The Importance of Serum CXCL-16 Levels in Patients with Grade III-V Chronic Kidney Disease

Kronik Böbrek Hastalığı Evre 3-5 Hastalarda Serum CXCL-16 Düzeylerinin Önemi

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ABSTRACT

OBJECTIVE: A number of studies report CXCL-16 as a new chemokine that mediates the collection of leukocytes and adhesion of macrophages to coronary artery smooth muscle cells, and stimulates atherosclerosis. However, there is a limited number of studies evaluating the levels of CXCL-16 in patients with Chronic Kidney Disease (CKD). We aimed to determine the serum level of CXCL-16 in patients with CKD and to clarify the relationship between CXCL-16 and hsCRP and glomerular filtration.

MATERIAL and METHODS: Two hundred and twenty two patients with CKD were included in the study. The patients were divided into 3 groups according to the glomerular filtration rate (GFR) in accordance with the K/DOQI guideline. Patients with primary glomerulonephritis or tubulointerstitial nephritis, heart failure, or hepatic disease, patients who used immunosuppressive or cytotoxic drugs and renin-angiotensin system blockers were excluded from the study.

RESULTS: There was a positive correlation between the grade of renal failure and CXCL-16 levels and a negative correlation between the GFR and CXCL-16 levels ($p<0.001$).There was a positive correlation between CXCL-16 and hsCRP ($p <0.001$). Decreased GFR, increased PTH and hsCRP levels, and the presence of DM and HT were associated with serum CXCL-16 elevation on multiple regression analysis.

CONCLUSION: The results indicated that decreased GFR levels were associated with increased hsCRP and CXCL-16 levels in chronic kidney disease.

KEY WORDS: Chronic kidney disease, Chemokine ligand-16, Glomerular filtration rate, Endothelial dysfunction, Cardiovascular diseases

ÖZ

AMAÇ: Yeni bir kemokin olarak kemokin ligand-16 (CXCL-16) lökositlerin toplanmasına, makrofajların koroner arter düz kas hücrelerine adezyonuna aracılık ettiği ve aterosklerozu hızlandırdığı birçok çalışmayla gösterilmiştir. Kronik böbrek hastalığı grubunda CXCL-16 düzeyleri ile ilgili fazla çalışma yoktur. Amacımız, kronik böbrek hastalığında serum CXCL-16 düzeyleri ile hsCRP, glomerüler filtrasyon değeri arasındaki ilişkiyi değerlendirmektir.

GEREÇ ve YÖNTEMLER: Kronik böbrek hastalıklı 222 hasta çalışmaya alınmıştır. Hastalar K/DOQI kılavuzunda belirlenen glomerüler filtrasyon değerine (GFD) göre 3 gruba ayrılmıştır. Çalışmaya alınan tüm kişilerden venöz kan örneği alınmış ve detaylı metabolik panele ilaveten CXCL-16 ve hsCRP için de kan örnekleri alınmıştır. Aktif glomerülonefrit veya tubulointerstisiyel nefritli hastalar, kalp yetmezliği ve hepatik hastalığı nedeniyle takip edilen hastalar, immünosupresif veya sitotoksik ilaç kullananlar ile renin anjiyotensin sistemini bloke eden ilaç kullanan hastalar çalışmaya alınmamıştır.

BULGULAR: Kronik böbrek hastalığında progresyon oldukça yani hasta evre 3'ten evre 5'e kadar ilerledikçe serum CXCL-16 değerleri artmış, GFD ile CXCL-16 düzeyleri arasında negatif bir korelâsyon saptanmıştır (r=-0,457, p<0,001). Kronik böbrek hastalığı ilerledikçe endotel fonksiyonu da giderek bozulmuş ve bunun bir göstergesi olarak hsCRP değerleri de artmıştır (p<0,001). CXCL-16 ile hsCRP arasında da pozitif bir korelasyon saptanmıştır (r=0,359 p<0,001). Yapılan çoklu regresyon analizinde serum CXCL-16 artışı ile GFD azalma, DM ve HT varlığı, yüksek PTH, hsCRP ve PTH değerleri ilişkili bulunmuştur.

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SONUÇ: Sonuçlar kronik böbrek hastalığında GFD azalmasına hsCRP artışının yanında serum CXCL-16 artışının da eşlik ettiğini göstermiştir. Framingham risk faktörleri ile ilişkili olan bu kemokinin böbrek hastalığının progresyonunda ve komplikasyonların gelişiminde önemli bir rol oynadığı düşünülmektedir.

ANAHTAR SÖZCÜKLER: Kronik böbrek hastalığı, Kemokin ligand-16, Glomerüler filtrasyon değeri, Endotelyal disfonksiyon, Kardiyovasküler hastalıklar

INTRODUCTION

Chronic kidney disease (CKD) is a syndrome characterized by chronic, progressive and irreversible nephron loss that presents for many reasons (1). It is difficult to know the real incidence and prevalence of chronic kidney disease. The first phase of chronic kidney disease is mostly asymptomatic. The prevalence of chronic kidney disease has been calculated as 15.7% in a study from Turkey (2). There is an important correlation between mortality and morbidity in chronic kidney disease and cardiovascular disease. Cardiovascular complications increase in parallel with decreased glomerular filtration rate in this patient group (3-5).

Cardiovascular complications other than an impaired lipid profile are seen at high rates in this patient group due to the chronic inflammation and increased oxidative stress (6,7). Many studies have verified that oxidative lipoproteins play an important role in inflammation and oxidative stress that play a part in the progression of chronic kidney disease (8,9). Oxidized low-density lipoproteins (oxLDL) are known to accumulate both in the circulatory and renal interstitium (10,11). Oxidized low-density lipoproteins are potent atherogenic lipoproteins and are recognized by scavenger receptors. The scavenger receptor activity has been shown to be related to chemokine ligand-16 (CXCL-16) in vitro (12-14). As a soluble protein, CXCL-16 accelerates the migration of effector T cells to atherosclerotic lesions and plays a key role in the development of proatherogenic inflammation (15-17). CXCL-16 is a chemokine belonging to the CXC family that is synthesized as a transmembrane molecule in many cells and particularly in macrophages, fibroblasts, and podocytes (18).

Evaluation of the renal biopsy samples membranous nephropathy patients has revealed increased CXCL-16 expression in the podocytes, together with increased oxLDL levels and decreased ADAM 10 (a disintegrin and metalloproteinase domain). It was determined that when proinflammatory cytokines such as TNF alpha and interferon gama swing increased, CXCL-16 levels of proinflammatory cytokines were also increased in human podocytes (19-21,33).

The number of studies on CXCL-16 levels in the chronic kidney disease group is inadequate. Our aim was to evaluate the relationship between serum CXCL-levels and impaired laboratory markers and especially glomerular filtration rate in chronic kidney disease.

MATERIAL and METHODS

Patients with chronic kidney disease diagnosed using the Kidney Disease Outcomes Quality Initiative guidelines criteria and who satisfied the study criteria included in the study. Patients with primary glomerulonephritis and patients who were being followed-up for congestive heart failure and hepatic disease were excluded from the study. Patients with known active infection were also excluded from the study. Patients who used immunosuppressive or cytotoxic drugs, or renin angiotensin system blockers were again excluded. Patients who took part in the study were divided into subgroups according to their glomerular filtration rate (GFR). GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula and 3 subgroups were created according to GFR .

These subgroups were as follows: Group 1 with GFR 30-59 ml/min (73 patients), Group 2 with GFR 15-29 ml/min (73 patients), and Group 3 with GFR <15 ml/min (75 patients). Characteristics according to the distribution of the phase of renal failure in the patient groups are presented in Table I**.**

Clinical Data and Laboratory Results

Glucose, total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol were studied with the enzymatic colorimetric method while low-density lipoprotein (LDL) cholesterol was estimated with Friedewald's Formula. Complete blood count and other routine biochemical examinations were performed with the autoanalyzer. The subjects were informed and consent was obtained. The subjects' venous blood samples were then drawn. The serum and plasma were separated and stored at -80 ^{o}C. Blood samples for serum CXCL-16 levels were studied with the Enzyme-Linked ImmunoSorbent Assay (ELISA) measurement method (Human CXCL16 Quantikine ELISA kit/ R&D system) at the same time and at a single center.

Statistical Analysis

The one-sample Kolmogorov-Smirnov test was used to determine the distribution characteristics of the variables. The variances were properly tested with the One-Way Analysis of Variance (ANOVA) and Chi Square Tests to determine the presence of a significant difference between the 3 subgroups of patients with renal failure, . The Dunnet test was used as a Post Hoc test in ANOVA to determine the parameters that showed a statistical discrepancy. The correlation of variables with each

other was evaluated with the Pearson test. For multivariate analysis, the GFR, hsCRP and CXCL-16 levels were included in the model and evaluated with the stepwise linear regression method. p<0.05 was accepted statistically significant. Identifiers were given as a mean ± standard deviation.

RESULTS

The characteristics of the patient groups according to laboratory values are presented in Table II. We had divided the patients into 3 subgroups according to GFR and the difference between groups in terms of GFR was found to be statistically significant as expected. As renal failure progressed, a decrease was detected in hemoglobin, hematocrit and serum albumin values and the difference between the groups was statistically significant (p<0.05). The CXCL-16 value increased parallel to the decrease in the glomerular filtration rate (Table II). Comparison of all 3 phases led to an estimated p value of <0.001. A negative correlation was detected between the GFR and the CXCL-16 level (r=-0.457, p<0.001). (Figure 1).

The level of the inflammation marker high-sensitive C-reactive protein (hsCRP) showed a statistically significant

Table I: Demographic data of the patients.

	Stage 3 (30-59 ml/min)	Stage 4 (15-29 ml/min)	Stage 5 (<15 ml/min)	p
Age	52±13	53±12	52±12	0.86
Gender (M/F)	29/44	34/39	31/45	0.66/0.65
Diabetes mellitus (+/-)	16/57	56/17	59/17	0.98/0.94
Hypertension (+/-)	13/60	9/64	10/66	0.59/0.60
Smoking (+/-)	32/41	28/45	37/39	0.44/0.45

Table II: Characteristics of the studied group and the levels of selected biochemical markers.

Variables	Stage III (N:73)	Stage IV (N:73)	Stage V (N:76)	p
eGFR (estimated glomerular filtration rate) (ml/min/1.73 m²)	43.7±8.9	23.8±5.7	8.1±4.3	<0.001
Proteinuria (mg/day)	2106.1±1183.3	1744.3±1032	2104.5±1223,9	0.09
Systolic blood pressure (mmHg)	133.5±11.1	133.9±11.4	134.5±10.1	0.84
Diastolic blood pressure (mmHg)	85.4±4.4	84.3±5.5	84.3±5.2	0.32
Plasma insulin (IU/ml)	7.5±1.8	7.0±2.0	7.3±1.8	0.38
Plasma glucose (mg/dl)	102.1±39.1	110.9±47.5	98.2±29.7	0.13
HOMA-IR	1.9±1.1	1.9±0.9	1.8±0.9	0.80
Total cholesterol (mg/dl)	201.5±19.9	197.5±19.1	195.6±19.1	0.17
Serum triglyceride (mg/dl)	146.3±15.1	145.5±13.7	140.1±19.8	0.05
LDL cholesterol (mg/dl)	125.7±15.4	129.1±14.3	122.3±21.3	0.06
HDL cholesterol (mg/dl)	41.4±5.3	41.6±6.1	42.4±7.2	0.55
Hemoglobin (g/dl)	11.9±2.1	11.8±2.4	10.7±1.7	<0.001
Hematocrit (%)	35.7±5.9	35.6±6.6	33.7±4.5	0.05
Serum albumin (g/dl)	4.2±0.4	4±0.30	3.9±0.3	<0.001
Calcium (mg/dl)	8.4±0.6	8.1±0.4	8.1±0.5	<0.001
Phosphate (mg/dl)	4.8±1.1	5.6±1.2	6.5±1.6	<0.001
Parathyroid hormone (pg/ml)	151.1±39.7	171.5±36.7	257.6±60.6	<0.001
hsCRP (high sensitivity C-reactive protein)	14.3±6.5	22.2±5.8	23.9±9.6	<0.001
C-X-C chemokine ligand 16 (ng/mL)	5.1±2.5	6.2±2.8	9.1±3.9	<0.001

increase from the beginning of CKD together with the progression of disease (Table II). A positive correlation was detected between CXCL-16 and hsCRP (p<0.001) (Figure 2).

Correlation analysis was performed for serum CXCL-16 and selected parameters in CKD with Spearman's correlation analysis (Table III). As expected, a negative correlation was found with GFR (p<0.001). We also found a positive correlation between CXCL-16 values and the hemoglobin, hematocrit, plasma insulin and glucose values. Increased plasma glucose and insulin values accompanied by an increase in CXCL-16 values also showed a positive correlation with HOMA-IR (p=0.006) (Table III).

Parameters found to be significant in multiple regression analysis, found by confirming the parameters responsible for increased CXCL-16, are summarized in Table IV. GFR, hsCRP, DM (Diabetes mellitus), HT (Hypertension), LDL-cholesterol, and PTH were found to be responsible for the increase in serum CXCL-16 levels.

Decreased GFR, presence of DM and HT, and increased hsCRP and PTH levels led to increased CXCL-16. No statistically significant relationship was found between the CXCL-16 levels and other parameters of the Framingham Risk Score such as age, smoking and gender.

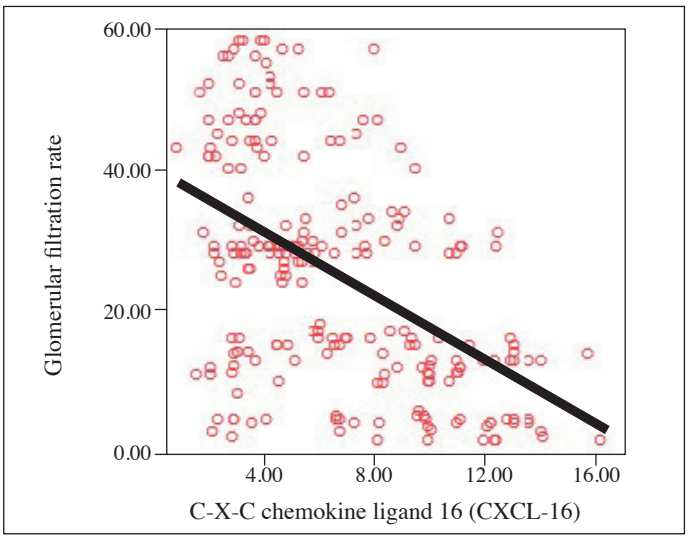

Figure 1: *CXCL-16 levels correlated with GFR.*

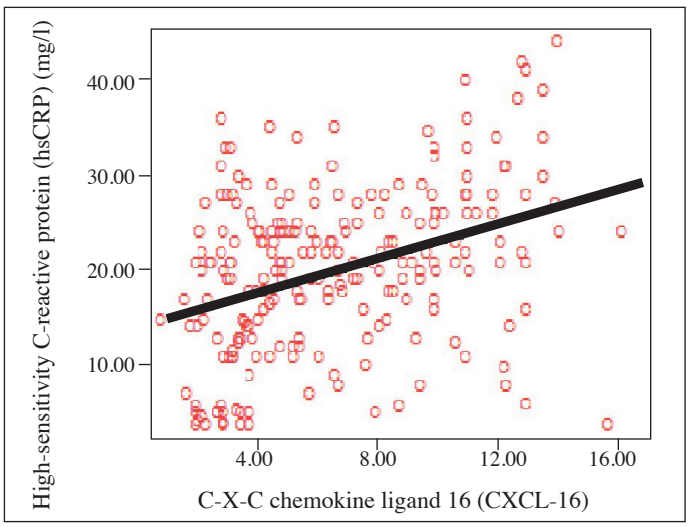

Figure 2: *The relationship between CXCL-16 and hsCRP.*

Table III: Correlations of CXCL16 levels with parameters and biochemical indexes.

Variables	r	p
Age	-0.066	0.327
eGFR (glomerular filtration rate) (ml/min/1.73 m²)	-0.457	<0.001
Serum albumin (g/dl)	-0.145	0.030
Proteinuria (mg/day)	-0.031	0.646
Systolic blood pressure (mmHg)	0.164	0.014
Diastolic blood pressure (mmHg)	-0.036	0.590
Hemoglobin (g/dl)	0.117	0.081
Hematocrit (%)	0.136	0.043
Plasma insulin (IU/ml)	0.056	0.405
Plasma glucose (mg/dl)	0.141	0.036
HOMA-IR	0.184	0.006
Calcium (mg/dl)	-0.154	0.021
Phosphate (mg/dl)	0.310	<0.001
Parathyroid hormone (pg/ml)	0.442	<0.001
hsCRP (high-sensitivity C-reactive protein) (mg/l)	0.359	<0.001

Table IV: Multiple stepwise regression analysis showing variables independently associated with the serum level of CXCL16.

Parameters	Beta	p
eGFR	-0.218	0.04
DM	0.352	<0.001
hs-CRP	0.214	<0.001
PTH	0.194	0.006
HT	0.104	0.041
LDL cholesterol	-0.100	0.048

eGFR: Estimated glomerular filtration rate, **DM:** diabetes mellitus, **hsCRP:** High-sensitivity C-reactive protein, **PTH:** Parathyroid hormone, **HT:** Hypertension

DISCUSSION

Lin et al have reported that CXCL-16 levels increase considerably in chronic kidney disease, similar to our results. The levels were also estimated to be significantly higher than in healthy individuals ($p<0.001$). Evaluation of the study results with multiple stage regression analysis showed plasma CXCL-16 levels to be independently associated with GFR, CRP and adiponectin levels (22). The CXCL-16 level was higher in the CKD group with DM than in the CKD group without DM in this study. The reason could be increased presence of coronary artery disease (CAD) and the close relationship between CAD and CXCL-16, or CXCL-16 could be the reason of the insulin resistance by itself. Further studies are needed to answer this question (22).

Many studies have shown that progression from phase 1 at endothelial dysfunction onset in CKD patients leads to gradually increased CRP and inflammation that reaches a peak in hemodialysis patients (23,24). Studies on the association between CXCL-16 and endothelial dysfunction and atherogenesis are continuing. It has been suggested as a marker for acute coronary syndrome, atherosclerosis and inflammation. CXCL-16 induction has been shown to be inhibited by aspirin, nuclear factor kappa-B inhibition and peroxisome proliferative activated receptor (PPAR) gamma agonists by macrophages in patients (25-28).

The role of CXCL-16 in endocarditis, experimental hepatitis, rectal malignancies and experimental autoimmune encephalomyelitis has been proven but its role in the inflammation in renal failure has not been fully clarified (29-31).

The role of this chemokine was evaluated in rats where anti-GBM disease had been developed. This chemokine significantly blocked the progression of glomerular damage and deposition of monocytes/macrophages both in the acute inflammation phase and an advanced stage of glomerulonephritis (32). Whatever its etiology, renal fibrosis is one of the distinctive feature of chronic kidney disease. Renal interstitial fibrosis is characterized by massive fibroblast activation and overproduction and storage of extracellular matrix, leading to the progressive collapse and destruction of renal parenchyma. The source of these fibroblasts is not known precisely. Recent studies have shown that they might be related to migration from epithelial/endothelial cells to mesenchymal cell and bone marrow source progenitor cells (34). CXCL-16, CXCR6 and fibroblast precursors in tubular epithelial cells and the circulation have been evaluated in the unilateral ureteral obstruction model of renal fibrosis. In mice where CXCL-16 was inactivated, significantly less bone marrow-derived fibroblast precursors were detected in the obstructed kidney. CXCL-16 deletion caused inhibition of myofibroblasts, decreased collagen deposition, and suppression of collagen-1 and fibronectin (34,35).

Evaluation of our results reveals that decreased GFR, the presence of DM, and the elevation of CRP and PTH were responsible for the CXCL-16 increase. There was a positive correlation between CXCL elevation and the presence of Framingham risk factors such as hypertension and LDL cholesterol elevation but a statistically significant relation was not found. Inhibition of CXCL-16 will offer new therapeutic alternatives to prevent both the progression of renal disease and the complications related to renal disease, but more studies on this subject are needed.

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