Relationship Between Fetuin-A, Inflammation, Coronary Artery Calcification in Hemodialysis and Peritoneal Dialysis Patients

Hemodiyaliz ve Periton Diyaliz Hastalarının Koroner Arter Kalsifikasyonu, Fetuin-A ve İnflamasyon Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Vascular calcification is commonly seen in patients with end-stage renal disease (ESRD). Fetuin-A has been found to be a vascular calcification inhibitor and its level is significantly low in ESRD patients. The aim of our study was to investigate the relation between coronary artery calcification, inflammation and fetuin-A levels in peritoneal dialysis (PD) and hemodialysis (HD) patients.

MATERIAL and METHODS: 46 PD (M/F=28/18) and 34 (M/F=20/14) HD patients were included in the study. Coronary artery calcification scoring was made by multi slice computed tomography. PD and HD patients were divided into 2 groups according to their median CACS values Serum levels of fetuin-A, CRP, IL-6 and TNF-α are studied.

RESULTS: There were no differences in demographic features of PD and HD patients. There was a correlation between CACS, advanced age, dialysis vintage and fetuin-A. We could not find any correlation between inflammatory markers and CACS. There was a statistically significant difference between fetuin-A and CACS groups.

CONCLUSION: Age, duration of dialysis, fetuin-A levels were found to be related to CACS in PD and HD patients. Fetuin-A may play a role in increased mortality in this population via facilitating CACS.

KEY WORDS: Hemodialysis, Peritoneal dialysis, Vascular calcification, Fetuin-A, Inflammation

ÖZ

AMAÇ: Son dönem böbrek yetersizliği (SDBY) gelişen hastalarda damarsal kalsifikasyon yaygın olarak gözlenmektedir. Fetuin-A, vasküler kalsifikasyon durdurucu olarak bulunmuş ve SDBY'li hastalarda serum fetuin-A düzeyinin ileri derecede düşük olduğu saptanmıştır. Çalışmamızın amacı periton diyaliz (PD) ve hemodiyaliz (HD) hastalarında koroner arter kalsifikasyonu (KAKS), inflamasyon ve Fetuin-A arasındaki ilişkiyi incelemektir.

GEREÇ ve YÖNTEMLER: Çalışmamıza 46 PD (E/K=28/18) ve 34 HD (E/K=20/14) hastası alınmıştır. Hastalara çoklu kesit alan bilgisayarlı tomografi ile koroner arter kalsiyum skorlaması yapıldı. PD ve HD hastaları medyan KAKS değerlerine göre olmak üzere 2 gruba ayrıldı. Serumda Fetuin-A, CRP, IL-6 ve TNF-α çalışıldı.

BULGULAR: HD ve PD hastalarında demografik veriler açısından bir fark yoktu. PD ve HD hastalarında yaş ve diyaliz süresi artıkça KAKS artıyordu. PD ve HD hastalarında fetuin-A ile KAKS arasında olumsuz ilişki bulundu. PD ve HD hastalarında, inflamatuvar belirteçler ile KAKS arasında ilişki bulunmadı. Fetuin-A ile KAKS grupları arasında istatistiksel olarak anlamlı ilişki saptandı.

SONUÇ: PD ve HD hastalarında yaş, diyaliz süresi, fetuin-A düzeyi ve KAKS arasında ilişkili olduğu saptanmıştır. Bu populasyonda, fetuin-A, KAKS'ı arttırmak suretiyle mortaliteyi arttırıyor olabilir.

ANAHTAR SÖZCÜKLER: Hemodiyaliz, Periton diyalizi, Vasküler Kalsifikasyon, Fetuin-A, İnflamasyon

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INTRODUCTION

Cardiovascular diseases (CVD) including coronary artery calcification (CAC) are the main cause of mortality and morbidity in both young and adult end-stage renal disease patients (ESRD) receiving hemodialysis and peritoneal dialysis (1-3). Deterioration of kidney function was found to be independently associated with risk factors such as inflammation, endothelial dysfunction and CAC (4-6). However, the main pathogenesis of increased extraosseous calcification remains unknown in this population. To highlight this process previous studies demonstrated multiple risk factors including advanced age, dialysis vintage, vitamin D therapy, and cellular factors rather than only a passive process due to calcium-phosphate precipitation in the vessel wall. This suggest that mechanisms involved in the pathogenesis of CAC are involved in an orchestrated event that can be attributed to programmed process regarding oxidative stress, active inflammation and osteogenesis at vascular level (7-9).

Fetuin-A (a2-Schmid Heremans glycoprotein, AHSG) is a hepatocyte-derived serum protein (molecular weight, ~60 kD). Serum concentrations are relatively high with levels between 0.5–1.0 g/L in average populations. One of the biological function of fetuin-A is inhibition of calcification, thus potently limiting hydroxyapatite crystal formation (10). In a recent study, Turkmen et al (11) found an inverse relationship between serum fetuin-A levels and total CACS in HD patients.

In the present study, we aimed to investigate the relationship between fetuin-A, inflammation markers including TNF-α, IL-6, coronary artery calcification in both peritoneal dialysis (PD) and hemodialysis patients (HD).

MATERIAL and METHODS

The study protocol was approved by the Medical Ethics Committee of Selcuk University (Meram School of Medicine, Konya, Turkey). Written informed consent was obtained from all subjects included in the study.

This was a cross-sectional study involving 46 PD patients (18 females, 28 males; mean age, 50.4±15 years) and 34 HD patients (14 females, 20 males; mean age, 47.7±12.3 years) treated for ≥6 months in the Dialysis Unit of Selcuk University between February and June 2009.

Patients aged 18–70 years willing to participate were screened. A review of medical records (including information: on age; sex; weight; duration of renal replacement treatment; medications; primary disease of ESRD) was undertaken. Inclusion criteria include ESRD patients received HD and PD for at least 6 months between 18-70 years old. Exclusion criteria were: (i) nephrotic-range proteinuria.; (ii) active infection; (iii) autoimmune disease; (iv) severe secondary hyperparathyroidism (patients with iPTH > 500 pg/mL). Ninety-four patients were evaluated and 14 patients excluded from the study. Of these 14 patients, 8 patients had active infection; 3 patients had secondary hyperparathyroidism; and 3 patients had autoimmune disease (including systemic lupus erythematosus and microscopic polyangiitis). None of the patients included in the study had nephrotic-range proteinuria and arrhythmia based on electrocardiography (ECG). The remaining 80 ESRD patients fulfilled the above criteria and were enrolled in the study. HD patients were receiving thrice-weekly dialysis for a 4-h period with a standard bicarbonate-containing dialysate bath using a biocompatible HD membrane (Polysulfone, FX-80 series, Fresenius, Germany). Dialysate flow rates were 500 ml/min and blood-flow rates were 250–300 ml/min. All PD patients used the same conventional 1.36%, 2.27% and 3.86% glucose-based lactate buffered PD solutions from the Fresenius Medical Care (Heidelberg, Germany) and Baxter Healthcare (Deerfield, IL, U.S.A). None of the patients used amino-acid or icodextrin containing PD solutions.

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of patients and healthy subjects was measured in the upright sitting position after ≥5 min of rest using an Erka sphygmomanometer (PMS Instruments Limited, Berkshire, UK) with an appropriate cuff size. Two readings were recorded for each individual. The mean value of two readings was defined as the blood pressure. Patients with SBP and DBP >140 mmHg and 90 mmHg, respectively, or who were already on antihypertensive treatment were assumed to be hypertensive.

Twenty-three patients were taking antihypertensive drugs (14 of them on angiotensin-converting enzyme (ACE) inhibitors; 8 receiving an angiotensin-II receptor blockers (ARB); and 1 receiving a calcium-channel blocker and an ACE inhibitor). Calcitriol and calcium-containing phosphate binders usage were 79% and 63% in PD patients and %78 and 65% in HD patients, respectively. Of the 34 HD patients, only 4 (12%) were using statin whereas of 46 PD patients, 10 (22%) were taking statin.

Biochemical analyses

Venous blood samples for biochemical analyses were drawn after an overnight fast before first exchange in PD patients and before the midweek session in patients receiving HD. All biochemical analyses including those for total cholesterol (TC) and plasma triglyceride (TG) concentrations were undertaken using an oxidase-based technique by the Roche/Hitachi Modular System (Mannheim, Germany) in the Central Biochemistry Laboratory of the Meram School of Medicine.

Coronary Artery Calcium Scoring:

Coronary artery calcium scoring (CACS) was performed by a 64-MDCT scanner (Somatom Sensation 64, Siemens Medical Solutions, Erlangen, Germany). CACS were calculated by a method that was designed by Agatston and et al (6). A calcification was defined as a minimum of two adjacent pixels (>0.52 mm^2) with a density over 130 Hounsfield units. The peak

intensity (in Hounsfield unit) and area (in square millimeter) of the individual calcifications were calculated. As described by Agatston et al. (6), calcium scores were obtained by multiplying each area of interest by a factor indicating peak density within the individual area. Image quality and scoring accuracy were assessed by one radiologist who carefully made vessel-by-vessel and calcific focus-by-calcific focus inspections of each image. The radiologist was blinded to the clinical and laboratory results of the patients. The intraobserver coefficient of variation for CACS was 2.5%.

Statistical Analyses

Statistical analyses were carried out using the Statistical package for Social Sciences for Windows version 15.0 (SPSS, Chicago, IL, USA). Parametric data were mean ± SD and non-parametric data were the median (interquartile range) with a significance level of $P < 0.05$. The normal distribution of all variables was tested using the Kolmogorov-Smirnov Test. Dichotomous variables were compared using the chi-square test. Statistical differences between parametric data of two groups were analyzed using the Student's *t*-test. The Mann–Whitney U test was used to determine differences between non-parametric data. Linear associations between continuous variables were assessed using the Spearman correlation test.

RESULTS

Demographic and clinical characteristics, biochemical parameters, fetuin-A levels and inflammation parameters of PD and HD patients are depicted in table 1. The etiology of the 46 PD patients and 34 HD patients was diabetic nephropathy (n=4, n=3, respectively), hypertensive nephropathy (n=5, n=4, respectively), chronic glomerulonephritis (n=1, n=3, respectively), polycystic kidney disease (n=1, n=3, respectively), chronic pyelonephritis (n=3, n=2, respectively), amyloidosis (n=1, n=1, respectively) and unknown etiology (n=31, n=18, respectively). There were no differences in age, gender, body mass index (BMI), predialysis systolic and diastolic blood pressure levels, biochemical parameters including serum LDL cholesterol, PTH, fetuin-A, CRP levels and total CACS between PD and HD patients.

Mean CACS values of PD and HD patients were 225.1±285.8 and 262.7±405.1, respectively (p=0.627). PD and HD patients were divided into two groups according to

Table I: Demographic, clinical, biochemical fetuin-A levels, inflammatory parameters and total CACS of patients.

Parameter	ESRD Patients (n=80) (mean±SD) (median IQR)	PD Patients (n=46) (mean±SD) (median IQR)	HD Patients (n=34) (mean±SD) (median IQR)	P value
Male/Female	38/42	18/28	20/14	0.85
Age (years)	49.3±14	50.4±15	47.7±12.3	0.48
Dialysis vintage (years)	4.85±3.4	4.6±2.2	5.2±4.5	0.80
Vitamin D usage (%)	78.6	78.9	78.3	0.95
BMI (kg/m^2)	26.7±5.1	26.9±5.0	26.6±5.4	0.61
SBP (mmHg)	139±29	134±28	145±28	0.13
DBP (mmHg)	86±16	84±17	89±17	0.24
Calcium (mg/dL)	9.2±0.98	8.92±0.87	9.6±1.0	0.002
Phosphorus (mg/dL)	4.63±1.32	4.24±1.0	5.17±1.53	0.004
CaxP (mg^2/dL^2)	42.7±13.2	37.9±10.3	49.2±14.1	0.0001
PTH (pg/mL)	280 (286)	308(243)	249 (323)	0.75
Albumin (g/dL)	3.85±0.48	3.6±0.45	4.17±0.3	0.0001
LDL (mg/dL)	112.2±28.4	108.5±26.9	117.2±29.9	0.117
CRP (mg/L)	8.7 (10)	8.8(10)	8.7 (11)	0.74
IL-6 (pg/mL)	22.5 (41)	40.3 (108)	18 (14)	0.01
TNF-α (pg/mL)	0.09 (0.06)	0.09 (0.06)	0.08 (0.02)	0.03
Fetuin-A (ng/ml)	262.1±43.2	257±39.9	269±46.9	0.215
Total CACS	241.1±339.7	225.1±285.8	262.7±405.1	0.627

PTH; parathyroid hormone **SD;** Standard Deviation, **IL;** Interleukin, **TNF;** Tumor necrosis factor, **CRP;** C reactive protein, **SBP;** systolic blood pressure, **DBP;** diastolic blood pressure, **CACS;** coronary artery calcification score

Table II: Demographic characteristics and biochemical parameters of PD patients according to Coronary Artery Calcification Scores

Parameter	CACS GROUP 1 (n=23) (mean±SD) (median) (IQR)	CACS GROUP 2 (n=23) (mean±SD) (median) (IQR)	P value
Age (years)	44.7±13.3	56.1±14.8	0.009
Dialysis vintage (years)	3.74±1.96	5.48±2.17	0.007
BMI (kg/m^2)	25.8±4.9	28.0±4.9	0.12
Calcium (mg/dL)	8.9±0.9	8.9±0.8	0.7
Phosphorus (mg/dL)	4.2±1.1	4.3±0.9	0.8
PTH (pg/mL)	234 (221)	368 (210)	0.07
Albumin (g/dL)	3.6±0.48	3.6±0.43	0.9
CRP (mg/L)	7.2 (10)	9.8 (10)	0.27
IL-6 (pg/mL)	39.3 (95)	44.4 (129)	0.68
TNF-α (pg/mL)	0.09 (0.05)	0.1 (0.1)	0.13
Fetuin-A (ng/ml)	292.2±16.9	221.8±19.6	<0.0001

PTH; parathyroid hormone **SD;** Standard Deviation, **IL;** Interleukin, **TNF;** Tumor necrosis factor, **CRP;** C reactive protein, **BMI:** Body Mass Index, **CACS;** coronary artery calcification score

median total CACS value. Median CACS was found 110 in PD patients and 12.6 in HD patients. PD patients were assigned into group 1(CACS≤110) and group 2 (CACS>110) whereas HD patients were assigned into group 1 (CACS≤12,6) and group 2 (CACS> 12,6). Demographic, clinical features, biochemical parameters, fetuin-A levels and inflammation parameters of PD and HD patients are shown in table 2 and table 3, respectively. Of 46 PD patients, 12 (26%) had zero CACS (CACS=0), 11 (24%) had mild CACS (CACS=1-99), 13 (28%) had moderate CACS (CACS=100-399), and 10 (22%) had severe CACS (CACS>400). However, of 34 HD patients, 15(44%) had zero CACS (CACS=0), 5 (12%) had mild CACS () (CACS=1-99), 4 (29%) had moderate CACS (CACS=100-399), and 10 had severe CACS (CACS>400).

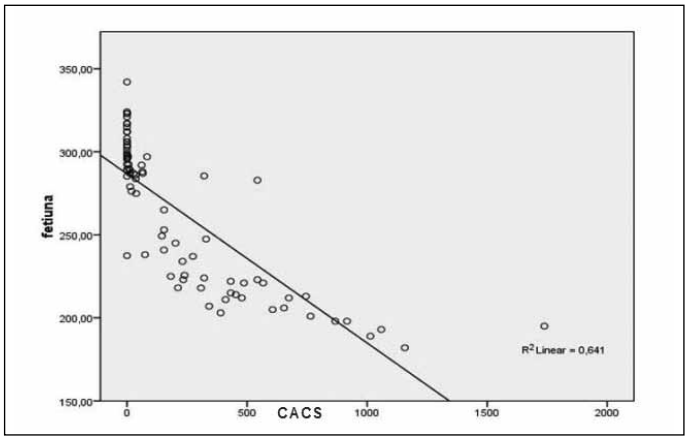

Figure 1: *The relationship between CACS and fetuin-A in ESRD patients*

According to CACS groups, there were no differences in gender, BMI, Ca, P, CaxP product, PTH and serum albumin levels in PD patients (Table 2). CACS was found to be positively correlated with age, dialysis vintage, serum LDL levels and duration of hypertension (r=0.449, p=0.012; r=0.393, p=0.006; r=0.413, p=0.006, r=0.388, p=0.02, respectively).

In HD patients, according to CACS groups, there were no differences in gender, duration of hypertension, BMI, Ca, P, CaxP product, PTH and serum albumin and LDL levels . CACS was found to be significantly associated with age and dialysis vintage (r=0.447, p=0.0001; r=0.549, p=0.002, respectively) in HD patients.

Relationship between CACS, CRP, TNF-α, IL-6, and Fetuin-A Levels of ESRD Patients

There was a negative correlation between CACS and fetuin-A in ESRD patients (r=-0.91, p<0.0001, Figure 1).

In PD patients, there were no differences in terms of TNF-α, IL-6 and CRP levels between patients according to CACS groups (Table 2).Serum fetuin-A levels were found to be significantly lower in group 2 HD patients compared to group 1 (292.2±16.9, 221.8±19.6, p<0.0001, respectively). In the bivariate correlation, there was no correlation between CACS and TNF-α, IL-6 and CRP in PD patients (Table 4). However, serum fetuin-A levels were found to be significantly correlated with CACS in these patients (r=-0.95, p<0.0001).

In HD patients, there were also no differences in terms of TNF-α, IL-6 and CRP levels between patients according to CACS groups (Table 3). We also found a statistically significant difference between group 1 and group 2 HD patients in terms

Table III: Demographic characteristics and biochemical parameters of HD patients according to Coronary Artery Calcification Scores

Parameter	CACS GROUP 1 (n=17) (mean±SD) (median) (IQR)	CACS GROUP 2 (n=17) (mean±SD) (median) (IQR)	P value
Age (years)	42.2±13.5	53.3±8.1	0.007
Dialysis vintage (years)	3.0±2.0	7.35±5.3	0.003
BMI (kg/m^2)	25.2±4.9	28.0±5.7	0.13
Calcium (mg/dL)	9.6±0.5	9.6±1.3	0.98
Phosphorus (mg/dL)	5.2±1.7	5.1±1.3	0.83
PTH (pg/mL)	234 (330)	270(392)	0.49
Albumin (g/dL)	4.1±0.3	4.2±0.3	0.62
CRP (mg/L)	7.5 (6)	13(16)	0.10
IL-6 (pg/mL)	18.1(17)	16.9(16)	0.85
TNF-α (pg/mL)	0.08(0.01)	0.08(0.07)	0.81
Fetuin-A (ng/ml)	303.8±22.6	234.2±38.3	<0.0001

PTH; parathyroid hormone **SD;** Standard Deviation, **IL;** Interleukin, **TNF;** Tumor necrosis factor, **CRP;** C reactive protein, **BMI:** Body Mass Index, **CACS;** coronary artery calcification score.

Table IV: Linear relationship between CACS, fetuin-A and inflammation parameters in PD patients.

Parameters	**r**	**p**
CRP (mg/L)	0.18	0.23
IL-6 (pg/mL)	0.10	0.49
TNF-α (pg/mL)	0.11	0.26
Fetuin-A (ng/ml)	-0.95	<0.0001

IL; Interleukin, **TNF;** Tumor necrosis factor, **CRP;** C reactive protein, **CACS;** coronary artery calcification score

Table V: Linear relationship between CACS, fetuin-A and inflammation parameters in HD patients.

Parameters	**r**	**p value**
CRP (mg/L)	0.12	0.50
IL-6 (pg/mL)	0.002	0.99
TNF-α (pg/mL)	0.16	0.36
Fetuin-A (ng/ml)	-0.86	<0.0001

IL; Interleukin, **TNF;** Tumor necrosis factor, **CRP;** C reactive protein, **CACS;** coronary artery calcification score

of serum fetuin-A levels (303.8±22.6, 234.2±38.3, p<0.0001, respectively). In the bivariate correlation, there was no correlation between CACS and TNF-α, IL-6 and CRP in HD patients (Table 5). Fetuin-A levels were also found to be significantly correlated with CACS in these patients (r=-0.86, p<0.0001).

CONCLUSION

The main findings of this cross-sectional study were as follows; a) CACS were found to be positively associated with advanced age, dialysis vintage and negatively associated with fetuin-A levels in both PD and HD patients, b) There was no correlation between inflammation markers including TNF-α, CRP, IL-6 and CACS in PD and HD patients, c) There was a positive correlation between duration of hypertension and CACS in PD and ESRD patients, d) LDL levels and CACS were found to be positively correlated in PD and ESRD patients, e) PD patients had higher inflammation markers including TNF-α and IL-6 compared to HD patients.

Cardiovascular calcification or progression of calcification were identified as independent risk predictors for cardiovascular and all-cause mortality (12). Age was the most consistent risk factor for severe or progressive calcification, while diabetes, time on dialysis, male sex, high serum intact PTH and/or alkaline phosphatase levels, inflammation (C-reactive protein levels), calcium intake, hyperphosphataemia and increased calcium x phosphate product were identified in some but not in all studies (10-11, 13). In the present study, age and dialysis vintage were found to be predictors of CACS in both PD and HD patients. These findings could be attributed to increased plaque burden and inflammation with aging.

Fetuin-A is responsible for approximately half of the precipitation inhibitory properties within the extracellular space. In humans, serum fetuin-A levels are found to be significantly reduced in dialysis patients. Fetuin-A deficiency was also found to be a cardiovascular mortality and vascular calcification predictor in dialysis patients (14-16). In the present study, we

found a negative correlation between CACS and fetuin-A in PD and HD patients. Both PD and HD patients with low CACS had significantly high fetuin-A levels and vice versa. These results are consistent with results obtained from these studies.

In the present study, we found that PD patients had higher IL-6 and TNF- α levels than HD patients. Deschamps-Latscha et al (17) demonstrated that the concentrations of several cytokines are elevated in patients with uremia, independently of the patients baseline status, whether it is the pre-dialysis stage, hemodialysis or peritoneal dialysis. In the past, inflammation was much more seen in hemodialysis patients especially secondary to frequently use of bioincompatible dialyser membranes (18) and impure dialysate (19). In our study, we used biocompatible dialyser membranes and ultrapure dialysate. This can explain why PD patients had higher inflammatory levels than HD patients.

Inflammation is a significant risk factor for cardiovascular events and mortality in both in general and ESRD population (20). Inflammation may also facilitate CAC via affecting some circulating factors such as fetuin-A (21). However, we could not find any relationship between CACS and inflammation parameters including TNF-α, CRP, and IL-6 in PD and HD patients. This result was consistent with others (11, 22). Thus, beyond the effect of inflammation, the role of serum fetuin-A levels in vascular calcification may be far more complex than previously thought (23).

Hypertensive patients were found to be more prone to atherosclerosis and vascular calcification (24). Jensky et al. (25) recently showed that different measures of BP are associated with significant calcification in multiple vascular beds and these associations vary with age. Our results are also consistent with previous studies and we also demonstrated that there was a positive correlation between duration of hypertension and CACS in PD and ESRD patients.

Increased vascular calcification (VC) and progression of VC have been linked to hyperlipidemia in some studies (26-27). Our results were in accordance with these study results. We also found that LDL levels and CACS were found to be positively correlated in PD and ESRD patients. This relationship may be affected by inflammation and nutrition of ESRD patients.

Our study has some limitations; for example, the sample size was relatively small. Since this is not a prospective controlled study we can not draw cause and effect relations from our findings. Lastly, 25-OH Vit D levels were found to be associated with vascular calcification in previous studies. Unfortunately, we did not measure the 25-OH Vit D levels of our patients.

In conclusion, we showed an inverse relationship between fetuin-A and CACS in patients with ESRD both receiving hemodialysis and peritoneal dialysis. Further experimental and clinical studies are needed to define exact relationship between factors that induce and inhibit vascular calcification in this population.

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