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Is Pentraxin-3 a Stronger Marker of Inflammation than C-Reactive Protein in Chronic Kidney Disease?

Pentraksin-3 Kronik Böbrek Hastalığında C-Reaktif Proteinden Daha Güçlü Bir Enflamasyon Belirteci midir?

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ABSTRACT

OBJECTIVE: Pentraxin-3 (PTX-3) is elevated in uremic patients and related with albuminuria and endothelial dysfunction. We aimed to clarify the relationship of PTX-3 with inflammatory markers (hsCRP and IL-6) in patients with chronic kidney disease (CKD).

MATERIAL and METHODS: The study was performed with four groups: hemodialysis (HD) group (23 patients), peritoneal dialysis (PD) group (25 patients), predialysis group (stage-4 CKD, 25 patients) and the healthy control group (18 individuals). GFR was estimated by the MDRD formula. PTX-3, IL-6, fibrinogen, hsCRP levels, glucose, urea, creatinine, uric acid, parathyroid hormone, albumin, LDL cholesterol, HDL cholesterol, triglyceride, ferritin, and hemoglobin were studied from the serum and whole blood samples.

RESULTS: PTX-3 levels were highest in the HD group followed by the PD group, pre-dialysis group and control group (3.58±4.29, 2.15±2.75, 1.29±2.36, 0.73±0.96 ng/ml, respectively). IL-6 levels were highest in the PD group followed by the HD, predialysis and control groups. There was no difference between groups regarding hsCRP levels. There was no correlation of PTX-3 with hsCRP, while it was correlated with IL-6. IL-6 was the only determinant of PTX-3 level independent of the study groups and vice versa.

CONCLUSION: Uremic patients have elevated PTX-3 levels and it is strongly correlated with IL-6. PTX-3 may be superior to CRP as an inflammation marker in the uremic population.

KEY WORDS: C-reactive protein, Inflammation, Interleukin-6, Pentraxin-3, Uremia

ÖZ

AMAÇ: Pentraksin-3 (PTX-3) düzeyleri üremik hastalarda yüksektir ve hem albüminüri ile hem de endotelyal disfonksiyonla ilişkilidir. Bu çalışmada, kronik böbrek hastalığı (KBH) olan hastalarda PTX-3'ün enflamatuvar belirteçler (hsCRP ve IL-6) ile arasındaki ilişkiyi araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışma 4 grupta yapıldı: hemodiyaliz (HD) grubu (23 hasta), periton diyalizi (PD) grubu (25 hasta), prediyaliz grubu (evre-4 KBH, 25 hasta) ve sağlıklı kontrol grubu (18 kişi). Glomerüler filtrasyon hızı (GFH), MDRD formülüne göre hesaplandı. Serum ve tam kan örneklerinden; PTX-3, IL-6, fibrinojen, hsCRP düzeyleri, glukoz, üre, kreatinin, ürik asit, paratiroid hormonu, albümin, LDL kolesterol, HDL kolesterol, trigliserid, ferritin, hemoglobin düzeyleri çalışıldı.

BULGULAR: PTX-3 düzeyi HD grubunda en yüksek idi, onu PD, prediyaliz ve kontrol grupları izledi (sırasıyla 3,58±4,29, 2,15±2,75, 1,29±2,36, 0,73±0,96 ng/ml). IL-6 seviyeleri PD grubunda en yüksek idi, ardından HD grubu, prediyaliz ve kontrol grupları izledi. hsCRP düzeylerinde gruplar arasında anlamlı bir fark yoktu. PTX-3 ile IL-6 arasında anlamlı korelasyon izlenirken, PTX-3 ile hsCRP arasında ilişki saptanmadı. IL-6 çok değişkenli analizde PTX-3'ün tek bağımsız belirleyicisi olarak bulunurken, IL-6'nın tek bağımsız belirleyicisi de PTX-3 idi.

SONUÇ: Üremik hastalarda PTX-3 düzeyleri yükselmiştir ve IL-6 ile kuvvetli ilişki göstermektedir. PTX-3, üremik popülasyonda bir enflamasyon belirteci olarak hsCRP'den üstün olabilir.

ANAHTAR SÖZCÜKLER: CRP, Enflamasyon, İnterlökin-6, Pentraksin-3, Üremi

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INTRODUCTION

Chronic kidney disease (CKD) is associated with increased cardiovascular morbidity and mortality even in the early stages of the disease (1). It has been shown that innate and acquired immune system has a role in atherogenesis and hence in cardiovascular risk (2, 3). The pro-inflammatory/anti-inflammatory phenotype is disturbed on the pro-inflammatory side in CKD patients (4). The immune cells located at the atherosclerotic sites produce many cytokines such as interleukins (IL), tumor necrosis factor, interferon-α and platelet derived growth factor (5). Fibrinogen, IL-6, IL-18, myeloperoxidase, C-reactive protein (CRP) and hyaluronan levels have been reported to be elevated in uremic patients (6-10). IL-6 has pro-inflammatory effects, promotes the production of proteins that have roles in the early stages on inflammation, and activates peripheral mononuclear cells and differentiation of B cells.

Recent studies propose IL–6 as a more valuable marker than CRP in the determination of the degree of inflammation and cardiovascular risk (11). On the other hand, there is no consensus about their role in the diagnosis of these diseases because one reason for elevated serum levels is the decreased renal elimination in uremic patients. There are contradicting reports about the correlation between the clinical-radiological findings and inflammatory markers in CKD patients (12). Additionally, CRP and homocystein have been claimed recently to be anti-atherogenic (13-15).

Pentraxins are a family of pattern recognition proteins; and are divided into two groups. CRP and amyloid-p protein account for the short pentraxins and pentraxin-3 (PTX-3) is the prototype of the long pentraxins. PTX-3 is produced by vascular endothelial cells, smooth muscle cells, macrophages and adipose tissue in response to pro-inflammatory signals and stimulation of Toll-like receptors (16). PTX-3 expression has been shown in renal proximal tubular cells, renal fibroblasts and mesangial cells (17). It has a molecular weight of 40.6 kDa, and is present in the circulation in the form of multimers. It facilitates opsonization; it activates the complement system and leads to killing of opsonized cells and microbes (18). It is regarded as an independent marker of disease activity due to its synthesis directly at the site of inflammation. Uremic patients have high PTX-3 levels, which are related with increased mortality independent of CRP (6, 19); it has a more stable course than CRP (20). The relationship of PTX-3 with CRP has been reported to be weak in some studies (13, 21). Suliman et al found that PTX-3, albuminuria and endothelial dysfunction are all interrelated (22). Herein we aimed to clarify the relationship of PTX-3 with CRP and IL-6 in patients in various stages of CKD.

MATERIAL and METHODS

The study was a cross-sectional study involving four groups: the hemodialysis (HD) group consisted of HD patients between the ages of 18 and 80 years with a duration of HD of at least three months and Kt/V and urea reduction ratio above the target level described by international guidelines. The peritoneal dialysis (PD) group consisted of PD patients between the age of 18 and 80 years with duration of PD of at least three months and Kt/V values over target levels as described by international guidelines. The modality of PD was not a criterion for inclusion. The predialysis (stage 4 CKD) group consisted of patients between the age of 18 and 80 years with a stable estimated glomerular filtration rate (eGFR) less than 30 ml/min. The control group consisted of nonuremic volunteers between the age of 18 and 80 years without any infectious or inflammatory disease within the last three months.

The study was initiated after the approval of the local ethics committee of our hospital on 13.04.2009. An informed consent form was signed by all the participants. Patients with diabetic nephropathy, acute infectious/inflammatory disease, acute ischemic vascular disease, chronic inflammation, chronic liver disease and those with venous catheters as vascular access were excluded from the study.

Demographic parameters (age, gender, body mass index-BMI-), systolic and diastolic blood pressures, primary kidney disease and comorbidities (hypertension, morphologically proven coronary artery disease, peripheral artery disease) and the duration of dialysis were recorded. GFR was estimated by the MDRD formula. Blood samples were obtained from HD patients before the midweek session; and from PD patients after 12 hours of fasting with their abdomen left empty the night before. PTX-3, IL-6, fibrinogen, hsCRP as well as blood glucose, urea, creatinine, uric acid, parathyroid hormone (PTH), albumin, LDL cholesterol, HDL cholesterol, triglyceride, ferritin, and hemoglobin (Hb) levels were measured from the serum and whole blood samples. PTX-3 and IL-6 levels were measured by the ELISA (enzyme linked immunosorbent assay) technique.

Statistical analysis was performed using SPSS (for Windows 15.0, standard version) software. Quantitative data were presented as mean value±standard deviation (SD). The Student t-test and Mann-Whitney U test were used in the comparison of two groups, as appropriate. One-way analysis of variance (ANOVA) or Kruskal Wallis-H variance analysis was appropriately used in the comparison of more than two groups. Bonferroni correction was applied to alpha significance level. Pearson or Spearman's (rho) correlation test was used in the correlation analysis between quantitative parameters. $P<0.05$ was accepted as significant. The parameters found to be related with PTX-3 in univariate analyses were examined by multivariate analysis using the "stepwise" method.

RESULTS

Ninety one individuals were included in the study (23, 25 and 25 patients in the HD, PD and predialysis groups respectively; and 18 nonuremic subjects as the control group). The demographic

and clinical data of the patients are presented in Table I. The mean ages in the predialysis and control groups were higher than in the PD group (p=0.025 and p=0.023, respectively). Groups were similar regarding gender.

Patients in the predialysis, PD and control groups had higher BMI values than the HD group (p=0.003, p=0.011 and p<0.001 respectively). The duration of dialysis was longer in the HD group (56.71±41.97 months vs. 32.12±19.67 months, p=0.046). There was no difference between the groups regarding primary kidney disease (p=0.553). There were two patients in the HD group with radiologically proven coronary artery disease (p=0.09); while no patient had documented peripheral vascular disease (p=0.325).

The biochemical and hematological parameters and the comparisons between each group are presented in Table II.

Table I: Demographic and clinical parameters.

		HD group (n=23)	PD group (n=25)	Predialysis group (n=25)	Control group (n=18)
Age (years)		48.2±11.9	45.7±12.5	55.3±16.2	54.9±8.3
Female/male ratio		9/14	16/9	14/11	10/8
BMI (kg/m^2)		23.16±3.65	28.13±7.18	26.47±3,67	27.96±4.5
Systolic BP(mmHg)		119±10	136±28	133±14	115±10
Diastolic BP(mmHg)		73±7	81±13	81.60±12	71±8
Primary kidney disease	Unknown	8	8	8	-
	Nephrosclerosis	6	4	5	-
	Chronic glomerulonephritis	4	5	5	-
	Chronic Pyelonephritis	3	2	3	-
	ADPCKD	1	5	1	-
	Amyloidosis	1	1	3	-

BMI: Body mass index; **BP:** Blood pressure; **ADPCKD:** Autosomal dominant polycystic kidney disease.

Table II: Biochemical and hematological parameters (mean ± standard deviation).

	HD group	PD group	Predialysis group	Control group	p
Glucose (mg/dl)	101±25	99±23	112±40	100±9	NS
Urea (mg/dl)	108±34	99±19	108±37	31±10	<0.001[a,b,c]
Creatinine (mg/dl)	7.3±1.9	7.9±2.6	3.5±1.5	0.8±0.1	<0.001[a,b,c, d, e]
Uric acid (mg/dl)	5.3±1.6	5.8±1.4	7.6±1.5	5.0±1.3	<0.001[a,d,e]; 0.047[c]
eGFR (ml/min)	-	4.1±4.2	21.7±7.5	104±16	<0.001[a,c,e]
Albumin (g/dl)	4.1±0.4	3.6±0.3	3.8±0.8	4.2±0.3	0.037[a]; <0.001[c]
PTH (pg/ml)	581±523	548±445	286±156	67±44	<0.001[a,b,c,d], 0.013[e]
LDL cholesterol (mg/dl)	107±35	112±35	130±56	137±30	0.007[b]; <0.001[c]
HDL cholesterol(mg/dl)	38±11	44±15	43±10	49±13	0.006[b]; <0.001[c]
Triglyceride (mg/dl)	214±134	202±223	149±71	114±57	0.001[b]; 0.03[c] ; 0.027[d]
Hb (g/dl)	11.8±1.2	10.5±1.7	11.3±2.0	13.5±1.1	<0.001[a,b,c] ; 0.004[f]
Ferritin (ng/ml)	764±415	431±912	186±173	81±55	<0.001[b,c,d,f]; 0.028[e]

NS: Not significant, **[a]:** Predialysis-control, **[b]:** HD-control, **[c]:** PD-control, **[d]:** Predialysis-HD, **[e]:** Predialysis-PD, **[f]:** HD-PD.

Levels of inflammatory markers are presented in Table III. PTX-3 levels were highest in the HD group followed by the PD, predialysis and the control groups. PTX-3 levels in the HD and PD groups were statistically significantly higher than the control group. Predialysis patients had significantly lower PTX-3 levels compared with the HD group. IL-6 levels were highest in the PD group followed by the HD and predialysis groups. Patients in the HD and PD groups had significantly higher IL-6 levels than those in the control group. There was no difference between the hsCRP levels of the patient groups. Fibrinogen levels were similar in predialysis and control groups but was lower than the values reported in HD and PD groups.

The analysis was repeated after dividing the subjects into three groups as the dialysis group (PD and HD groups), predialysis group and control group (Table IV). Uremic patients (dialysis and predialysis) had higher levels of PTX-3, IL-6, hsCRP and fibrinogen levels than the control group. All these inflammatory markers were significantly different between the dialysis group and control group. Additionally, the predialysis group had higher fibrinogen levels than the control group; and the dialysis group had a higher mean hsCRP level than the predialysis group.

In univariate analysis; PTX-3 was found to be positively correlated with serum creatinine (r=0.241, p=0.024), PTH (r=0.232, p=0.038) and IL-6 (r=0.784, p<0.001) (Figure 1); while it was negatively correlated with eGFR (r=-0.247, p=0.02). There was no correlation of PTX-3 with CRP (r=-0.018, p=0.873) and fibrinogen (r=0.239, p=0.052). IL-6 was correlated positively with fibrinogen (r=0.270, p=0.027); and negatively with albumin (r=-0.295, p=0.015). When correlation analysis was repeated excluding the control group, significant correlations were found between IL-6 and PTX-3 (r=0.790; p<0.001). There was no relation of PTX-3 and IL-6 levels with CRP levels.

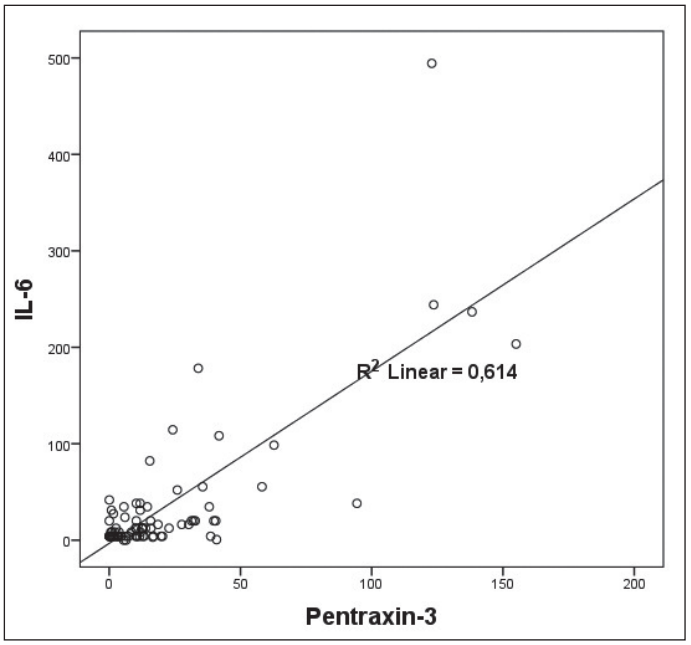

Figure 1: *The figure showing correlation between IL-6 and PTX-3*

Table III: Levels of inflammatory markers.

	HD group	PD group	Predialysis group	Control group	p
IL-6 (pg/ml)	40±64	47±102	24±49	16±28	0.046[b]; 0.008[c]
PTX-3 (ng/ml)	3.58±4.29	2.15±2.75	1.29±2.36	0.73±0.96	<0.001[b]; 0.034[c]; 0.006[d]
hsCRP (mg/l)	0.97±0.79	1.02±1.29	1.06±0.82	0.47±0.59	0.024[a]
Fibrinogen (mg/dl)	436±112	568±110	401±89	347±104	<0.001[c,e]; 0.001[f]; 0.012[b]

NS: Not significant, **[a]:** Predialysis-control, **[b]:** HD-control, **[c]:** PD-control, **[d]:** Predialysis-HD, **[e]:** Predialysis-PD, **[f]:** HD-PD,

Table IV: Levels of inflammatory markers when HD and PD patients are considered as the dialysis group.

	Dialysis group	Predialysis group	Control group	p
IL-6 (pg/ml)	42.2±85.6	24.0±49.2	16.0±28.3	0,019[a]
PTX-3 (ng/ml)	2.81±3.57	1.29±2.36	0.73±0.96	0,001[a]
hsCRP (mg/l)	0.99±1.07	1.06±0.82	0.47±0.59	0.016[a], 0,005[c]
Fibrinogen (mg/dl)	505±128	401±89	347±104	0.001[a], 0,015[b]

NS: Not significant, **[a]:** Dialysis-control, **[b]:** Predialysis-dialysis, **[c]:** Predialysis-control.

Multivariate analysis was conducted using the parameters with p values less than 0.1 in univariate analysis with the addition of age, gender, study group, blood pressures and creatinine values. IL-6 was the only determinant of PTX-3 level independent of the study groups and vice versa ($p<0.001$). Fibrinogen and hsCRP levels did not have a significant effect on PTX-3 levels. The factors affecting hsCRP were creatinine ($p=0.004$) and fibrinogen ($p<0.001$) levels and the study group ($p=0.049$).

DISCUSSION

CKD has been shown to be associated with chronic low-grade inflammation together with increased cardiovascular risk in many studies. Many biochemical markers detected those at risk but were not accepted as a surrogate marker for diagnosis and follow-up. IL-6 plays a central role in the onset of inflammation. We aimed to evaluate the inflammatory status of patients in different stages of CKD and to study the correlation of PTX-3 with other inflammatory markers, especially CRP. We found out that there was a strong relationship between IL-6 and PTX-3. Furthermore, PTX-3 was the only parameter that showed a relationship with IL-6 in multivariate analyses regardless of renal function status. There was no correlation between IL-6 and CRP level in univariate analyses.

PTX-3 is one of the markers found to be elevated in CKD with levels increasing with the degree of renal impairment and the duration of dialysis (6). It was reported to be related with endothelial dysfunction, malnutrition, proteinuria and increased mortality rate (22, 24, 25). In our study, the PTX-3 level also increased with an increasing degree of renal impairment. The lower levels in the PD group compared with the HD group, although statistically not significant, may be explained by the absence of the potential reactions to dialysis membranes, lack of potential infections of vascular access and residual renal function that is sustained for longer periods in PD treatment. The higher residual renal function detected in the PD patients of the study group is consistent with this fact. Otherwise, longer duration of dialysis may be another possible explanation for higher PTX-3 levels. The higher mean age in the HD group may also be suspected as a cause but the linear regression analysis revealed no association between age and PTX-3 levels. The primary explanation should be the difference in IL-6 levels. Subclinical infections not determined by usual methods may be another factor influencing the levels.

There are some studies supporting our results. Tong et al (6) found that the relation between IL-6 and PTX-3 was stronger than that between IL-6 and CRP. It has been shown by previous studies that PTX-3 has a more stable course (20). It was shown to be weakly correlated with CRP (13, 21), while more closely related with IL-6 (6). IL-6 has been found to be correlated with PTX-3 strongly and to also stimulate its synthesis (26). IL-6 has been reported to be more strongly associated with increased cardiovascular risk (11). Hence these data combined with our findings may lead to the idea that PTX-3 is superior to CRP as a marker of inflammation in patients with uremia.

The difference in PTX-3 levels between PD and HD groups, although statistically nonsignificant, may also be caused by the difference in the clearance of PTX-3, which has a molecular weight of 40.6 kDa. Better residual renal function and higher clearance of high molecular weight substances in PD may cause higher PTX-3 clearance although there is no clear knowledge about the route of clearance (27). The strong correlation between IL-6 and PTX-3 may be a finding supporting the use of PTX-3 as a reliable marker of inflammation.

CRP, known as a marker of inflammation and cardiovascular risk, was found to be correlated with PTX-3 in some studies while not in others (21). The relationship of PTX-3 with mortality was shown in a study in which no correlation with CRP levels was detected in patients in the intensive care unit (21). However, prospective studies are warranted to show the power of PTX-3 as a cardiovascular prognostic factor.

The major defect of the present study is the cross-sectional nature with non-homogeneous groups. However, we included age, gender and study group in multivariate analyses to eliminate the probable effect of these parameters.

CONCLUSION

PTX-3 is superior to CRP as an inflammation marker and strongly correlates with IL-6 in the uremic population. This may be a finding supporting the use of PTX-3 as a reliable marker of inflammation.

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