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Brief Report

Potential Correlation Between Circulating Fetuin-A and Pentraxin-3 With Biochemical Parameters of Calcification in Hemodialysis Patients

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Abstract

Background: The strong correlation between vascular calcification and cardiovascular risk, which is a major cause of mortality in hemodialysis (HD) patients, has been well established. Fetuin-A is an inhibitor of vascular calcification, and pentraxin 3 (PTX3) is produced at the site of inflammation, which is associated with cardiovascular disease (CVD). The main purpose of this study was evaluating the correlation between fetuin-A and PTX3with some biochemical parameters effective upon vascular calcification in HD patients.

Methods: We included 84 HD patients and 84 healthy controls matched for age, gender, and body mass index (BMI) in this study. Blood samples were drawn from all subjects and the serum levels of creatinine, urea, albumin, calcium (Ca), phosphorus (P), low-density lipoprotein cholesterol (LDL-C), parathyroid hormone, fetuin-A, high sensitive C-reactive protein, and PTX3were measured by biochemical methods.

Results: We found that the serum levels of PTX3, C-reactive protein (CRP), parathyroid hormone (PTH), Ca, and P in the patient group were significantly higher than the control group but the serum levels of fetuin-A and albumin were significantly lower in the patient group. Also, fetuin-A had a significant correlation with high sensitive CRP (hs-CRP) as well as duration of dialysis. In addition, it was shown that the correlation between PTX3 and PTH was significant only in the patient group.

Conclusion: In this study, increased PTX3 and decreased fetuin-A levels were observed in the HD patients. According to our results, these 2 parameters may potentially serve as suitable markers for inflammation and prediction of vascular complications in these patients.

Keywords: Fetuin-A, Hemodialysis patients, Pentraxin-3

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Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in hemodialysis patients (HD) with a risk 10 to 20 times in patients with end-stage renal disease (ESRD) compared to general population. Vascular calcification is known as a marker of atherosclerosis and arterial calcification in HD patients.[1]

Fetuin-A is a glycoprotein that acts as an inhibitor of vascular calcification and the reduction in its level has been shown during acute inflammation.[2] Pentraxin-3 (PTX3) is an acute phase protein produced in vessels at the site of inflammation by a variety of cell types.[2] Therefore, cross-checking the inflammatory markers such as C-reactive protein (CRP), PTX3 and other associated factors, as well as fetuin-A can be helpful for identification and better treatment of HD patients by controlling the CVD.

Briefly, the purpose of the current study was evaluating fetuin-A as a vascular calcification and atherosclerosis inhibitor factor and its correlation with PTX3 and parathyroid hormone (PTH) as facilitating factors for atherosclerosis, as well as analysis of some blood biochemical parameters effective upon the vascular calcification process in HD patients.

Materials and Methods

Subjects and Blood Samples

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In this case-control study, plasma samples were collected from 84 HD patients and also 84 healthy subjects (as the control group). The ethics committee of North Khorasan University of Medical Sciences approved the study, and written informed consent was obtained from each participant. There was no significant difference between the HD patients and controls in the distribution of sex (*P* value = 0.602, chi-square test), age (*P* value = 0.323, independent samples *t* test), and BMI (*P* value = 0.673, independent samples *t* test). HD patients with active infection, liver complication, diabetes mellitus, cardiovascular problems and hormone therapy with PTH, as well as smokers were excluded from this study. The controls had a normal level of serum urea and creatinine, and were assessed for the health of liver, kidney, and any diseases or infections. Also, the blood pressure of all subjects was controlled, and those with abnormal blood pressure were replaced with subjects having normal blood pressure. A 10 mL blood sample was taken from each patient and all subjects in the control group after 12 hours of overnight fasting. Then, the sera were separated and supernatant serum was quickly frozen at -70°C until analysis.

Measurement of Vascular Calcification Parameters (Biochemical Analysis)

Serum levels of creatinine, urea, albumin, total calcium, phosphorus (P), and low-density lipoprotein (LDL) were measured by colorimetric methods using commercially available kits (Pars Azmoon Co) according to the manufacturer's instructions on Biolis 24i premium automated clinical analyzer system. Intact parathyroid hormone (iPTH, Biomerica, California, USA), Fetuin-A (Glory Science, Co., Ltd, China), high sensitive C-reactive protein (hsCRP, Monobined, California, USA) and pentraxin-3 (Cusabio biotech Co., LTD, Wuhan, China) were measured by enzyme-linked immunosorbent assay (ELISA) using ELISA plate reader (STATFAX 2100, USA).

Statistical Analysis

Statistical analysis was performed using SPSS version 21. To compare the 2 groups, Chi-square test and independent *t* tests were used. In addition, to compare groups, multivariate analysis of covariance, adjusted for sex, age, and body mass index (BMI), was used and its effect sizes were presented. Also, to investigate the correlation between biochemical parameters in the two groups, Pearson correlation coefficients were calculated.

Results

A total of 168 participants were studied in the current study. The mean age was 46.98 ± 18.62 and 46.82 ± 18.55 years in case and control groups, respectively, and average BMI was 22.88 ± 5.63 in the case group and 23.31 ± 5.16 in the control group. There was no significant difference between the two groups in terms of gender (*P* = 0.602), age (*P* = 0.968), and BMI (*P* = 0.710). Significant differences between urea and creatinine levels in patients and healthy individuals indicate acute kidney problems (*P* < 0.001; Figure 1).

We observed that the average levels of serum fetuin-A and albumin in the patient group were significantly lower than the control group. In addition, the average levels of serum PTX3, CRP, iPTH, and coefficient of Ca x P product were significantly higher in the patient group than the control group (*P* ≤ 0.001) (Table 1).

Also, we found that the serum level of fetuin-A had a significant correlation with hsCRP in both patient (*P* = 0.06) and control groups (*P* = 0.07). We also demonstrated a significant correlation between serum fetuin-A and serum PTH (*P* = 0.03), as well as between fetuin-A and duration of dialysis (*P* = 0.04) only in the patient group. Interestingly, we observed that the relationship between serum fetuin-A and PTH in the control group was similar to the patient group, whereas this relationship was not significant (*P* = 0.107). Moreover, a significant relationship was observed with respect to PTX-3 and hsCRP in both patient (*P* = 0.04) and control (*P* = 0.02) groups; however, PTX-3 and PTH had a significant relationship only in patient group (*P* = 0.04). Finally, we showed that the serum level of LDL had a significant correlation with Ca levels in both patient and control groups (*P* = 0.02 and *P* < 0.001, respectively);

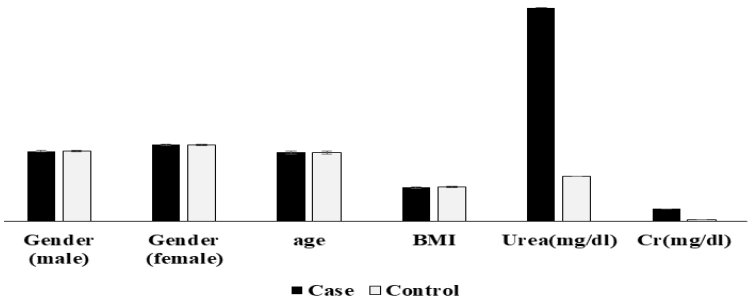

Figure 1. Distribution of Mean Age, Body Mass Index, Blood Urea, and Creatinine in Both Groups.

Table 1. Comparison of Vascular Calcification Index Between Hemodialysis Patients and Healthy Persons

	Patient[a]	Control[a]	*P* Value	Two groups comparison, Adjusted for Age, Sex, and BMI	
				P Value	Effect Size
Fetuin (ng/mL)	226.24 ±171.73	633.05 ±335.14	<0.001	<0.001	0.379
Pentraxin-3 (ng/mL)	6.2 ±3.1	1.98 ±1.2	<0.001	<0.001	0.297
hsCRP (mg/L)	8.96 ±10.88	3.17 ±3.45	0.001	0.001	0.126
iPTH (pg/dL)	597.87 ±690.99	50.07 ±44.04	<0.001	<0.001	0.251
Alb (g/dL)	3.94 ±0.32	4.16 ±0.27	0.011	0.032	0.081
Ca (mg/dL)	9.42 ±0.99	9.71 ±0.62	0.098	0.087	0.035
P (mg/dL)	5.55 ±1.38	4.29 ±0.68	<0.001	<0.001	0.283
Ca ×P	52.27 ±14.34	41.82 ±7.84	<0.001	<0.001	0.186
LDL-C (mg/dL)	69.14 ±20.26	83.77 ±24.12	0.003	0.002	0.112

[a] Mean ± SD.

nevertheless, we observed that the relationship between LDL with Ca × P product was only significant in the control group ($P = 0.008$).

Discussion

Vascular calcification and inflammation are common complications in patients with chronic kidney disease (CKD), which increases the risk of cardiovascular problems and mortality in these patients.[1] Fetuin-A is a negative acute phase reactant. It has been shown that lower levels of fetuin-A can be related to MIA (malnutrition, inflammation, and atherosclerosis) syndrome and increase the risk of mortality.[3] In the present study, we observed that the mean level of fetuin-A was significantly lower in the patient group and a significant negative correlation was found between this protein with other main vascular calcification factors including LDL, albumin, PTH, calcium, and calcium-phosphate product (Ca × P). According to our findings, the correlation between fetuin-A, PTX3, and other related vascular calcification factors in HD patients can be related to vascular calcification and mortality in these patients, which was in line with the results of other studies.[4] In comparison of the 2 groups, it was observed that PTH and fetuin-A correlation were negative in both groups, and this correlation was not dependent upon the presence of disease. The anti-inflammatory feature of serum fetuin-A was first shown by Ombrello et al in 2001.[5] Sezer et al showed that fetuin-A is a novel prognostic marker for ischemic stroke.[6] Moe and colleagues revealed that vascular calcification can be inhibited by adding fetuin-A to vascular smooth muscle cells.[7] In general, the role of fetuin-A in vascular calcification is probably much more complex than previously thought.

As a sensitive marker of inflammation, long PTX3 can be rapidly produced in the site of inflammation (up to 200-800 ng/mL) in response to inflammatory signals such as Interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α) and oxidized LDL by a variety of cells such as macrophages, fibroblast cells, endothelial cells and neutrophils; however, PTX3 level is very low (<2 ng/mL) in normal conditions.[6] The HD process can induce inflammation; therefore, it can be noted that the presence of vascular calcification and inflammation can increase the risk of cardiovascular problems and mortality in these patients.[8]

In the present study, an increased level of PTX3 was observed in HD patients. Previous studies have also shown increased levels of PTX3 in patients with HD, as well as increased incidence of CVD in chronic HD patients.[9] The reasons for increased PTX3 levels in HD patients can be low grade inflammatory response due to incompatibility of dialysis membrane tissue, contamination of dialysis and endothelial damage, which results in the production of PTX3 from various immune cells, especially vascular endothelial cells.[9]

PTX3 can also be produced from oxidized LDL from vascular endothelial cells, which indicates the direct interference of inflammatory factors on blood vessels. Thus, PTX3 can be strongly expressed in vascular cells and atherosclerotic vascular inflammatory cells, as well as in patients with heart failure.[10] In addition, Sjöberg et al introduced PTX3 as a sensitive initial marker of inflammation associated with HD.[9] Therefore, it can be concluded that PTX3 is a more reliable and sensitive biomarker for inflammation compared to CRP.

Cardiovascular complications have been noted as the major cause of mortality in HD patients. Increased PTX-3 and decreased fetuin-A levels were observed in HD patients in the present study. Taken together, our findings indicated that the plasma levels of PTX3 and fetuin-A may have potential value in vascular calcification detection and might serve as suitable biomarkers for CVD in HD patients. PTX-3 along with serum fetuin-A levels can be considered as suitable predictive factors for prevention of cardiovascular heart problems in HD patients.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

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