



## Thioredoxin reductase activity, serum IL6, HsCRP and NT-proBNP levels in patients on dialysis

### Diyaliz hastalarında tiyoredoksin redüktaz aktivitesi, serum IL6, HsCRP ve NT-proBNP seviyeleri

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#### Abstract

**Aim:** Cytokines have a direct stimulating effect on natriuretic peptide secretion. N-terminal probrain type natriuretic peptide (NT-proBNP) is a valuable biomarker for mortality in dialysis patients. The aim of this study was to compare thioredoxin reductase, NT-proBNP, IL6 levels and high sensitive C reactive protein (HsCRP) in peritoneal dialysis (PD), and hemodialysis (HD) patients and investigate relationship among these parameters.

**Material and Methods:** In age and sex matched 30 HD patients, in 30 PD patients and 20 healthy controls, HsCRP, thioredoxin reductase, serum IL6, and NT-proBNP levels were measured.

**Results:** HsCRP, IL6 and NT-proBNP levels in HD and PD patients were significantly higher than in controls ( $p < 0.05$ ). There was no difference according to HsCRP, IL6, and NT-proBNP between HD and PD patients ( $p > 0.05$ ). Thioredoxin reductase was not different in 3 groups ( $p > 0.05$ ). Thioredoxin reductase was not correlated with any studied parameters. HsCRP levels were positively correlated with BMI ( $r: 0.275$ ,  $p: 0.034$ ), IL6 ( $r: 0.633$ ,  $p: 0.000$ ), and NT-proBNP ( $r: 0.277$ ,  $p: 0.032$ ), and negatively correlated with serum albumin levels ( $r: -0.425$ ,  $p: 0.001$ ). Serum IL6 levels were positively correlated with HsCRP ( $r: 0.633$ ,  $p: 0.000$ ), BMI ( $r: 0.775$ ,  $p: 0.034$ ) and negatively correlated with albumin ( $r: -0.342$ ,  $p: 0.007$ ). Serum NT-proBNP levels were negatively correlated with serum albumin ( $r: -0.385$ ,  $p: 0.002$ ), and positively correlated with age ( $r: 0.315$ ,  $p: 0.002$ ), HsCRP ( $r: 0.277$ ,  $p: 0.032$ ), systolic ( $r: 0.421$ ,  $p: 0.001$ ) and mean blood pressure ( $r: 0.311$ ,  $p: 0.015$ ). In multiple regression analyses the predictors of HsCRP were IL6 ( $\beta: 0.677$ ,  $p: 0.000$ ), the predictor of serum IL6 was HsCRP ( $\beta: 0.677$ ,  $p: 0.000$ ). The predictors of serum NT-proBNP levels were serum albumin ( $\beta: -0.416$ ,  $p: 0.000$ ) and mean blood pressure ( $\beta: 0.414$ ,  $p: 0.000$ ).

**Conclusion:** NT-proBNP levels are not related with IL6 levels and thioredoxin reductase in patients on dialysis.

**Keywords:** IL6; Thioredoxin Reductase; NT-Probnp, HsCRP.

#### Öz

**Amaç:** Sitokinler natriüretik peptid sekresyonunda direkt uyarıcı etkiye sahiptir. N terminal pro-beyin tip natriüretik peptid diyaliz hatalarının mortalitesinde önemli bir biyobelirteçtir. Bu çalışmanın amacı peritonel diyaliz(PD) ve hemodializ(HD) hastalarında; tiyoredoksin redüktaz aktivitesi ile NT-proBNP, IL6 ve yüksek duyarlılık C reaktif protein seviyelerini (HsCRP) karşılaştırmak ve aralarındaki ilişkiyi araştırmaktır.

**Gereç ve Yöntemler:** Yaş ve cinsiyet değişkenlerine göre 30 HD, 30 PD ve 20 kontrol sağlıklı denek gruplarına ayrılarak HsCRP, serum IL6, NT-proBNP seviyeleri ile tiyoredoksin redüktaz aktivitesi ölçüldü.

**Sonuç:** HsCRP, serum IL6, NT-proBNP seviyeleri HD ve PD hastalarında kontrol grubuna kıyasla istatistiksel olarak anlamlı derecede yüksek bulundu ( $p < 0,05$ ). HsCRP, IL6, and NT-proBNP düzeyleri bakımından HD ve PD grupları arasında anlamlı fark bulunamamışken ( $p > 0,05$ ), tiyoredoksin redüktaz aktivitesi 3 grupta da fark göstermedi. Ayrıca tiyoredoksin redüktaz aktivitesi çalışmadaki hiçbir parametre ile korelasyon göstermedi. HsCRP; BMI( $r: 0.275$ ,  $p: 0.034$ ), IL6 ( $r: 0.633$ ,  $p: 0.000$ ), NT proBNP ( $r: 0.277$ ,  $p: 0.032$ ) ile pozitif korelasyon gösterirken, serum albumin konsantrasyonu ile negative korelasyon ( $r: -0.425$ ,  $p: 0.001$ ) gösterdi. Serum IL6 seviyeleri HsCRP ( $r: 0.633$ ,  $p: 0.000$ ) ve BMI ( $r: 0.775$ ,  $p: 0.034$ ) ile pozitif, albumin ile negative ( $r: -0.342$ ,  $p: 0.007$ ) korelasyon gösterdi. Serum NT-proBNP seviyeleri ise serum albumini ile negatif; yaş ( $r: 0.315$ ,  $p: 0.002$ ), HsCRP ( $r: 0.277$ ,  $p: 0.032$ ), sistolik ( $r: 0.421$ ,  $p: 0.001$ ) ve ortalama kan basıncı ile ( $r: 0.311$ ,  $p: 0.015$ ) ise pozitif korelasyon gösterdi.

**Anahtar Kelimeler:** IL6; Tiyoredoksin Redüktaz; NT-proBNP, HsCRP.

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## INTRODUCTION

N-terminal probrain type natriuretic peptide (NT-proBNP) has been reported to be a valuable biomarker for predicting cardiac events and mortality in dialysis patients (1,2,3). However, some studies have shown higher BNP values in volume-overloaded dialysis patients without overt cardiac dysfunction (4).

A close relationship between inflammation and cardiovascular mortality and morbidity is well known. High-sensitivity C-reactive protein (hs-CRP) is a diagnostic indicator of systemic inflammation. Interleukin-6 is a proinflammatory cytokine that induce synthesis of CRP in the liver (5). All these biomarkers have been shown to predict cardiovascular complications and mortality in patients with end stage renal disease (ESRD) (6,7).

It is shown that cytokines (particularly TNF-, IL-1, and IL-6) have a direct stimulating effect on cardiac natriuretic peptide secretion independent of other stimuli (8). Chiurciu et al demonstrated an association between BNP and inflammatory cytokines. It was reported that mechanistically, BNP has immunomodulatory activity on macrophages and directly regulates the production of major inflammatory cytokines such as TNF- $\alpha$  (9). A positive feedback mechanism may exist, as TNF- $\alpha$  has been shown to induce secretion of BNP from cardiomyocytes *in vitro* (10,11). An interdependent relationship between BNP and inflammatory cytokines in the progression of cardiac interstitial fibrosis was reported.

The involvement of oxidative stress in the initiation and progression of the inflammatory process is well documented (12). Thioredoxin reductase (TrxR-1) is a redox-active selenoprotein that efficiently regenerates oxidized thioredoxin protein (Trx-1) to its reduced form. Reduced Trx-1 has an antioxidant function because it maintains the reduced state of many proteins (13). Furthermore, TrxR-1 is overexpressed and released during oxidative stress and has been detected in plasma (14). Elevated Trx-1 levels have been found during heart failure (15,16).

The aim of this study was to compare NT-proBNP, IL6, thioredoxin reductase levels and HsCRP of PD and HD patients and age and sex matched healthy controls and to examine the correlation between NT-proBNP, IL6 levels, thioredoxin reductase activity and HsCRP in dialysis patients.

## MATERIALS and METHODS

Age and sex matched 30 HD patients (18 men, 12 women) and 30 PD patients (15 men, 15 women) on dialysis for longer than 2 months and 20 healthy controls (12 men, 8 women) were studied. This study was approved by the institutional ethical committee.

The demographic information and medical history were obtained at baseline by interview and a review of the medical records. The exclusion criteria for the patients were: atrial fibrillation, previous surgical procedures on

the heart, valvular and congenital heart disorders, myocardial ischemic events, pericardial effusion, pulmonary disorders, decompensated liver, and cancer.

Weight, height, systolic and diastolic blood pressure, serum creatinine, albumin, calcium, phosphate, parathyroid hormone (PTH), NT-proBNP, HsCRP, IL6 and thioredoxin levels were measured.

All HD patients received regular dialysis using polysulphan hollow-fiber dialyzer three times per week in sessions lasting 4 hours. The dialysate was bicarbonate buffered and contained 135 mmol/L sodium. All patients on CAPD received four exchanges per day using standard dialysis bags (8 L/day).

Blood pressure was determined using a standard mercury sphygmomanometer and cuffs adapted to arm circumference. The systolic blood pressure was taken as the point of appearance of Korotkoff sounds, and the diastolic blood pressure as the point of disappearance of the sounds. Mean arterial pressure: Diastolic BP + (systolic BP - diastolic BP) $\div$ 3

All blood samples were immediately centrifuged, separated, and stored at - 70 ° C until further analysis. Routine biochemical parameters were performed in the biochemistry department using commercially available kits. Samples designated to be used for the determination of serum IL6, thioredoxin, NT-proBNP levels were collected in tubes containing EDTA.

HsCRP levels were measured using commercially available enzyme-linked immunoassay (ELISA) kit (CUSABIO, CHINA). Serum levels of IL6, were determined with commercial human enzyme linked immunosorbent assay kits (Immundiagnostik AG, Bensheim, Germany). NT-proBNP levels were determined using chemiluminescent immunometric assay (Siemens Healthcare Diagnostics Products Ltd. Llanberis, Gwynedd LLSS 4EL, United Kingdom). Interleukin-6 and TNF- $\alpha$  were measured with high-sensitivity enzyme linked immunoassay (14).

### Statistical Analyses

All results are expressed as mean  $\pm$  SD and range where appropriate. Associations between categorical variables and serum BNP levels were examined by using Pearson's chi square tests. Associations with variables were examined with the use of two-tailed Fisher's exact tests, and with Mann-Whitney rank-sum tests.

## RESULTS

The mean age was 51.7  $\pm$  18.3 years in HD, 50.2  $\pm$  15.4 years in PD and 47.4  $\pm$  11.9 years in controls. Causes of renal failure in CAPD patients were diabetic nephropathy (n=6; 20%), chronic glomerulonephritis (n=6; 20%), hypertensive nephrosclerosis (n=10; 33.3%), others (n =1; 3.3%), and unknown (n=7; 23.3%). Causes of renal failure in HD patients included diabetic nephropathy (n=9,30%), hypertensive nephrosclerosis (n=8, 26.7%), chronic glomerulonephritis (n=10, 33.3%), and unknown (n=3, 10%).

There was no significant difference between HD and CAPD patients with regards to age, sex, dialysis duration ( $p>0.05$ ). Demographic and laboratory characteristics of the patients and controls were shown at the Table 1.

Serum HsCRP levels in HD and PD patients were significantly higher than those of controls ( $18.2\pm 37.2$ ,  $12.5\pm 13.2$ ,  $3.6\pm 3.9$   $\mu\text{mol/L}$  respectively;  $p: 0.009$ ). HD and PD patients had significantly higher serum IL6 levels than those of controls ( $3.5\pm 3.1$ ,  $2.8\pm 2.1$ ,  $1.3\pm 0.6$  respectively  $\text{pg/mL}$ ). NT-proBNP levels were higher in both HD and PD patients ( $5949.66\pm 7617.72$ ;  $11357.46\pm 12321.52$   $\text{pg/mL}$  respectively) compared to those of controls ( $45.39\pm 43.48$   $\text{pg/mL}$ ) ( $p:0.000$ ). There was no difference according to serum HsCRP IL6, and NT-proBNP levels between HD and PD patients. (Table 1). There was no difference among HD and PD patients and controls according to thioreductase. No difference was found between PD and HD patients according to BMI, serum creatinine, NT-proBNP levels, systolic and diastolic blood pressure, and dialysis duration ( $p>0.05$ ). Serum albumin, phosphate and PTH levels was higher in HD patients whereas serum calcium and daily urine output was higher in PD patients ( $p<0.05$ ). In PD patients daily urine output was significantly higher than those of HD patients ( $523.3\pm 570.2$ ,  $101.7\pm 209.1$   $\text{ml/day}$  respectively,  $p:0.000$ ) (Table2).

Serum HsCRP levels were positively correlated with IL6 levels ( $r:0.633, p:0.000$ ), BMI ( $r:0.275, p:0.034$ ), and NT-proBNP ( $r:0.277, p:0.032$ ) levels, whereas serum HsCRP levels were negatively correlated with serum albumin ( $r:-0.425, p:0.001$ ). Serum HsCRP levels were not correlated

with age, dialysis duration, serum creatinine, albumin, calcium, phosphate, and PTH levels ( $p>0.05$ ) (Table 3).

Serum IL6 levels were positively correlated with HsCRP levels ( $r:0.633, p:0.000$ ), BMI ( $r:0.775$ ,  $p:0.034$ ) whereas serum IL6 levels were negatively correlated with albumin ( $r:-0.342$ ,  $p:0.007$ ). Serum IL6 levels were not correlated with age, dialysis duration, serum creatinine, calcium, NT-proBNP, PTH levels, systolic and diastolic blood pressure ( $p>0.05$ ). The variables found to be negatively correlated with serum NT-proBNP levels were serum albumin ( $r:-0.385$ ,  $p:0.002$ ) levels, while Serum NT-proBNP levels were positively correlated with age ( $r:0.315$ ,  $p:0.002$ ) and serum HsCRP ( $r:0.277$ ,  $p:0.032$ ) and systolic blood pressure ( $r:0.421$ ,  $p:0.001$ ). Serum NT-proBNP levels were not correlated with BMI, dialysis duration, serum creatinine, albumin, calcium, phosphate, ADMA, PTH levels, and diastolic blood pressure ( $p>0.05$ ).

In multiple regression analyses the predictors of serum HsCRP levels were IL6 ( $\beta:0.677$ ,  $p:0.000$ ) whereas being on HD, gender, serum albumin, NT-proBNP levels and BMI had no independent effect ( $p>0.05$ ). In linear regression model the predictors of serum IL6 levels were HsCRP ( $\beta:0.677$ ,  $p:0.000$ ) whereas being on HD, gender, BMI, and serum albumin had no independent effect ( $p>0.05$ ). The predictors of serum NT-proBNP levels were serum albumin ( $\beta:-0.416$ ,  $p:0.000$ ) and higher systolic blood pressure ( $\beta:0.414$ ,  $p:0.000$ ) whereas being on HD, gender and HsCRP and age had no independent effect ( $p>0.05$ ) (Table 4).

**Table 1.** Demographic and laboratory parameters of the patients and controls

	HD patients Mean± Std. Deviation	PD patients Mean± Std. Deviation	Controls Mean± Std. Deviation	p
Age (years)	51.7±18.3	50.2±15.4	47.4±11.9	0.730
BMI (kg/m <sup>2</sup> )	25.8±6.5	24.9±4.8	27.3±2.9	
Thioreductase	7.6200±4.34927	7.0533±4.45620	7.0350±4.04426	0.847
hsCRP	18.2±37.2	12.5±13.2	3.6±3.4	0.009 <sup>b,c</sup>
IL6	3.5±3.1	2.8±2.1	1.3±0.6	0.001 <sup>b,c</sup>
Nt-proBNP (pg/mL)	5949.7±7617.7	11357.5±12321.5	45.4±43.5	0.000 <sup>b,c</sup>

a.HD -PD  $p<0.05$ , b.HD-controls  $p<0.05$ , c PD-controls  $p<0.05$

**Table 2.** Demographic and laboratory parameters of the patients

	HD patients Mean±Std. Deviation	PD patients Mean±Std. Deviation	P
Age (years)	51.7±18.3	50.2±15.4	0.701
Duration of dialysis (months)	67.3±50.5	48.8±41.4	0.067
BMI (kg/m <sup>2</sup> )	25.8±6.5	24.9±4.8	0.690
Creatinine (mg/dL)	9.2±3.2	8.6±3.1	0.438
Albumine (g/dL)	3.3±0.4	2.9±0.6	<b>0.014</b>
Phosphate(mg/dL)	5.5±1.6	4.2±1.2	<b>0.001</b>
Cystolic blood pressure (mm/Hg)	126.1±25.3	136.1±30.1	0.196
Diastolic blood pressure (mm/Hg)	78.3±17.5	83.4±15.6	0.164
Mean blood pressure	94.2±19.8	100.9±6	0.204
Urine volume (ml/day)	101.7±209.1	523.3±570.2	<b>0.000</b>
Thioreductase	7.6200±4.34927	7.0533±4.45620	0506
hsCRP	18.150±37.23199	12.4913±13.22032	0.470
IL6	3.4907±3.06446	2.8033±2.12659	0.333
NT-proBNP (pg/mL)	5949.7±7617.7	11357.5±12321.5	0.199

**Table 3.** Correlation analysis results

	NT-proBNP		hsCRP		IL6		Thioreductase	
	r	p	r	p	r	p	r	p
proBNP			.277*	.032	.203	.119	.130	.321
hsCRP	.277	.032		1.000	.633**	.000	.199	.128
IL6	.203	.119	.633**	.000		1.000	.225	.085
Age	.315*	.014	.097	.463	.032	.806	.112	.396
Dialysis time	.092	.483	-.032	.811	.037	.781	-.295	.022
BMI	-.125	.341	.275	.034	.275*	.034	.076	.564
Creatinine	-.175	.182	-.088	.505	-.069	.601	.017	.900
Albumin	-.385	.002	-.425**	.001	-.342	.007	-.187	.152
Phosphorus	.021	.874	-.033	.805	.107	.415	.048	.714
Cystolic TA	.421**	.001	-.048	.713	-.211	.105	.081	.540
DiastolicTA	.165	.209	-.083	.528	-.185	.157	-.022	.870
Mean blood pressure	0.311	0.015	-0.091	0.491	-0.215	0.100	0.051	0.700
Urine Volume	-.081	.538	-.042	.751	-.140	.286	-.073	.581
Thioreductase	.130	.321	.199	.128	.225	.085		

**Table 4.** Linear regression analysis results

	HsCRP	R <sup>2</sup> :0.458
IL6	β 0.677	p 0.000
Being on HD, gender, BMI, NT-proBNP, and albumin were excluded		
	IL6	R <sup>2</sup> :0.448
HsCRP	β 0.677	p 0.000
Being on HD, gender, BMI, albumin were excluded		
	NT-proBNP	R <sup>2</sup> :0.238
Serum albumin	β -0.416	p 0.000
Mean blood pressure	0.321	0.000
HsCRP, gender, being on HD, and age were excluded		

## DISCUSSION

BNP belongs to the family of natriuretic peptides which are vasodilatory cardiac neurohormones predominantly released from the ventricles in response to left ventricular volume expansion and pressure overload. There are some causes of BNP increase in dialysis patients. The first one is an altered cardiac condition such as heart failure or ventricular hypertrophy and dysfunctions. In these cases, the BNP increase is not expected to be easily reversible and is associated with an increased risk of cardiac event and mortality in these patients (17,18). The second cause of BNP increase in HD patients is fluid overload and it is reversible by fluid removal, as described in incident dialysis patients (19). As patients progress through the stages of chronic kidney disease sodium retention typically occurs, leading to expansion of the extracellular fluid volume with the compensatory release of natriuretic peptides due to cardiac wall stretch. In addition to increased secretion, these peptides increase with CKD because they are naturally degraded by renal tubular neutral endopeptidases. As such, cardiac natriuretic peptides are often increased in dialysis patients CKD (2). In our study NT-pro BNP levels in both dialysis group were significantly higher than those of controls.

Higher levels of inflammatory parameters have been reported in HD or PD patients (20). Tonbul et al. (21) found similar CRP and fibrinogen levels and erythrocyte

sedimentation rates in their study comparing PD and HD. In our study the dialysis type did not affect Hs-CRP, serum thioredoxin reductase activity, NT-proBNP and IL-6 levels.

Jacobs et al reported that cardiac troponin T, BNP, NT-proBNP and high-sensitivity CRP were significantly related, showing a complex relation between overhydration, malnutrition, inflammation and cardiac biomarkers in dialysis patients (22).

In our study the variables found to be negatively correlated with serum NT-proBNP levels were serum albumin levels, while age, serum HsCRP and systolic and mean blood pressure were positively correlated with serum NT-proBNP levels. However, the relationship between serum HsCRP and NT-proBNP levels detected in univariate analysis disappeared in multivariate analysis. The predictors of serum NT-proBNP levels were serum albumin and mean blood pressure whereas being on HD, gender and HsCRP and age had no independent effect. Being consistent with our result Booth et al. did not find a relationship between plasma CRP and NT-proBNP levels in 72 stable HD patients (23).

Moreover, in our study the BNP levels were found negatively correlated with albumin blood levels. Although these could be a dilutional effect due to fluid overload, these could also reflect poor nutrition and be part of the malnutrition inflammation syndrome. It is also

the case negative correlation in stable patients between prealbumin and BNP levels (24) and albumin and NT-proBNP levels (23). These correlations between usual nutritional, cardiac, and inflammation markers show the tight relationship between these components of the MIA syndrome as described by Stenvinkel et al. (25).

Similarly, malnutrition may also contribute to an elevated ratio of extracellular water to total body water as a result of loss of fat weight (26). These findings are in keeping with recent reports of raised BNP being associated with inflammation (22,27) and overhydration (28). However, we did not find any association between CRP and NT-proBNP in multiple regression analysis, in keeping with other reports (28). One previous report found a correlation between log NT-proBNP and CRP, but interestingly in that study a raised CRP did not predict a raised log NT-proBNP, and their median CRP values were higher than in our cohort (22).

Previous studies have reported an association between NT-proBNP and inflammation, as assessed by plasma interleukin-6 (IL-6) concentrations, in PD patients (29). Proinflammatory cytokines are capable of modulating cardiovascular function by various mechanisms. It is now known that virtually every nucleated cell type in the myocardium, including the cardiac myocyte, is able to secrete proinflammatory cytokines in response to various myocardial damage or stressors. In our study we could not find any association between NT-proBNP and IL 6.

The thioredoxin (TRX) system (TRX, TRX reductase, and NADPH) is a ubiquitous thiol oxidoreductase system that regulates cellular reduction/oxidation (redox) status. The impairment of cell redox state alters multiple cell pathways, which may contribute to the pathogenesis of cardiovascular disorders including hypertension, atherosclerosis, and heart failure.

No relationship was found and Hs-CRP levels, antioxidant enzyme and NT-proBNP levels. This lack of correlation has already been described in the serum of patients with rheumatoid arthritis, although both parameters had been changed by the disease (30). Although the extracellular reduced Trx-1 has proinflammatory effects by potentiating cytokine release from fibroblasts and monocytes (13), our results reveal that TrxR-1 seems to have no relationship with the inflammatory response in dialysis patients.

## CONCLUSION

Our results showed that NT-proBNP levels in dialysis patients were not related with IL6 levels and thioredoxin reductase activity.

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