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Original Research Article

Correlation of Clinical Effects with Levels of Fetuin-A, FGF-23 and intact Parathyroid in Peritoneal Dialysis Patients

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Abstract

Objective: We aimed to demonstrate the clinical effects of fetuin–A, fibroblast growth factor-23 and intact parathyroid on the risk factors for metabolic disorders and cardiovascular diseases in peritoneal dialysis patients.
Materials and Method: A total of 41 patients who had undergone peritoneal dialysis therapy were included in the study. The study groups were divided into two groups according to intact parathyroid levels, which were below and above 72 pg/ml. Serum levels of fetuin-A, fibroblast growth factor-23, biochemical parameters and carotid intima media thickness were measured in both the groups. Echocardiography was performed.
Result: Mean fetuin-A levels were not found to be lower and no statistically significant difference was determined between the two groups. No correlations were demonstrated between the levels of fetuin-A and the risk factors for cardiovascular diseases and biochemical parameters. Mean fibroblast growth factor-23 levels were significantly higher. No statistically significant difference was observed in the levels of fibroblast growth factor-23 between the groups. No correlation was determined between the levels of fibroblast growth factor-23 and the risk factors for cardiovascular diseases and biochemical parameters, except LDL-cholesterol. A significant negative correlation was found between the levels of fibroblast growth factor-23 and LDL-cholesterol.
Conclusion: No unfavorable effects of serum fetuin-A and fibroblast growth factor-23 levels on cardiovascular morbidity were found. Dialysis adequacy, duration of dialysis, used treatment and different mechanisms may be the cause of changes in clinical effects and levels of fetuin-A and fibroblast growth factor-23 in dialysis patients.
Keywords: Cardiovascular disease, fetuin-A, fibroblast growth factor, peritoneal dialysis

1.Introduction

Cardiovascular diseases are accepted as the most frequent and important cause of morbidity and mortality at every stage of chronic kidney diseases**.** It has been reported that inflammation, oxidative stress, endothelial dysfunction and vascular calcification may contribute to the development of cardiovascular disease in chronic kidney diseases.

It is known that vascular calcification may play an important role in increased cardiovascular morbidity and mortality at every stage of chronic kidney disease. Currently, the mechanism of the calcification process has yet to be clarified. It is known that there are many calcification inhibitors [fetuin-A (or alpha 2-Heremans-Schmid glycoprotein, AHSG), matrixGla - protein (MGP), osteoprotegerin (OPG), osteopontin (OPN), bone morphogenetic proteins (BMPs), and inorganic pyrophosphate (PPi)] in circulation[1].

Fetuin-A is an important calcification inhibitor in multifunctional glycoprotein naturaly produced in the liver. The results of clinical studies have suggested that fetuin-A deficiency might be associated with vascular calcification in chronic kidney patients and dialysis patients[2][3]. In

addition, fetuin-A contributes to the development of the inflammation process, and it may also help to diagnosis many diseases, including metabolic disorders[2]. In recent years, it has been thought that FGF-23 might have an impact on the progression of renal dysfunction and cardiovascular mortality, and might even be a sensitive marker [4].

FGF-23, which is secreted by osteoblasts, might be elevated due to decreased renal clearance in chronic kidney disease. FGF-23 has been shown to be an effective hormone in the regulation of the serum levels of phosphorus (P) through the metabolism of vitamin D[1-3]. FGF-23 has been defined as a phosphaturic hormone. Also, it has an important role in the pathogenesis of secondary hyperparathyroidism in chronic kidney diseases[5][6]. It has been shown that FGF-23 levels increase in the early stages of chronic kidney disease and before the serum levels of P are elevated. Many studies have shown that there might be the relationship between increased serum levels of FGF-23 and the increased risk of cardiovascular diseases, such as endothelial dysfunction and arterial stiffness, at every stage of chronic kidney disease[7][8]. However, the clinical effects of elevated levels of serum FGF 23 in dialysis patients are not clear[9]. Our aim was to show the effects of fetuin-A and FGF-23 on cardiovascular disease risk factors and biochemical parameters, according to the different levels of intact parathyroid in peritoneal dialysis patients.

2. Materials and Methods

A total of 41 (female/male: 32/9) patients were treated and followed-up at the same clinic, with a mean age of 47.4±14.4 years. Those who were receiving peritoneal dialysis replacement therapy were included in this study. Informed consent was obtained from all participants and the protocol was approved by the Ethics Committee of the Istanbul University School of Medicine.

Patients were excluded from the study who had inadequate dialysis and who did not have ideal dry body weight, those with duration of dialysis of less than one year and patients with active infections (respiratory tract infections, urinary tract infections or diabetic foot) during the study, the presence of chronic inflammatory disorder history (such as rheumatoid arthritis and systemic lupus erythematosus), the presence of known ischemic heart disease and those with a diagnosis of malignity. The demographic and clinical characteristics (age, gender, BMI, mean arterial blood pressure, existence of diabetes mellitus), dialysis adequacy and the treatments of patients were recorded. The daily urine output of the patients included in the study was less than 100-200 cc. Therefore, urine output was not evaluated in the patients. Venous blood samples were collected from all the patients following a period of 12 hours of fasting. In all patients hemoglobin, albumin, uric acid, C-reactive protein (CRP), low-density lipoprotein (LDL) - cholesterol, high-density lipoprotein (HDL) - cholesterol, Ca, P, intact parathyroid (iPTH) and fetuin-A and FGF-23 levels were measured. The mean values of daily elemental Ca and active vitamin D therapies were recorded and the amounts received over the previous 6 months were calculated in all patients. In order to evaluate the existence of cardiovascular disease risk factors, echocardiography was performed by the same cardiologist, using the same device. All patients were evaluated for the existence of left ventricular hypertrophy and ejection fraction. The presence of arrhythmia was evaluated by electrocardiogram (ECG). Carotid intima media thickness was measured by the same radiologist, using the same ultrasound device.

Evaluation was undertaken of the correlation between serum fetuin-A and FGF-23 levels, demographic and clinical characteristics and the risk factors for cardiovascular disease in all of the patients. The patient groups were divided into two groups on the basis of the cut-off value for serum PTH levels at 72 pg/ml. The groups were divided as serum PTH levels lower and greater than 72 pg/ml and the correlation between serum fetuin-A and FGF-23 levels and cardiovascular and metabolic parameters was evaluated.

All peritoneal dialysis patients were on continuous ambulatory peritoneal dialysis. The peritoneal dialysis solution contained 1.36%, 2.27%, and 3.86% glucose dialysates and 40 mmol/l lactate and pH 5.2 (range 4.0 to 6.5) (Dianeal; Eczacibasi-Baxter, Istanbul, Turkey). The adequacy of peritoneal dialysis treatment was estimated by measurement of total weekly Kt/V urea by standard methods. Dialysis adequacy was considered to be acceptable at Kt/V > 1.7.

An Erka Perfect Aneroid Sphygmomanometer (MPN: 2374; Germany) was used to measure the patients' arterial blood pressures. The mean arterial pressure (MAP) was calculated using the following equation: MAP = DP+1/3(SP-DP) (DP, diastolic pressure, mmHg; SP, systolic pressure, mmHg). The body mass index (BMI) of patients was calculated using the formula recognized by the World Health organization (WHO): BMI= $(weight)^2$ /$(height)^2$.

An autoanalyzer (Olympus AU 800; Olympus Diagnostica GmbH, Hamburg, Germany) was used for biochemical analyses. CRP was nephelometric

assay calculated (Behring BNII; Dade Behring, Deerfield, IL, USA) (normal range < 5 mg/dl).

iPTH levels were defined using the immunoassay method (Liaison N-tact: DiaSorin Inc., Stillwater, MN) (normal range: 14-72 pg/ml).

A commercial kit (30 Triad South Drive St. Charles, MO 63304, cat. No: E63501-1), based on the sandwich enzyme-linked immunosorbent assay (ELISA) principle was used to define the levels of fetuin-A. The normal range of fetuin-A was considered to be 15-1008 ng/ml.

A commercial kit based on the sandwich ELISA principle was used to determine plasma levels of FGF-23 (C-Term) (Immunotopics Inc., San Clemente, CA, 92673. cat. No:60-6100, USA). The normal range was accepted as 400-500 RU/ml.Echocardiogram was performed by a single cardiologist, in order to evaluate the existence of left ventricular hypertrophy,ejection fraction and valvular calcification in the patients. An ultrasound device was used with an A probe of 2.5-2 with a Hewlett Packard Sonos 2500 (Sonos 2500, United States). ECG was obtained using the same device (Edan-SE 1200 Express ECG, United States) and evaluated by the same physician.

Carotid intima media thickness was measured. The evaluation was performed by the same radiologist using a General Electric Logiq ultrasound device (LOGİQ e ultrasound device, United States). A segment of 1 cm, not involving atherosclerotic plaque, was defined at 2 cm, proximal to the bulb of the common carotid artery, and intima media thickness was measured.

Hand radiographs of the patients were taken using a SmithHeimann brand standard X-ray device and evaluated by a single radiologist. Hand graphics were studied through the horizontal line running over the metacarpal bones, and the existing linear calcifications were found. Phleboliths were excluded.

2.1 Statistical Analysis

Student's t-test was used for the comparisons of continuous variables with normal distribution, and the Mann Whitney U test was used for comparison of continuous variables without normal distribution.The relationship between fetuin-A and FGF-23 levels and the cardiovascular disease risk factors were investigated using Pearson's r and Spearman's rho correlation analysis. Data were expressed as mean±standard deviation. A p value of <0.05 level was considered to be statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA; version 16.0) for Windows.

3. Results

The chronic kidney disease etiologies of peritoneal dialysis patients included in the study were evaluated. The etiology of kidney failure was not known in 9 (21.95%) patients who received peritoneal dialysis replacement therapy, because their kidney function loss was detected in the late period (they were not treated in the nephrology polyclinic and had stage V CKD at the time of diagnosis) (Table 1).

Since it was an important risk factor for cardiovascular disease, the existence of diabetes mellitus type 2 was recorded. The relationships of the demographic features and clinical findings with the serum levels of fetuin–A and FGF-23 were compared in peritoneal dialysis patients, who were treated at the same clinic, and no statistically significant correlation was found (Table 1).

The patients were divided into two groups by accepting a cut-off value for serum iPTH levels of 72 pg/mL. The demographic features and clinical findings of the patients were not found to be statistically significantly different (Table 2).

The patients were divided into two groups by accepting a cut-off value for serum iPTH levels of 72 pg/mL. The correlation between mineral metabolism and the serum levels of fetuin-A and FGF-23 was evaluated (Table 3).The levels of FGF-23 were found to be higher in all the patients. No correlation was determined between the levels of FGF-23 and mineral metabolism (p=0.309) (Table 3).The levels of fetuin-A were not found to be lower in any of the patients. No correlation was determined between the levels of fetuin-A and mineral metabolism (p= 0.236) (Table 3).CaxP product was observed to be higher in the presence of high serum levels of iPTH. The number of calcified plaques and the thickness of the intima-media of the carotid artery were found to be increased in the patients with low serum levels of iPTH (p=0.023) (Table 3).The relationship of FGF-23 and fetuin-A and iPTH with cardiovascular disease risk factors was compared in peritoneal dialysis patients (Table 4)

No correlation was determined between the levels of FGF-23 and cardiovascular disease risk parameters, except LDL-cholesterol (Table 4). A significant negative correlation was found between levels of FGF-23 and LDL-cholesterol (p=0,033, r=-0,334; Table 4).No correlation was determined between fetuin-A levels and cardiovascular disease risk parameters (Table 4).

Table 1: The relationship between demographic features and clinical findings according to the levels of fetuin-A and fibroblast growth factor -23 in peritoneal dialysis patients

Variables	Findings (n=41)	r	p
Age (years)	47.4±14.4	0.034	0.835
Female/Male	32/9	0.055	0.734
BMI (kg/m^2)	25.8±5.2	0.005	0.977
MAP (mmHg)	97.8±12.9	-0.168	0.295
Etiology of chronic renal failure (Diabetic/Non-diabetic)	7/34	0.074	0.647
Time of dialysis (month)	70.2±42.8	0.267	0.091
Kt/V urea (weekly)	1.93±0.21	0.165	0.302
Fetuin-A (ng/ml)	419.2 ±108.3	-	-
FGF-23 (RU/ml)	2743.2±2322.9	-	-

BMI, body mass index; MAP, mean arterial pressure; Kt, urea clearance; (V) volume of distribution of urea; FGF-23, fibroblast growth factor 23.

Table 2: Demographic and clinical features of peritoneal dialysis patients with low and high serum levels of intact parathyroid

Variables	High serum levels of intact parathyroid (n=31)	Low serum levels of intact parathyroid levels (n=10)	p
Age (years)	46.1±14.9	51.6±12.8	0.323
Female/Male	24/7	8/2	0.864
Etiology of chronic kidney failure (diabetic/non-diabetic)	4/27	3/7	0.212
Body mass index (kg/m^2)	25.4±5.1	26.9±5.9	0.345
Time on dialysis (month)	68.9	74.7±51.7	0.988
Kt/V urea (weekly)	1.93±0.22	1.94±0.18	0.852

Data are presented as mean±standard deviation or number/number, where appropriate.
Kt, urea clearance; V, volume of distribution of urea.

Table 3: Correlation between fetuin-A and fibroblast growth factor-23 and calcification and inflammation risk factors according to the levels of intact parathyroid

Variables	High serum levels of intact parathyroid (n=31)	Low serum levels of intact parathyroid levels (n=10)	p
Fetuin-A (ng/ml)	448.4±109.9	390.0±106.8	0.236
FGF-23 (RU/ml)	2962.1±2396.2	2064.7±2041.2	0.309
Hemoglobin (g/dl)	10.9±1.3	11.0±1.5	0.077
Albumin (g/dl)	3.04±0.52	3.03±0.50	0.976
Uric acid (mg/dl)	5.2±0.7	5.4±1.1	0.670
LDL-cholesterol (mg/dl)	101.4±35.6	109.4±43.7	0.844
HDL-cholesterol (mg/ dl)	42.8±10.9	39.5±10.3	0.466
C-reactive protein (mg/dl)	17.2±26.8	8.4±5.8	0.648
Calcium (mg/dl)	9.0±0.7	8.5±0.7	0.120
Phosphorus (mg/dl)	5.3±1.1	4.2±1.1	0.045
Calcium x Phosphorus (mg/dl)	48.0±9.2	38.9±10.7	0.019
Intact parathyroid hormone (pg/ml)	627.0±445.1	42.0±30.0	-
Average dose of elemental calcium (mg/day)	1250.0±1412.7	650.0±444.0	0.358
Average dose of active vitamin D (µg/day)	1.5±0.8	0	-
Calcified plaque on carotid artery	12	8	0.023
Carotid intima-media thickness assessed by Doppler ultrasonography (mm)	0.69±0.14	0.82±0.21	0.330
Metastatic calcification on hand X-ray	12	2	0.278
Presence of bone cysts on hand X-ray	7	6	0.069
Valvular calcification	28	9	0.689

Data are presented as mean±standard deviation or number, where appropriate.

Table 4: Relationship between fibroblast growth factor-23 and Fetuin-A, and intact parathyroid and risk factors for cardiovascular disease in peritoneal dialysis patients

Variables	Findings (n= 41)	p	r	p	r
FGF-23 (RU/ml)	2743.2± 2322.9	-	-	0.707	0.061
Fetuin-A (ng/ ml)	434.1± 110.8	0.707	0.061	-	-
Hemoglobin (g/dl)	11.0± 1.3	0.077	-0.279	0.314	0.161
Calcium (mg/dl)	8.9± 0.7	0.473	0.115	0.913	0.018
Phosphorus (mg/dl)	5.0± 1.1	0.672	-0.068	0.361	0.146
CaxP (mg / dl)	45.8± 1.0	0.110	0.253	0.295	0.168
Intact parathyroid hormone (pg/ml)	505.3± 444.4	0.215	0.198	0.156	0.226
CRP (mg/dl)	15.0± 23.7	0.102	0.259	0.238	-0.189
Albumin (g/ dl)	3.0± 0.5	0.106	-0.256	0.514	0.105
Uric acid (mg/ dl)	5.3± 0.8	0.909	0.018	0.565	-0.093
LDL- cholesterol (mg/ dl)	103.4± 37.3	0.033	- 0.334	0.206	0.202
HDL- cholesterol (mg/ dl)	42.0± 10.8	0.698	0.062	0.799	-0.041
Metastatic calcification on hand X-ray	14	0.329	0.156	0.685	-0.065
Valvular calcification	37	0.462	0.118	0.277	0.174
Calcified plaque on carotid artery	20	0.368	0.144	0.403	-0.134
Left ventricular hypertrophy	15	0.111	-0.253	0.464	-0.118
Carotid intima-media thickness assessed by Doppler ultrasonography (mm)	0.73± 0.17	0.827	-0.035	0.397	-0.136

FGF-23: fibroblast growth factor, Ca: Calcium, P: Phosphorus, CRP: C- reactive protein.
p: the significance of the relationship between FGF-23 and the variables, r: the correlation coefficient between FGF-23 and the variables, p: the significance of the relationship between fetuin-A and variables, r: the correlation coefficient between fetuin-A and variables.

4. Discussion

Since vascular calcification is a precursor of atherosclerosis, vascular calcification is important in the development of cardiovascular disease in chronic kidney patients. Some studies report that the prevalence of calcification can be 60% in peritoneal dialysis patients and 60-100% in hemodialysis patients[10].

Fetuin-A is known as a calcification inhibitor which contributes to the development of inflammation process and atherosclerosis. Currently fetuin-A is used as biological biomarker in the diagnosis of many diseases (metabolic disorders, insulin resistance)[11]. However, the results of many studies support the notion that serum fetuin-A levels could be helpful in the estimation of cardiovascular disease, that may develop especially in dialysis patients.The serum levels of FGF-23 effect on mineral metabolism in the patients with chronic renal disease and it has also been shown in many studies that increased of the serum levels of FGF-23 associated with left ventricular hypertrophy, endothelial dysfunction, dyslipidemia and metabolic syndrome.[4] Recently the relationship between elevated serum levels of FGF-23 with vascular calcification, cardiovascular disease and increased risk of mortality has been shown in the chronic kidney patients who have a glomerular filtration of 60 ml/min/1.73 $m^2$and below.

We aimed to show that fetuin-A, FGF-23 and intact parathyroid could be used as important and sensitive biomarkers for estimating the development of cardiovascular disease, and to demonstrate the relationship between fetuin-A, FGF-23 and intact parathyroid and cardiovascular disease risk factors. Serum levels of fetuin-A were not decreased in peritoneal dialysis patients and no relationship was found between serum levels of fetuin-A and biochemical parameters, in our study. However, it was shown that fetuin-A did not affect cardiovascular disease risk factors.

In a few studies, the relationship was compared between the serum levels of fetuin-A and atherosclerotic risk factors and biochemical parameters, and an inverse association was found between fetuin-A and serum levels of CRP, but no relationship was found between the serum levels of fetuin-A and the other biochemical parameters. In consequence of these studies, it was shown that fetuin-A could be an important predictive biomarker in determination of the risk factors for cardiovascular disease in dialysis patients[12][13].

The results of these studies show that the clinical effects of fetuin-A in dialysis patients could be altered by the dialysis therapies and treatments used (active D vitamin, calcium-containing phosphate binding agents etc.) and the etiology of chronic kidney disease. In the studies performed by Mehrotra *et al*., the authors showed that increase of the serum levels of fetuin-A could associate with the risk of development of cardiovascular disease in the patients with stage 3- 4 chronic kidney disease and diabetic nephropathy[14]. The results of many studies

suggest that serum levels of fetuin-A could increase through the existence of diabetic nephropathy, metabolic syndrome, and insulin resistance in the chronic kidney patients and dialysis patients. In our study, decreased serum fetuin-A levels were not shown. This result could be explained by the increased risk of obesity, insulin resistance or metabolic syndrome etc. in the patients with peritoneal dialysis. The results of some studies demonstrate that the possibility of development of metabolic syndrome could increase due to use of glucose-based dialysis solutions, and weight gain may occur in the peritoneal dialysis replacement therapy[15].

It was suggested that dialysis adequacy and duration of dialysis, ethnic differences and measurement techniques could affect the behavior and clinical effects of fetuin-A[16]. In our study, we found that there was no association between the serum levels and clinical effects of fetuin-A.Increases in serum levels of FGF-23 could cause a 2-4 fold increase in calcification risk, and the association was shown with cardiovascular disease in the chronic kidney patients and dialysis patients[17].

Use of active vitamin D could have a positive effect on the prevention of cardiovascular disease in the chronic kidney patients and dialysis patients. Moreover, many studies have demonstrated that the clinical effects of FGF-23 could be changed by using active D vitamin in the dialysis patients. In our study, we found that serum levels of FGF23 increased in the peritoneal dialysis patients, but we determined no association between increased serum levels of FGF-23 and the risk factors for cardiovascular disease and biochemical parameters, except LDL-cholesterol. Also an inverse association was found between FGF-23 and LDL-cholesterol. This result might be caused by regular use of active vitamin D therapy and lipid lowering therapies in the peritoneal dialysis patients. Similarly, Ashikaga *et al.* determined an inverse correlation between the increased of serum levels of FGF-23 and LDL-cholesterol in the hemodialysis patients, and they interpreted that this condition could be due to the effects of lipid lowering treatments[18].

In our study; it was found that the ratio of calcified plaque in the carotid artery increased when the intact parathyroid was <72 pg/ml in the peritoneal dialysis patients. The results of our study supported the association between the levels of intact parathyroid and risk factors for cardiovascular disease and calcification. Currently, the relationship is known between calcification and the levels of intact parathyroid and risk of cardiovascular disease in the dialysis patients. Risk for the development of calcification and cardiovascular disease increases when the serum levels of intact parathyroid are below 65 pg/ml and above 480 pg/ml in the dialysis patients[19].

We believe that the correlation between the serum levels of fetuin-A, FGF-23 and intact parathyroid and biochemical parameters should not be evaluated alone, and the etiology of the disease, the treatments used, the duration of dialysis, dialysis adequacy, content of dialysis solutions used during dialysis therapies, and measurement techniques should be considered to evaluate the clinical effects of FGF-23 in the dialysis patients more correctly. In summary: the clinical effects of fetuin-A and FGF-23 could be independent from levels of serum in the peritoneal dialysis patients.

5. Conclusion

Fetuin-A and FGF-23 effect on mineral metabolism and contribute to the development of inflammation, atherosclerosis, calcification, mineral metabolism disorders and metabolic disorders in the dialysis patients. Understanding of the mechanism of the action of fetuin-A and FGF-23 may contribute to the prevention of development of inflammation processes, which is one of the most important causes of morbidity and mortality in the dialysis patients. Therefore, a contribution may be provided to the life expectancy of dialysis patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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