Serum Thiol/Disulfide Homeostasis in Hemodialysis, Peritoneal Dialysis, and Renal Transplantation Patients

Hemodiyaliz, Periton Diyalizi ve Böbrek Trasplantasyonu Hastalarında Tiol/Disülfit Dengesi

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ABSTRACT

OBJECTIVE: We aimed to evaluate thiol/disulfide homeostasis as an oxidative stress parameter in end-stage renal disease patients receiving different substitutive therapies.

MATERIAL and METHODS: Twenty-four renal transplantation (46.2±8.1 years), 24 peritoneal dialysis (47.8±8.5 years), and 25 hemodialysis patients (45.7±16.0 years), and 24 healthy controls (47.6±8.1 years) were included. Serum native thiol, total thiol, and disulfide levels were measured for all subjects.

RESULTS: Serum total thiol and native thiol levels in the ESRD patients were significantly lower than those in the controls (P<0.001). Native and total thiol levels were significantly lower in PD (256 ± 45 μmol/L, and 287 ± 57 μmol/L) compared to HD (324 ± 44 μmol/L and 356 ± 46 μmol/L) group (p<0.01 and p=0.03). Disulfide/native thiol and disulfide/total thiol levels increased significantly in the PD and transplantation patients compared to control group (P<0.001). Positive correlation was observed between total thiols (r= 0.491 P<0.001), disulfide/native thiol ratio (r=0.383, P<0.001), and blood urea nitrogen; disulfide levels and blood urea nitrogen showed a negative correlation (-0.415, P<0.001). Disulfide levels and glomerular filtration rate showed a positive correlation (r=0.276, P=0.030).

CONCLUSION: Serum thiol/disulfide homeostasis can be an indicator of oxidative stress in end-stage renal disease and that thiol/disulfide homeostasis analysis should be included in the routine monitoring of end-stage renal disease patients.

KEY WORDS: Hemodialysis, Peritoneal dialysis, Renal transplantation

ÖZ

AMAÇ: Çalışmada son dönem böbrek yetmezliği hastalığı için farklı renal replasman tedavisi alan hastalarda bir oksidatif stres belirteci olarak tiol/disülfit dengesinin araştırılması amaçlanmıştır.

GEREÇ ve YÖNTEMLER: Yirmi dört böbrek nakli yapılmış (46,2±8,1 yaş), 25 hemodiyaliz (45,7±16,0 yaş) ve 24 periton diyalizi (47,8±8,5 yaş) hastaları ile 24 sağlıklı kontrol (47,6±8,1 yaş) çalışmaya dahil edildi. Tüm olgularda nativ tiyol, total tiyol ve disülfit seviyeleri ölçüldü.

BULGULAR: Hastalarda kontrol grubu ile karşılaştırıldığında total tiyol ve nativ tiyol seviyeleri anlamlı olarak düşüktü (p<0,001). Nativ ve total tiyol düzeyi periton diyalizi hastalarında (256±45 μmol/L ve 287±57 μmol/L) hemodiyaliz hastalarına (324±44 μmol/L ve 356±46 μmol/L) göre anlamlı düşüktü (p<0,01 ve p=0,03). Periton diyalizi ve transplantasyon hastalarında disulfit/nativ tiyol ve disülfit/total tiyol düzeyleri kontrol grubuna gore anlamlı olarak yüksek bulundu (p<0,001). Total tiyol (r=0,491 P<0,001) ve disulfit/nativ tiyol oranı (r=0,383, P<0,001) ile kan üre nitrojeni arasında pozitif korelasyon; disülfit seviyeleri ve kan üre nitrojeni arasında negatif korelasyon (-0,415, P<0,001) saptandı. Disülfit seviyeleri ve glomerülar filtrasyon değeri arasında pozitif korelasyon (r=0,276, P=0,030) bulundu.

SONUÇ: Tedavi alan son dönem böbrek hastalarında rutin hasta takibinde serum tiyol/disülfit oranı oksidatif stres belirteci olarak kullanılabilir.

ANAHTAR SÖZCÜKLER: Hemodiyaliz, Periton diyalizi, Böbrek transplantasyonu

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INTRODUCTION

End-stage renal disease (ESRD) is characterized by the irreversible loss of kidney function, and ESRD patients require hemodialysis (HD), peritoneal dialysis (PD), or a renal (kidney) transplant (1). According to the Turkish Society of Nephrology (TSN), at the end of 2013, the prevalence of ESRD was 870 per million. The most commonly used treatment for ESRD is HD (79%), followed by transplantation (14%), and PD (7%) (2).

Oxidative stress, which is found to be increased in patients with ESRD, occurs when the generation of reactive oxygen species (ROS) exceeds the antioxidant capacity, which is the endogenous natural defense of the body against oxidative stress (3). Renal replacement therapy, either HD or PD, may also lead to increased oxidative stress (4). Oxidative stress can also be induced due to uremia and can be further aggravated by chronic inflammation, loss of low-molecular weight molecules during dialysis, and recurrent contact of the blood with dialysis membranes (4-6). Oxidative stress is supposed to be associated with the pathophysiology of cardiovascular complications of ESRD. Restoration of kidney function after kidney transplantation has been shown to mitigate oxidative stress (7).

A thiol is a compound that contains the functional group –SH. The thiol pool in blood plasma constitutes an important component of the anti-oxidant defenses, and an increase in oxidative stress leads to the formation of disulfide bonds between low molecular weight thiols and proteins, which are then again reduced to thiol groups to achieve thiol-disulfide homeostasis (8). Plasma protein thiols located primarily on albumin are depleted in patients with ESRD, and oxidized thiols that include homocysteine and cysteine accumulate, leading to the oxidation of reduced free and protein-bound thiols (4). An impaired homeostasis of blood thiols has been observed in ESRD patients, especially in those who have previously received HD therapy (9-11).

An automated assay involving –S–S–, –SH, –S–S–/–SH, –S–S–/(–SH + –S–S–), and –SH/(–SH + –S–S–) quantitation has been described recently for determining dynamic thiol/disulfide homeostasis (8). A number of studies using this assay for analyzing low molecular weight thiol compounds have been conducted in the past. However, no studies for the examination of dynamic thiol/disulfide homeostasis in ESRD patients have been conducted using this new method. Therefore, the aim of the study was to evaluate thiol/disulfide homeostasis as a new oxidative marker in patients with ESRD receiving HD, PD, or renal transplantation.

MATERIALS and METHODS

Study Subjects

We enrolled patients admitted to the Nephrology department and transplantation unit between November 2015 to January 2016 for this case-control study. All the experiments were carried out in accordance with the tenets of the Declaration of Helsinki (2013 Brazil version) of the World Medical Association. The study protocol was approved by the Regional ethics committee, and all the patients signed an informed consent form.

A total of 73 adult patients who had been treated for ESRD for at least 6 months were enrolled in this study. The HD group included 25 patients with a mean age of 45.7±16.0 years. All the HD patients underwent high-flux HD on polysulfone membrane dialyzers with bicarbonate containing solutions for 4 hours three times a week. The PD group comprised 24 patients with a mean age of 47.8±8.5 years. All the patients in the PD group were on continuous ambulatory PD and had been free of peritonitis in the 3 months preceding blood sampling. The renal transplantation group comprised 24 patients with a mean age of 46±8 years. The patients had no underlying inflammatory diseases (such as rheumatologic diseases and vasculitis) and no viral infections (hepatitis B, hepatitis C, and acquired immunodeficiency syndrome). Patients with diabetes, liver, respiratory, or malignant disorders, and acute infections, or those who smoked cigarettes or consumed antioxidant supplements were excluded from the study. Twenty-four age- and sex-matched healthy volunteers without any medical problems and those who did not take vitamin supplements or smoke cigarettes were selected as the control group. All patients remained on renal replacement therapy from 8 to 139 months (mean: 44.2±32.5 months).

Methods

Venous blood samples were collected from all the patients. For the PD group, fasting samples were obtained in the morning without interrupting the ongoing continuous PD; in the HD patients, the samples were obtained before the start of a HD session. All blood samples were centrifuged immediately for 15 minutes at 2500 × *g* and 4°C and stored at –80°C if they were not to be analyzed immediately.

Blood urea nitrogen (BUN), creatinine, protein, albumin, uric acid, sodium, potassium, high density lipoprotein (HDL), and triglycerides were measured using commercial kits on a Mindray BS2000 Chemistry analyzer (Shenzhen, China). The estimated glomerular filtration rate (GFR) was calculated using the 7-item Modification of Diet in Renal Disease (MDRD) study equation:

$[GFR = 170 \times (creatinine)^{-0.999} \times (age)^{-0.76} \times (urea)^{-0.170} \times (albumin)^{+0.318} \{\times 0.762 \text{ if female}\}]$(12).

Disulfide/Thiol Homeostasis Analysis

Reducible disulfide bonds were reduced to form free functional thiol groups. Unused reductant sodium borohydride was added and then removed using formaldehyde, and all the thiol groups including the reduced and native thiol groups were analyzed after the reaction using 5,5'-dithiobis-(2-nitrobenzoic) acid. Half of the difference between the total thiols and the native thiols was recorded as the dynamic disulfide amount. After the

native thiol (SH) and total thiol levels were determined, the disulfide (SS) amounts, disulfide/total thiol percent ratios (SS/SH+SS), disulfide/native thiol percent ratios (SS/SH), and native thiol/total thiol percent ratios (SH/SH+SS) were calculated (8).

Statistical Analysis

The data were analyzed using SPSS software version 21.0 (SPSS Inc. Chicago, IL, USA) and expressed as the mean±standard deviation (SD). The normality of the distributions was checked for each variable using the Kolmogorov-Smirnov test. Since four groups defined according to study protocol were analyzed, ANOVA was used to determine the significance of differences between the means. If the groups were not distributed normally, the Kruskal-Wallis test was used. If the overall differences between groups proved to be significant ($p<0.05$) *post hoc* comparisons (Tukey test) were performed. Pearson's correlation coefficient was used to determine the correlation between variables with normal distribution, while the Spearman's coefficient was used for variables with non-normal distribution. $P<0.05$ was considered to indicate statistically significance.

RESULTS

The clinical data from patients and those of normal subjects are summarized in Table I. A Tukey post-hoc test reveled that serum total thiol and native thiol levels in the ESRD patients were significantly lower than those in the controls ($P<0.001$). Native and total thiol levels were significantly lower in PD (256 ± 45 μmol/L, $p<0.01$ and 287 ± 57 μmol/L, $p=0.03$) compared to HD (324 ± 44 μmol/L and 356 ± 46 μmol/L) group. Disulfide levels were similar ($p=0.075$). Disulfide/native thiol and disulfide/total thiol levels increased significantly in the PD and transplantation patients compared to control group ($P<0.001$) (Table II). Negative correlation was observed between total thiols and BUN ($r=-0.343$, $P<0.01$) (Table III).

Disulfide/native thiol and disulfide/total thiol ratios were significantly higher in the PD patients than in HD patients and the controls ($P<0.001$) (Table II).

Positive correlation was observed between total thiol levels and BUN ($r=0.491$, $P<0.001$), and disulfide/ native thiol ratio ($r=0.383$, $P<0.001$), and negative correlation was observed between disulfide levels and BUN ($r=-0.415$, $P<0.001$). A weak

Table I. Characteristics of the study population. Data are expressed as mean±standard deviation (SD) when normally distributed and as percentages when categorically distributed.

Parameters	Chronic Kidney Disease Patients		Control Group		
	Peritoneal Dialysis	Hemodialysis	Renal Transplant		P
Number of Patients	24	25	24	24	
Age (years)	47.8±8.5	45.7±15.0	46.2±8.1	47.6±8.1	0.531*
BMI	27.7±5.7	26.8±4.9	27.0±5.0	27.5±3.6	0.962*
TA	120(20)	115(27)	120(10)	124(10)	0.112**
	80(10)	70(20)	80(10)	80(10)	0.036**
BUN, mg/dL	90±33	75±20	25±1.6	20±0.8	<0.001*
Creatinine, mg/dL	5.9±2.5	9.5±2.0	1.6±0.5	0.8±0.6	<0.001*
GFR ml/min^{-1}/1.73 m^2	11(7)	5(2)	48(18)	98(100)	<0.001**
Albumin, mg/dL	3.6±0.4	3.9±0.2	3.9±1.0	4.2±0.5	<0.001*
Protein,mg/dL	6.4±0.5	6.5±0.6	5.9±2.0	6.7±1.4	0.886*
Uric acid, mg/dL	4.6(2.0)	6.3(1.9)	5.9(2.5)	4.2(2.5)	<0.001**
Sodium, mmol/L	135±3.3	135±3.8	136±2.8	138±3.6	0.003*
Potassium, mmol/L	4.3±0.4	5.0±0.7	4.1±0.5	4.3±0.3	<0.001*
HDL, mg/dL	45±19	32±10	29±10	42±10	<0.001*
Triglycerides, mg/dL	198±130	211±84	203±84	148±71	<0.001*
T Chol, mg/dL	207±60	158±56	124±44	177±57	<0.001*

BMI: Body mass index, **TA:** Tansion arterial, **GFR:** Glomerular filtration rate, **HDL:** High density lipoprotein, **T Chol:** Total cholesterol, **BUN:** Blood Urea Nitrogen, *One-way ANOVA, results are mean±SD ; ** Kruskal –wallis, results are median(interquartile range).

negative correlation was observed between age and native thiol levels. Negative correlation was also observed between total thiols levels and GFR (r=-0.289, P=0.022), and disulfide levels and GFR showed a positive correlation (r=0.276, P=0.030) (Table III).

DISCUSSION

In this study, we used a previously described assay to evaluate serum thiol/disulfide homeostasis in ESRD patients receiving HD, PD, or renal transplantation and found that the levels of native thiols and total thiols and the native thiol/total thiol ratio were lower in ESRD patients than in healthy individuals. We also revealed a parallel increase in disulfide/native thiol and disulfide/total thiol ratios in ESRD patients when compared to those in the healthy control group. These results indicate that the level of oxidative stress is higher in patients with ESRD than in healthy individuals. Our findings are consistent with previous reports wherein patients with ESRD have been shown to have decreased plasma protein thiols and increased S-thiolated proteins (9,13,14). In addition, Przemysław et al. (14) found that the total concentration of glutathione, which is a low molecular weight thiol-tripeptide, was decreased in terminal renal failure patients and that total concentrations of the remaining thiols in these patients were significantly increased compared to those in the healthy subjects.

The accumulation of substances that are normally cleared by the kidneys in the plasma is indicative of impaired kidney function (15). Measuring BUN in the serum is an indirect and rough method of analyzing the effect of the protein in the diet on renal function. While the level of urea is affected by protein intake, creatinine level is not. In our study, correlation analyses

Table II: Thiol disulfide homeostasis in groups.

	Control	PD	HD	Transplantation
Native thiol levels, µmol/L	393±61	256±45*, **	324±44*	292±49*
Total thiol levels, µmol/L	426±65	287±57*,**	356±46*	334±59*
Disulfide levels, µmol/L	16±9	16±9	15±6	20±8
Disulfide/Native thiol levels %	3.9±1.7	6.2±3.2*	4.8±2.5	7.0±2.5*,**
Disulfide/Total thiol levels %,	3.6±1.4	5.3±2.6*	4.0±1.9	6.1±1.9*,**
Native Thiol/Total thiol levels %,	92.7±2.9	89.2±5.2*	91.4±3.9	87.7±3.8*,**

PD: Peritoneal dialysis, **HD:** Hemodialysis; results are mean±SD. Differences were considered significant, when p>0.05.

*Significantly different from control (One-way ANOVA, followed by post-hoc Tukey test).

**Significantly different from HD (One-way ANOVA, followed by post-hoc Tukey test).

Table III: Correlation between variables.

		Age	BUN	Creatinine	BUN/Creatinine Ratio	GFR
Total thiol levels (µmol/L)	**r**	0.057	0.491	0.212	0.154	-0.289
	P	0.621	<0.001*	0.081	0.207	0.022*
Native thiol levels (µmol/L)	**r**	-0.229	-0.146	-0.047	0.003	0.172
	P	0.040*	0.224	0.698	0.982	0.180
Disulfide levels (µmol/L)	**r**	-0.148	-0.415	-0.172	-0.136	0.276
	P	0.186	<0.001*	0.152	0.273	0.030*
Disulfide/native thiol levels	**r**	-0.100	0.383	-0.214	-0.027	0.178
	P	0.374	<0.001*	0.073	0.829	0.167
Disulfide/total thiol levels	**r**	0.022	-0.032	-0.068	0.196	0.028
	P	0.848	0.792	0.572	0.113	0.832

*Correlation is significant at p<0.05.

showed that BUN concentrations correlated with the disulfide/native thiol ratio. Total thiol levels correlated negatively and disulfide correlated positively with GFR. Previous studies have supported our finding indicating that the uremic state is associated with low concentrations of glutathione and reduced thiols (SH), which continue to decrease with the progression of kidney failure in dialysis patients (16). In addition, Matsuyama et al. showed that the redox state of Cys-34 (free thiol group) of human serum albumin correlated with the level of renal dysfunction in predialysis chronic kidney disease patients (17).

HD, PD, and kidney transplantation have distinct characteristics and are associated with different clinical outcomes and adverse events (18). Imbalance of antioxidant–oxidant status appears to be responsible for morbidity in dialysis patients (19). In our study, we found significant differences in the kidney function parameters (serum urea and creatinine concentrations) between the HD, PD, and renal transplant patients. The disulfide/native thiol levels were also different between the three groups; the disulfide/native thiol levels were slightly higher in the transplantation and PD groups compared to the HD group. While these results are consistent with few other previous studies, increased levels of oxidative stress in HD compared to those in PD have also been reported in some studies (20-24). We believe that the increased oxidative stress observed in the PD patients (compared to those in the HD patients) in our study may have been caused by inflammatory responses.

Kidney transplantation is generally accepted as the optimal form of renal replacement therapy. After renal transplantation, the restoration of kidney effectiveness is accompanied by an increase in the GFR and a decrease in urea and creatinine levels in the plasma. However, in our study, the oxidative stress was found to have been increased in the renal transplant patients. This result is consistent with a previous report indicating that successful renal transplantation does not normalize the oxidative imbalance and that the levels of oxidative and nitrosative stress are significantly increased compared to those in healthy subjects, presumably due to the effect of immunosuppressive therapy and other medications and renal dysfunction (7). Apeland et al. (25) also showed that previous kidney donors have abnormal plasma aminothiol redox status; these donors also have an increased risk of oxidative stress with low redox buffer capacity and disturbed cellular redox-dependent signaling pathways. Aveles et al. also found that the thiol content increases in the months following transplantation (26). Further, Antolini et al. observed an identical increase in total antioxidant status in HD and renal transplant patients in comparison with that in control subjects (27).

CONCLUSIONS

Our findings indicate that serum thiol/disulfide homeostasis is a good indicator of oxidative stress in ESRD patients receiving HD, PD, or renal transplantation. However, the study has some limitations. First, it had a single-center design with a relatively small patient population. A large multiracial, multicenter study is required to determine the importance of native thiol/disulfide homeostasis in ESRD patients. Nevertheless, the new assay method used here is easy to perform in routine clinical laboratories and might allow the early detection of the effect of different treatments on plasma oxidative imbalance in ESRD patients, thus aiding in the prevention of the same. Laboratory monitoring of plasma thiol/disulfide homeostasis should therefore be included in the routine monitoring of ESRD patients receiving therapy.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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