değerlendirildi. Ayrıca serum fetuin-A, CRP, ferritin, fibrinojen, ve albumin seviyeleri saptandı. Fetuin-A düzeylerine göre hastalar çeyreklere ayrıldı.

BULGULAR: Fetuin-A seviyesi HD hastalarında PD hastalarına göre daha düşüktü (hemodiyaliz 28,6±5,934 ng/ml, PD 32±4,8 ng/ml, p<0,001). KIMK ile fetuin-A seviyesi arasında anlamlı negatif korelasyon vardı. KIMK, PD hastalarında HD'e göre daha düşüktü. Fetuin-A seviyesi ile diyaliz

Received : 12.03.2011
Accepted : 29.11.2011

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yeterliliği ve albumin arasında pozitif korelasyon saptanırken fetuin-A ile yaş, fibrinojen, ferritin ve CRP arasında negatif korelasyon saptandı. Fetuin-A düzeyi aortik kalsifikasyonu olanlarda daha düşüktü ($p<0.05$).

SONUÇ: Fetuin-A seviyesi HD hastalarında daha düşük olarak saptandı. KAH prediktörleri ile ilişkisi düşünüldüğünde RRT almakta olan hastalarda özellikle HD hastalarında KVH için yeni bir belirteç olabilir.

ANAHTAR SÖZCÜKLER: Fetuin-A, Hemodiyaliz, İntima media kalınlığı, Peritoneal diyaliz, Valvular kalsifikasyon

INTRODUCTION

When compared with the general population, cardiovascular disease (CVD) in patients with end stage renal disease (ESRD) is 10-20 times higher albeit recent developments in RRT (1). In addition to traditional risk factors (such as age, smoking, hypertension, dyslipidemia) some novel risk factors which are specific to ESRD such as anemia, proteinuria, hyperparathyroidism, inflammation, hyperhomocysteinemia, malnutrition and uremic toxins are responsible for the increased frequency of CVD in this population (2-3). Known traditional cardiovascular risk factors do not suffice solely to account for early atherosclerosis development in ESRD patients. Thus, novel risk factors which affect atherosclerosis development in ESRD patients should be identified.

The key element of CVD seen in ESRD patients who are on dialysis treatment is accelerated calcific atherosclerosis. Previous studies reported increased frequency of coronary artery calcification even in younger dialysis patients (4). Other studies concluded that vascular and cardiac valvular calcifications were independent risk factors for CVD in dialysis patients (5-6). In some experimental studies conducted in rats, a number of vascular calcification inhibitors such as fetuin-A, Matrix Gla Protein and osteoprotegerin have been elucidated. Fetuin-A was deemed as the most important one which constitutes 50% of total serum precipitation inhibiting capacity alone among these factors (7-8).

Fetuin-A is a circulating serum protein with a molecular weight of approximately 60 kDa synthesized by hepatocytes reaching high serum concentrations (0.4–1.0 g/L). Fetuin-A is a negative acute phase reactant and represents a prominent part of the α2- band of serum electrophoresis.

Although it is not seen a significant decrease in fetuin-A level during HD, there seems to be a decrease in its level during PD in a similar fashion to that of albumin (9-10). Some investigators reported that fetuin-A deficiency was a more potent predictor of mortality in comparison to hypoalbuminemia and high serum CRP levels and was a key element of MIA syndrome (5-6). There are a limited number of studies in which HD and PD are compared in terms of fetuin-A level. Two previously conducted studies showed that fetuin-A level in HD patients were significantly lower when compared to that of PD patients (11-12). However, another study did not confirm these findings (13).

In this present study, we aimed to investigate the relation of fetuin-A with valvular calcification and predictors of CVD (CIMT, MIA syndrome, Inflammatory parameters) in patients who had been on HD or PD for more than 6 months and had no signs or symptoms of CVD. We also evaluated whether there was any difference between HD and PD with respect to these parameters.

MATERIAL and METHODS

We included 39 HD and 39 PD patients who were being followed at our dialysis center. Local ethics committee approved study protocol and all participants of the study signed informed consent forms. Duration of dialysis, demographic data and medications of patients were recorded.

Exclusion criteria of the study were as follows; dialysis therapy for less than 6 months, malignity, serious trauma, surgical operation or burn during the last 1 month, presence of active infectious disease, clinically evident CVD (evidence of previous myocardial infarction findings in ECG, specific anginal pain, previous coronary by-pass operation or percutanous coronary intervention and peripheral arterial disease), chronic liver disease, hospitalization of any cause during the last three months, peritonitis during the last three months.

Carotid ultrasonography and echocardiography: Echocardiography and carotid artery evaluations were performed by an experienced cardiologist who was blinded to treatment status, clinical and laboratory data of study patients. Each evaluation was performed between 08.00 -11.00 AM, at least after 15 minutes rest. CIMT was measured at approximately 10 mm proximal to carotid artery bifurcation of two carotid arteries. Mean CIMT value was reached as calculating arithmetic mean of measurements of two carotid arteries. In addition, heart valve calcification was evaluated by means of echocardiography.

Biochemical Analyses

Blood samples were collected in appropriate tubes and then centrifuged at 4000 rpm for 5 minutes and serums were separated. Measurement of fetuin-A level was performed via ELISA kit method. Serum samples were used to measure lipid parameters (Lip (a), HDL, total cholesterol and triglyceride levels), ferritin, fibrinogen, homocysteine, electrolytes, albumin and CRP. Serum albumin analysis was performed with

spectrophotometric Beckman Coulter Synchron LX Systems as using color reaction to bromocresol. Serum CRP analysis was performed with Beckman Coulter Synchron LX System by using measurement of specific antigen-antibody complex which was formed by antigen-antibody reaction. Anticoagulated blood samples were used to analyze parathormone level; measurements were performed with commercial ELSA-PTH kit (CIS Bio International, Yvette Cedex, France) using immunoradiometric gamma counter method.

Weight and height measurements of patients were performed after morning exchange when the patients' peritoneal cavities were empty for PD patients and after midweek day HD session for HD patients. BMI was calculated using BMI (kg/m^2) = Weight / $(Height)^2$ equation.

MIA Syndrome; (MIA is an acronym which was created using initials of **M**alnutrution-**I**nflammation-**A**therosclerosis); we considered individual components of the syndrome were fulfilled should serum albumin level <3.5 gr/dl (**M**alnutrition), hs-CRP level >10 mg/dl (**I**nflammation), and CIMT >1mm (**A**therosclerosis).

Statistical Analysis

The patients' characteristics were presented as the mean ± SD. The student's t-test for independent samples was used for normally distributed continuous variables, and the Mann-Whitney U test was used for variables that were not normally distributed. Pearson correlation co-efficient was used to examine associations between two variables. Linearly associated parameters with fetuin-A were entered in the multivariate linear regression model to determine the independent predictors of fetuin-A. Differences among categorical variables were analyzed using the chi-square test the level of significance was $p < 0.05$ for all comparisons. All calculations were performed using a standard statistical package (SPSS 13.0 for Windows).

RESULTS

Fetuin-A and demographic characteristics of the patients

When all patients were evaluated according to dialysis type; HD and PD groups showed no difference in terms of age, time on dialysis, BMI, gender, smoking, frequency of diabetes mellitus and hypertension (p>0.05). Demographic and clinical characteristics of the patients are depicted in Table I.

Table I: Demographic and clinical characteristics of patients.

	HD	PD	P
Male/Female (n)	24/15	25/14	NS*
Age (years)	51.5 ± 14.4	50.2.4 ± 14.6	NS
Dialysis vintage (months)	28.8 ± 21.1	27.0 ± 24.7	NS
Body mass index (kg/m^2)	26.7 ± 6.4	25.9 ± 4.1	NS
Diabetes Mellitus (n)	12 (%30.8)	11 (%28.2)	NS
Hypertension (n)	31 (%71.8)	32 (%82.1)	NS
Antihypertensive drug use (n)	31 (%79.5)	36 (%92.3)	NS
Smoking (n)	7 (%17.9)	7 (%17.9)	NS
Pulse pressure (mmHg)	46.6 ± 8.6	47.6 ± 7.7	NS
Systolic blood pressure (mmHg)	124.3 ± 12.9	128.2 ± 16.0	NS
Diastolic blood pressure (mmHg)	77.6 ± 7.0	80.2.0 ± 10.6	NS
Fetuin-A (ng/mL)	28.6 ± 5.9	34.2 ± 4.8	<0.001
Homocysteine (μmol/L)	24.7 ± 8.6	20.3 ± 7.4	0.01
Albumin (gr/dL)	3.6 ± 0.3	3.7 ± 0.3	0.06
CRP (mg/L)	14.1 ± 8.9	13.0 ± 10.1	NS
Ferritin (ng/mL)	509.8 ± 251.9	355.3 ± 237.0	0.07
Fibrinogen (mg/dL)	367.2 ± 74.1	430.1 ± 75.3	<0.001
Calcium (mg/dL)	8.4 ± 0.4	8.7 ± 0.6	0.003
Ca x Phosphorus (mg^2/dL^2)	41.2 ± 13.3	40.1 ± 10.2	NS
Parathormone (pg/mL)	354.6 ± 272.8	460.5 ± 407.9	NS
Hemoglobin (g/dL)	11.5 ± 1.5	11.5 ± 1.7	NS
Kt/V	1.28±0.18	2.45±0.88	<0.001

***NS:** Not Significant

Table II: Distribution of HD and PD patients according to fetuin-A levels (ng/mL)

Fetuin Quartiles	Hemodialysis (n)	Peritoneal dialysis (n)	Total
Quartile 1 (17.0-27.0)	19	2	21
Quartile 2 (27,1-32.0)	9	13	22
Quartile 3 (32,1-36.0)	7	11	18
Quartile 4 (36,1-50.0)	4	13	17
Total	39	39	78

Fetuin-A level was significantly higher in PD patients than that of HD patients (34.2 ± 4.8 ng/mL, 28.6 ± 5.9 ng/mL respectively, p<0.001). When fetuin-A levels were divided into 4 quartiles, there were only 2 PD (5.1%) patients in contrast to 19 HD (48.7%) patients in the first quartile (Table II). There was a negative correlation between fetuin-A and age (r=-0.26 p=0.02). This correlation was due to the HD group (r= -0.37 P= 0.01), and in fact there was no relation in the PD group (r= -0.05 p= 0.76). Fetuin-A level was found to be significantly lower in diabetic patients (p= 0.01).

Nutritional parameters and fetuin-A

We did not find any significant difference between the two groups with respect to nutritional parameters. 23 HD patients

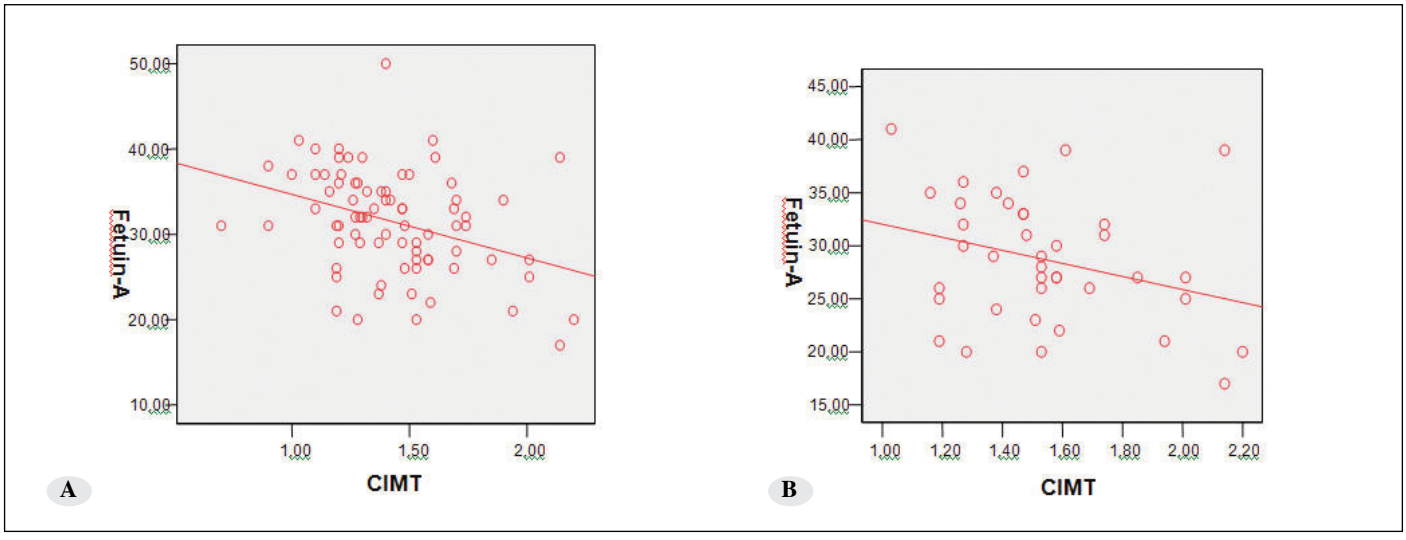

Figure 1: *Relation between fetuin-A and CIMT in all patients (**A**) and HD patients (**B**) (r= -0.35 P= 0.01 and r= -0.30 P= 0.06, respectively)*

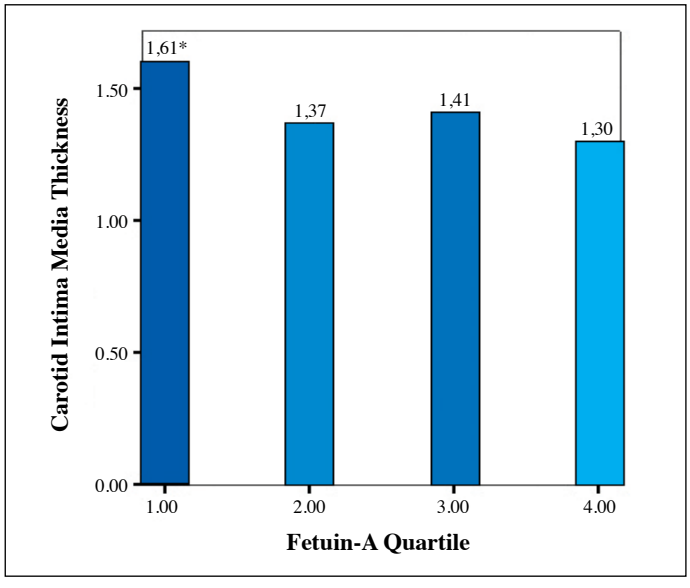

Figure 2: *Relation between fetuin-A quartile and CIMT*

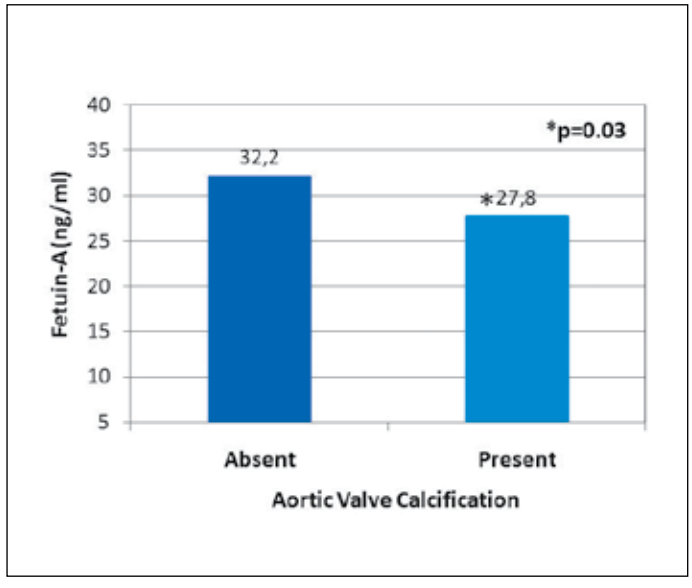

Figure 3: *Relation between fetuin-A and aortic valve calcification.*

had BMI greater than 25 kg/m^2 whereas 22 PD patients had. Eight HD and 6 PD patients were hypoalbuminemic (p=0.6). Though not of statistical significance, there was a tendency for HD patients to have lower albumin level compared with PD patients (p=0.06) (Table I). There appeared a positive correlation of fetuin-A with albumin (r= 0.30 p= 0.006). When HD and PD groups were evaluated separately, there was a positive correlation between fetuin-A and serum albumin in HD patients whereas this was not the case in PD group (r= 0.33 p= 0.03, r= 0.28 p= 0.08, respectively).

Fetuin-A, CIMT, and calcification

Mean CIMT was greater in HD patients than in PD patients (1.54 ± 0.29 mm, 1.31 ± 0.24 mm respectively, p=0.001). There was a negative correlation between serum fetuin-A and CIMT (r= -0.35 p= 0.01). When each dialysis modality was evaluated separately, there was no relation between fetuin-A and CIMT (r= -0.30 p= 0.06, r=-0.1 p=0.6) (Figure 1A,B). While the CIMT of patients, who were in the first quartile (in which fetuin-A level was the lowest) was the greatest, CIMT of patients who were in the 4th quartile was the smallest and the difference was statistically significant (Figure 2). No difference was evident between the two groups with respect to valvular calcification (Table III). When all patients were taken into account, patients who had aortic valve calcifications had significantly lower serum fetuin-A level (Figure 3). When aortic valve calcification were evaluated according to fetuin-A quartiles, only one patient had aortic valve calcification in the 4th quartile in which fetuin-A level was the highest (p=0.04). There was no difference between the groups in terms of aortic calcification. (p=0.1)

Fetuin-A, inflammatory markers and dialysis adequacy

There was a negative correlation between fetuin-A and CRP (r= -0.34 p= 0.002). This was also the case when HD and PD were evaluated separately. (r= -0.41 p= 0.008 and r= -0.36 p= 0.02, respectively). Similarly there was a negative correlation between fetuin-A and fibrinogen (r= -0.24 p= 0.02) and this relation held true for both groups (HD: r= -0.42 p= 0.006, PD: r= -0.45 p= 0.003). There existed a negative correlation between fetuin-A and ferritin (r= -0.36 p= 0.001). However, when HD and PD were evaluated separately, there was only negative correlation in the HD group. (HD: r = -0.31 p= 0.04). We also found a positive correlation between fetuin-A and dialysis adequacy (expressed as Kt/V) in whole patient population (r= 0.29 p= 0.009). Linear regression analysis showed that age, Kt/V and CRP were independent predictors of fetuin-A (Table IV)

Table III: Fetuin A levels according to place and presence of valvular calcification.

	AVC		MVC		AVC veya MVC		P
	Present (n=18)	Absent (n=60)	Present (n=10)	Absent (n=68)	Present (n=22)	Absent (n=56)	
HD (n=39)	27.5 ±6.4	29.2 ±5.7	27.6 ±6.8	28.8 ±5.8	27.3 ±6.1	29.3 ±5.8	NS
PD (n=39)	31.3 ±4.4	34.7 ±4.8	34.8 ±2.8	34.1 ±5.1	33.0 ±4.3	34.6 ±5.0	NS
All patients (n=78)	28.7±5.9	32.2±5.9*	31.2 ±6.2	31.5 ±6.0	29.6 ±6.0	32.1 ±5.9	0.03

AVC: aortic valvular calcification, **MVC:** Mitral valvular calcification, **HD:** hemodialysis patients, **PD:** peritoneal dialysis patients. *significant difference of fetuin-A levels in patients who had aortic valvular calcification., **NS:** Not significant

Table IV: The independent predictors of fetuin-A in multivariate linear regression model.

Variables	Beta	t	P
Kt/V	1.713	2.57	0.01
CRP	-0.20	-2.96	0.001
Age	-0.10	-2.35	0.02

Dialysis duration, Kt/V, Albumin, CRP, Age, Fibrinogen, ferritin and carotid intima media thickness were entered to multivariate linear regression model as an independent predictor of fetuin-A. The backward elimination method was used for the regression analysis. The remaining significant parameters are demonstrated in the table. Model R^2=0.32, F=6.95 and model statistics P=0.001

Table V: Fetuin A levels according to numbers of components of MIA syndrome.

Numbers of components of MIA syndrome	Numbers of patients (n)	Fetuin-A
1	32	34.3 ± 5.3*.#
2	35	29.9 ± 4.0
3	11	27.8 ± 6.7

*: There is a significant difference between patients who had one component and two components (p<0.05)
#: There is a significant difference between patients who had one component and three components (p<0.05)

Fetuin-A and components of MIA Syndrome

There was no statistically significant difference between the two groups in terms of components of MIA syndrome (Pearson Chi-Square = 4.07, p= 0.2). Regarding the relation of fetuin-A level with MIA syndrome; the more the number of the components of MIA, the lower the fetuin-A level (Table V). There was a significant difference between the patients who had one component of the MIA syndrome and patients who had 2 or 3 components in terms of serum fetuin-A levels. (p=0.002 and p=0.007 respectively). On the other hand there was no difference regarding serum fetuin-A level between the patients who had all three components of the MIA syndrome and who had two components (P= 0.4). Correlation between fetuin-A and CRP: in all patients, HD hemodialysis patients and PD patients was r= -0.34 p= 0.002, r= -0.41 p= 0.008 and r= -0.36 p= 0.02, respectively.

DISCUSSION

Our results showed that the fetuin-A level was lower in HD patients compared with PD patients and fetuin-A blood level was associated with major CAD predictors such as CIMT, aortic valve calcification (AVC), CRP, fibrinogen, albumin, dialysis adequacy and MIA syndrome. In particular, patients whose serum fetuin-A level was ≤27.0 ng/mL had many of the poor prognostic markers which were inherent in ESRD patients.

In studies investigating fetuin-A, serum fetuin-A level was found to be lower in ESRD patients compared to that of controls (13-15). However, limited data are available to compare HD and PD patients in terms of fetuin-A levels. Stenvinkel et al. (13) did not detect any significant difference between HD and PD patients with respect to serum fetuin-A. On the other hand, two other studies showed significantly lower levels of fetuin-A in HD patients when compared with PD patients (11-12). Our results also showed that HD patients had lower fetuin-A levels compared with PD patients (P=0.001). We think of that in the study by Stenvinkel et al. (13) duration of renal replacement therapies were relatively short (12 months), and this may be responsible for their failure to detect a difference between HD and PD in terms of serum fetuin-A level.

CIMT is a strong predictor of mortality and cardiovascular events in ESRD patients (16-18). A strong negative correlation between fetuin-A and CIMT was reported in ESRD patients (19-20). Similarly our study showed a negative correlation between serum fetuin-A level and CIMT. In particular, the patients in the first quartile whose serum fetuin-A were lower had increased CIMT measurements (1.6 mm). In our opinion, a serum fetuin-A level ≤27.0 ng/mL can be considered a cutoff value for subclinical atherosclerosis.

It was also shown that valvular calcification was an important predictor of all-cause and CV mortality in ESRD patients (6, 14, 21-22). Wang et al. (23) reported lower fetuin-A levels in PD patients who had valvular calcification. In a similar vein we found a reverse relation between fetuin-A and AVC (P=0.03). However, there was no significant relation between mitral valve calcification and fetuin-A. Among patients whose serum fetuin-A level >36.0 ng/mL, only one patient had AVC. Thus, we think that this value can be used as a cutoff for fetuin-A at which valvular calcification will be avoided.

Moe et al. (24) reported that there was a negative correlation between low fetuin-A level and coronary calcification and fetuin-A had an important role in the pathogenesis of coronary calcification. Another study involving 132 HD patients revealed a negative correlation between fetuin-A and coronary calcium scores which were measured by CT (14). To our opinion, when the findings of these two studies are taken together and findings regarding association of CIMT and valvular calcification with fetuin-A are taken into consideration, decreases in fetuin-A level of ESRD patients may be a potent predictor of CV mortality.

In most of the studies investigating fetuin-A, it was reported that fetuin-A was related to Kt/V and CaXP product (11, 15). On the contrary, Coen et al. (14) reported a negative correlation between fetuin-A and Kt/V and CaXP product in 132 HD patients. Our study showed that there was a positive correlation between fetuin-A and Kt/V (r= 0.29 p= 0.009). However, there was no correlation between fetuin-A and CaXP product. A number of factors such as diet, dialysis adequacy, medications, secondary hyperparathyroidism, can affect CaXP product. Because of these confounding factors, it seems complex to evaluate the true relationship between fetuin-A and CaXP product. Association of Kt/V with fetuin-A is clinically important. Because this indicates that as providing adequate dialysis it seems possible to keep fetuin-A serum levels higher and to avoid untoward effects of low levels of fetuin-A. Multiple regression analysis showed that CRP, Kt/V and age were independent predictors of serum fetuin-A levels in ESRD patients.

It is already known that the MIA syndrome was a determinant of survival of ESRD patients and patients who had all components of MIA syndrome had a shorter survival rate (25). Wang et al. (23), in a study in which they investigated relation of fetuin-A with MIA syndrome and valvular calcification in 238 PD patients, found that fetuin-A and valvular calcification were associated with the MIA syndrome and fetuin-A level was related to all clinical outcomes in PD patients. They also reported that the more the number of MIA syndrome components, the more fetuin-A level decreased and the greatest decrease in fetuin-A level was seen in patients who had all three components of MIA syndrome. Our findings were in agreement with that of Wang et al. (23).

Albumin is commonly used to evaluate the nutritional status of ESRD patients. It is known that patients with lower serum albumin had a higher prevalence of CVD (23, 26-27). Studies have shown that there was a positive correlation between serum fetuin-A level and albumin (7, 12**,** 23). We also confirmed this correlation in our study (r= 0.30 P= 0.006).

ESRD is a chronic inflammatory state. Inflammatory markers, especially CRP, have been shown to be an independent predictor of mortality in HD and PD patients (26**,** 28). Association of increased CRP levels with cardiovascular mortality has been established for a long time. Most of the studies have shown a negative correlation between fetuin-A and CRP (7, 12, 23). In a similar way we also found a negative correlation between these parameters both in HD and PD groups (P= 0.002). There was a negative correlation between fetuin-A and other inflammatory markers, i.e., fibrinogen and ferritin as well. (p= 0.02, p= 0.001, respectively).

Our study has some limitations; our sample size was relatively small. Since this is not a prospective controlled study we cannot draw cause and effect relations from our findings.

In conclusion, fetuin-A may be considered as a novel and important CVD risk marker because of its close relation with CAD predictors. Patients with a serum fetuin-A level ≤27.0 ng/mL can be taken into consideration as a more risky group in terms of CVD. Considering that HD and PD do not confer an advantage over one another as to CVD risk, it can be suggested that fetuin-A can be helpful in evaluation of CVD risk, especially in HD patients. However, prospective randomized studies are needed to better evaluate the reliability of the fetuin-A cutoff value to predict cardiovascular events.

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