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Evaluation of dynamic thiol-disulfide balance and ischemia modified albumin levels in patients with chronic kidney disease

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Abstract

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Objective: In this study, it was aimed to determine the dynamic thiol-disulfide balance and ischemia modified albumin (IMA) levels in patients with chronic kidney disease (CKD).
Method: Thirty hemodialysis (HD), 30 CKD patients (stage 3-5) and 30 controls were included in the study. The dynamic thiol-disulfide balance was determined by the colorimetric method developed by Erel et al. IMA levels were determined by using cobalt binding test developed by Bar- Or et al.
Results: Native and total thiol levels of CKD and HD patients were significantly lower than that of the control group (p=0.001 for both). However, disulfide levels were significantly higher in the HD group (p=0.001), but there was no significant difference between control and CKD groups(p=0.547). A statistically significant negative correlation was found between the native and total thiol levels and IMA (r=-0.628; -0.631), BUN (r=-0.747; -0.747), and creatinine (r=-0.732; -0.721). There was a significant positive correlation between GFR and the thiol levels (r=0.835;0.824). TrxR levels were significantly higher in the patient groups compared to the controls (p=0.001). CRP levels of the patient groups were significantly higher compared to the controls (p=0.001).
Conclusion: We have demonstrated that measurement of dynamic thiol-disulfide levels by using colorimetric method can contribute to the diagnosis and follow-up of the disease as a marker, because it is easily applicable in routine clinical biochemistry laboratories and related with disease severity in CKD patients. Also, we showed that albumin correction due to dialysis process should be consider in studies dealing with plasma thiol values and the final results should be given after the correction process.
Keywords: Chronic Kidney Disease, Hemodialysis, Oxidative Stress, Thiol-Disulphide Homeostasis, Ischemia Modified Albumin

Öz

Kronik böbrek hastalığı olan hastalarda dinamik tiyol-disülfid dengesi ve iskemi modifiye albümin düzeylerinin değerlendirilmesi

Amaç: Bu çalışmada Kronik böbrek hastalığı (KBH) olan hastalarda dinamik tiyol-disülfid dengesi ve iskemi modifiye albümin (IMA) düzeylerinin belirlenmesi amaçlanmıştır.
Yöntem: Çalışmaya 30 hemodiyaliz (HD), 30 KBH hastası (evre 3-5) ve 30 kontrol dahil edildi. Dinamik tiyol-disülfid dengesi, Erel ve arkadaşları tarafından geliştirilen kolorimetrik yöntemle belirlendi. IMA seviyeleri Bar- Or ve ark. tarafından geliştirilen kobalt bağlama testi kullanılarak belirlendi.
Bulgular: KBH ve HD hastalarının serbest ve toplam tiyol seviyeleri kontrol grubuna göre anlamlı derecede düşüktü (her ikisi için p=0.001). Ancak disülfid düzeyleri HD grubunda anlamlı olarak daha yüksekti (p=0.001), ancak kontrol ve KBH grupları arasında anlamlı fark yoktu (p=0.547). Serbest ve toplam tiyol seviyeleri ile IMA (r=-0.628;-0.631), BUN (r=-0.747;-0.747) ve kreatinin (r=-0.732;-0.721) arasında istatistiksel olarak anlamlı bir negatif korelasyon bulundu. GFR ile tiyol düzeyleri arasında anlamlı pozitif korelasyon vardı (r=0.835;0.824). Hasta gruplarında TrxR düzeyleri kontrollere göre anlamlı derecede yüksekti (p=0.001). Hasta gruplarının CRP düzeyleri kontrollere göre anlamlı derecede yüksekti (p=0.001).
Sonuç: Dinamik tiyol-disülfid düzeylerinin kolorimetrik yöntem kullanılarak ölçülmesinin, rutin klinik biyokimya laboratuvarlarında kolaylıkla uygulanabilmesi ve KBH hastalarında hastalık şiddeti ile ilişkili olması nedeniyle bir belirteç olarak hastalığın tanı ve takibine katkı sağlayabileceğini gösterdik. Ayrıca plazma tiyol değerleri ile ilgili çalışmalarda diyaliz sürecine bağlı albümin düzeltmesinin dikkate alınması gerektiğini ve düzeltme işleminden sonra nihai sonuçların verilmesi gerektiğini gösterdik.
Anahtar Kelimeler: Kronik Böbrek Hastalığı, Hemodiyaliz, Oksidatif Stres, Tiyol-disülfid Homeostazı, İskemi Modifiye Albümin

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INTRODUCTION

Chronic Kidney Disease (CKD) is a syndrome characterized by the progressive and irreversible loss of nephrons due to various diseases (1). The risk of mortality in hemodialysis (HD) patients is about 10 to 20 times higher than in the general population (2). In these patients, many molecules (e.g., uremic toxins) accumulate in the body which contributes to uremic symptoms and increases mortality (3). High levels of uremic toxins have been reported to increase oxidative stress, which has negative effects on macromolecules (4).

It is well known that oxidative balance is disrupted due to overproduction of free radicals and insufficient antioxidant system in HD patients. Therefore, there are many studies analyzing oxidative stress levels in HD patients (5-7). Thiols, also called mercaptans, are sulfhydryl group-containing (-SH) compounds (8). Thiol groups interact with free radicals to form reversible disulfide bonds then reduced back to thiol groups by several antioxidants. Thus, dynamic thiol-disulfide balance is achieved (9).

Dynamic thiol-disulfide balance has a vital role in the organism and is important to maintain this balance. It has been measured in only one direction since 1979, but henceforth with novel automated method developed by Erel et al., the level of both variables can be measured distinctly and collectively (10). In the literature, there is no study showing the effect of dynamic thiol-disulfide balance and hemodialysis on thioredoxin reductase enzyme levels.

Thioredoxin reductase (TrxR) is a homodimeric flavoenzyme responsible for the catalysis of thioredoxins (11-12). The sulfhydryl groups of thioredoxins are involved in cellular regulation of various biochemical mechanisms with different functions and the regeneration of inactive proteins as a result of oxidative stress (13-14). In this study, we addressed to indicate the relationship between the dynamic thiol-disulfide balance, systemic oxidative stress parameters and TrxR enzyme levels in CKD (stage 3-5) and HD patients.

METHOD

Study and Control Groups

Thirty HD patients and 30 patients with CKD (stage 3-5), and 30 healthy control group were included in the study.This study was conducted between Nov 2017 and Dec 2018. The mean duration of dialysis in the HD group was 70.1 ± 45.0 months.

Patients with acute and chronic infection, chronic inflammatory disease, hematologic disease, and malignancy were excluded from the study. Hatay Mustafa Kemal University Ethics Committee confirmed the study (protocol number: 2017/128). Informed written consent was obtained from all patients.

Samples Collection

Fasting venous blood samples were collected into vacutainer tubes containing EDTA and lithium-heparin from patients with CKD and control subjects. Blood samples were collected before and after the midweek dialysis session in HD patients. All samples were centrifuged at 1500 x g for 10 min after sampling. Then, samples were portioned and stored -80 °C until the time of assay.

Measurement of Biochemical Parameters

Assay Principle of Thiol/Disulfide Homeostasis Parameters

Total and native thiol measurements were performed using Modified Ellman method of Erel et al. (10). The reagent to be used for total thiol measurement was named 1 (R1) and for native thiol measurement (R1'). While these initial reagents were different in total and native thiol measurements, the other reagents were the same. R1 was used freshly prepared on the day of the study, with sodium borohydride (378 mg, $NaBH_4$) in 1 L of water-methanol mixture (with a volume ratio of 1/1) of 10 mM. This reducing solution was used to determine the total thiol content. R1' sodium chloride (585 mg, NaCl) in 1 L of water-methanol mixture (1/1 volume ratio) was prepared freshly on the day of the study, with a final concentration of 10 mM. The native thiol amount was determined by using this solution. Reagent 2 (R2) was prepared freshly by dissolving 0.5 mL of formaldehyde with a final concentration of 6.715 mM and 3.8 g of EDTA with a final concentration of 10 mM in 1 L of Tris buffer, 100 mM and pH 8.2. This solution was used for total and native thiol measurements. As to Reagent 3 (R3) 3.963 g of 5.5-dithiobis-2-nitrobenzoic acid (DTNB) was prepared freshly on the working day at a final concentration of 10 mM in 1000 mL methanol. This solution was used for total and native thiol measurements.

Total and Native Thiol Measurement Principle

For the total thiol measurement, 10 µL R1 and 10 µL sample were mixed. Then, the first absorbance reading (A1) was performed spectrophotometrically at 415 nm wavelength by adding R2 and R3 (Shimadzu UV-1800 spectrophotometer, Kyoto, Japan). The second absorbance (A2) reading was made at the 10th minute of the reaction at the same wavelength. Absorbance difference (A2-A1) was obtained and the measurement was completed. To determine the total and native thiol levels, the molar extinction coefficient of 5-thio-2-nitrobenzoic acid (TNB) was 14.100 mol / L^{-1} cm^{-1}. Measurement of disulfide level was calculated using the formula [(total thiol-native thiol) / 2].

We also calculated corrected native and total thiol and disulfide levels based on the serum albumin concentrations from the following formulas:

Table 1. Thiol-disulfide homeostasis parameters of the study and control groups

Variables	Control (n=30)	CKD (stage 3-5) (n=30)	Hemodialysis (n=30)	p
Native thiol (µmol/L)	463.1 ± 69.1	230.7 ± 59.9	202.6 ± 79.7	0.001[a],0.001[b],0.665[c]
Total thiol (µmol/L)	495.7± 68.7	267.7 ± 66.4	264.9 ± 98.6	0.001[a],0.001[b],0.999[c]
Disulfide (µmol/L)	16.3 ± 4.8	18.5 ± 7.4	31.2 ± 12.3	0.547[a],0.001[b],0.001[c]
Disulfide/Native thiol (%)	3.6± 1.46	8.5± 4.4	20.7 ± 14.6	0.001[a],0.001[b],0.001[c]
Disulfide/Total thiol (%)	3.3 ± 1.2	7.0 ± 3.3	13.4 ± 6.5	0.001[a],0.001[b],0.001[c]
Native thiol/Total thiol (%)	93.3 ± 2.5	85.7 ± 5.7	73.4 ± 13.1	0.001[a],0.001[b],0.001[c]
IMA (ABSU)	0.65 ± 0.06	0.88 ± 0,22	0.91 ± 0.17	0.001[a],0.001[b],0.935[c]
TOS (µmol H_2O_2 equiv./L)	19.4 ± 4.4	27.1 ± 11.2	52.2 ± 24.7	0.004[a],0.001[b],0.001[c]
TrxR (ng/mL)	5.2 ± 2.4	7.7 ± 2.1	27.3 ± 19.9	0.001[a],0.001[b],0.001[c]
**CRP (mg/L) Median (min-max)	4.02± 1.13 3.1 (3.1;6.0)	6.54± 3.01 5.3 (4.1;15.0)	9.86 ± 5.56 9.6 (1.2;20.9)	0.002[a],0.001[b],0.028[c]

*ANOVA, **Kruskal Wallis a: Control ve CKD (stage 3-5), b: Control and Hemodialysis, c: CKD (stage 3-5) and Hemodialysis
IMA: Ischemia -modified albumin, CRP: C-reactive protein, TOS: Total oxidant status, TrxR: Thioredoxin reductase

Corrected total thiol levels: total thiol (µmol/L) / albumin (g/L).

Corrected native thiol levels: native thiol (µmol/L) / albumin (g/L).

Corrected disulfide levels: disulfide (µmol/L) / albumin (g/L).

TAS and TOS Measurements

Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured colorimetric based on method developed by Erel (15). The measured data were expressed as µmol Trolox equivalent per liter for TAS and mmol H_2O_2 equivalent per liter for TOS. Then, oxidative stress index (OSI) (arbitrary unit) = TOS (µmol H_2O_2 Eq/L) / TAS (µmol Trolox Eq/L) × 100 were calculated.

Ischemia-Modified Albumin Levels

We measured IMA levels by using cobalt binding test developed by Bar- Or et al. (16). The results were indicated as absorbance units (ABSU) (Abbot Architect C-8000).

Measurement of Thioredoxin Reductase Levels

We measured serum TrxR levels by using commercial ELISA kit (Bioassay Human TrxR ELISA Kit, Catalog no: E3953Hu) and the values were expressed as ng /mL. The samples were pre-diluted 8-fold before measurement. The final results were calculated by multiplying with the dilution factor (7).

Table 2. Correlation analysis of thiol/disulfide homeostasis parameters of the study population

Variables		Age	BUN	Creatinine	GFR	TAS	TOS	OSI	IMA
Native thiol (µmol/L)	r	0.166	-0.747	-0.732	0.835	-0.389	-0.573	-0.380	-0.628
	p	0.124	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Total thiol(µmol/L)	r	0.164	-0.747	-0.721	0.824	-0.383	-0.560	-0.364	-0.631
	p	0.126	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Disulfide (µmol/L)	r	-0.057	0.143	0.254	-0.084	0.163	0.211	0.171	0.056
	p	0.603	0.240	0.020	0.537	0.192	0.057	0.123	0.617
Disulfide/Native thiol (%)	r	-0.097	0.597	0.672	-0.672	0.078	0.481	0.389	0.347
	p	0.373	0.001	0.001	0.001	0.197	0.001	0.001	0.001
Disulfide/Total thiol (%)	r	-0.098	0.651	-0.682	-0.682	0.269	0.470	0.351	0.390
	p	0.361	0.001	0.001	0.001	0.013	0.001	0.001	0.001
Native thiol /Total thiol (%)	r	0.099	-0.651	-0.725	0.682	-0.269	-0.470	-0.351	-0.390
	p	0.361	0.001	0.001	0.001	0.013	0.001	0.001	0.001

*Pearson correlation test

Table 3: Thiol-disulfide parameters in HD patients

Parameters	HD (before dialysis) (n=30)	HD (after dialysis) (n=30)	p
Native thiol (µmol/L)	202.6 ± 79.7	305.2 ±78.2	0.001
Total thiol (µmol/L)	264.9 ± 98.6	358.5 ± 83.2	0.002
Disulfide (µmol/L)	31.2± 12.3	26.6 ± 7.71	0.152
Disulfide / Native thiol (%)	20.7 ± 14.6	9.2 ± 3.3	0.001
Disulfide /Total thiol (%)	13.4 ± 6.5	7.65±2.34	0.001
Native thiol/ Total thiol (%)	73.4 ± 13.1	84.7±4.63	0.001
Alb (g/dL)	3.97±0.24	4.97±0.71	0.001
CRP (mg/L)	9.86±5.56	5.47±2.34	0.001
IMA (ABSU)	0.91 ± 0.17	0.87 ± 0.17	0.475
TAS (mmol Trolox equiv./L)	1.14 ± 0.24	0.65±0.28	0.001
TOS (µmol H_2O_2 equiv./L)	27.1±11.2	75.1 ± 40.2	0.007
OSI (AU)	2.5 ± 1.1	12.4 ± 8.3	0.001
TrxR (ng/mL)	27.3 ± 19.9	28.3 ± 19.4	0.555

*Paired samples t -test
Alb: Albumin, CRP: C-reactive protein, IMA: Ischemia -modified albumin, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, TrxR: Thioredoxin reductase

Statistical Analysis

SPSS 21.0 (IBM, USA) statistical package program were used to analyze the obtained data. Shapiro-Wilk test was used to determine the normal distribution of the groups. For normal distribution data, differences between more than two groups were compared with ANOVA test. For abnormally distributed data, differences between more than two groups were compared with Kruskal-Wallis test. The comparison of parameters before and after dialysis was performed with the paired sample t-test in the normal distribution data and Wilcoxon signed rank questionnaire in abnormally distributed data. Pearson correlation test was used for correlation analysis. Statistical significance level was accepted as $p < 0.05$.

RESULTS

Native and total thiol levels were found to be lower in patients with CKD (stage 3-5) and HD compared with the control subjects (230.7 ± 59.9 and 202.6 ± 79.7 µmol/L; 267.7 ± 66.4, and 264.9 ± 98.6 µmol/L respectively). However, disulfide levels were higher in patients with CKD and HD compared with the control subjects (18.5 ± 7.4 and 31.2 ± 12.3 µmol/L, respectively). Moreover, disulfide levels were significanlty high in the patients receiving HD compared with both patients with CKD (stage 3-5) and control subjects (31.2 ± 12.3 µmol/L, 18.5 ± 7.4 µmol/L and 16.3 ± 4.8 µmol/L respectively). Disulfide levels in HD patients increased significantly compared with patients with CKD and control subjects (p=0.001). In addition, plasma IMA levels were significantly different between control and CKD (stage 3-5) and control and HD groups (p = 0.001, Table 1).

Native and total thiol levels showed negative correlation with IMA, blood urea nitrogen (BUN), and creatinine levels (r=-0.628, p=0.001; r=-0.747, p=0.001, r=-0.732, p=0.001). In addition, it showed positive correlation with glomerular filtration rate (GFR) (r= 0.835, p=0.001; r=0.824, p=0.001). (Table 2). In patients receiving HD, native and total thiols in pre-and post-dialysis were significantly different (p=0.001), but disulfide levels did not significantly change (p=0.0152) by a single dialysis session. Albumin and CRP levels were significantly different before and after the dialysis session (p=0.001, Table 3). Therefore, we also calculated adjusted native and total thiol, and disulfide levels based on albumin concentrations in HD patients both before and after the dialysis. After albumin correction, there was no significant difference anymore in the native and total thiol levels of pre- and post- dialysis patients (p=0.143, p=0.567), however significant difference was observed in the disulfide levels (p=0.001).

DISCUSSION

We demonstrated that total and native thiol levels were significantly lower in patients with CKD (stage 3-5) and patients receiving HD than healthy subjects. However, disulfide levels were significantly higher only in patients receiving HD. Moreover, TrxR enzyme levels were significantly higher both in patients with CKD (stage 3-5) and patients receiving HD than healthy subjects. Our study also revealed that IMA and TOS levels were significantly higher in both CKD (stage 3-5) and HD groups compare to controls. However, OSI levels were significantly higher only in the HD group compare to control.

Coskun et al. showed that native and total thiol levels of the patients receiving HD treatment were significantly lower than the control group (17). They hypothesize that low native and total thiol levels occurred as a result of oxidative stress and chronic inflammation in HD patients. In another study, Ates et al. reported that native and total thiol levels were lower in HD patients compared to the control group and they associated this decrease with the reduced total thiol reserves in the organism (18).

In the same line with previous studies, it was found that native and total thiol levels in plasma samples of HD patients were lower than both CKD and control groups. One reason of the decrease in plasma thiol levels may be the continuous depletion of sulfhydryl-containing antioxidant molecules, particularly glutathione, to remove ROS as previously suggested (18). However, although the levels of glutathione as one of the antioxidants are known to be high in the cell, the contribution of other low molecular weight thiol compounds to the plasma sulfhydryl pool is relatively low compared to albumin (19). Therefore, reduced glutathione levels may not

be sufficient to explain the total thiol decrease alone in CKD (stage 3-5) patients.

Albumin is known to be irreversibly converted into end products as a result of prolonged oxidative damage. One of these albumin-transformed products is sulfenic acid (RSOH), resulting in sulfinic (RSO_2H) or sulfonic (RSO_3H) acid and these products have been suggested to be removed from the circulation through the liver. We may speculate that uremic toxins cause oxidative stress in CKD patients, and albumin is exposed to a constant oxidative stress. As a result, albumin may be irreversibly converted and withdrawn from the circulation into oxidation products such as sulfenic, sulfinic, and sulfonic acid as previously shown under long-term oxidative stress in CKD patients. In addition, the liver's depletion of plasma glutathione and sulfhydryl sources due to this increased detoxification metabolism may also contribute to low thiol depletion in plasma (20). In this study, we examined the correlations between thiol groups and GFR and found a positive and strong correlation between both native and total thiol levels and GFR. Plasma native and total thiol levels positively and highly correlated with GFR which suggests that thiols can be used as a test parameter related to disease prognosis in CKD patients.

It was also evaluated the effect of HD session on native and total thiol levels and disulfide parameters. Thiol levels of samples measured after dialysis were significantly higher compared to the ones before dialysis. However, there was no significant difference between two groups in terms of disulfide level after the correction with albumin. On the other hand, the decrease in disulfide levels of the samples after HD was statistically significant. In other words, single HD session did not have a significant effect on thiol levels, but resulted in a significant decrease in disulfide levels. We consider that volume correction may be especially important in comparing thiol values associated with albumin. In addition to that, this decrease in disulfide level may be related to the regeneration of plasma thiol redox status by hemodialysis as stated in the previous studies (21,22). In the literature, there are only two studies evaluating the effect of hemodialysis on plasma dynamic thiol balance by using Erel method (23,24). In these studies, a correction for a possible volume change due to hemodialysis was not mentioned. During the HD procedure, different degrees of hemoconcentration can occur in the blood due to volume withdrawal after HD treatment. In the present study, unlike the previous two studies, we determined albumin levels in blood against a possible hemoconcentration before and after the dialysis. Albumin values were significantly higher in the samples after the dialysis. In this study, increased serum TrxR enzyme levels in CKD patients may be explained by the over-expression of the enzyme to increase the antioxidant effect against increased oxidative stress, as suggested in previous studies. As a result, serum TrxR values were significantly higher in CKD (stage 3-5) and HD group compared to healthy controls. This increase was more prominent in the HD group. It was found that IMA levels were higher in the CKD and HD groups compared to the control. However, there was no significant difference between HD and CKD groups. In the literature, Turedi et al. reported that IMA levels of patients receiving HD were found to be higher compared to healthy controls (25). In this study, in accordance with the literature, increased IMA levels support the view that increased oxidative stress may lead to albumin modification.

CONCLUSION

Thirty HD patients [17 M (56%), 13 F (44%)], 30 CKD (stage) 3-5) patients [19 M (63%), 11 F (37%)] and 30 healthy controls [18 M (60%), 12 F (40%)] were included in the study**.** Dynamic thiol disulfide and TrxR enzyme levels play an important role in the pathogenesis of CKD and appear to be associated with oxidative stress. Measuring dynamic thiol-disulfide levels can contribute to the diagnosis and follow-up of the disease as a marker due to its applicability in clinical biochemistry laboratories and related with disease severity in CKD patients. Another result is the remarkable change in thiol values caused by albumin correction. It has shown that volume correction should be taken into account in studies dealing with plasma thiol values and results should be given after the correction process.

Study Limitations

First limitation is the lack of measuring TrxR enzyme activities. Another limitation is that thiol-containing compounds have not been examined separately.

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Peer-Review

Externally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical approval was obtained fromHatay Mustafa Kemal University Ethics Committee with date 2017 and number2017/128, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: OÖ, ÖE, HE, FT, Design: OÖ, ÖE, HE, FT, Data collection and entry: OÖ, ÖE, FT, HE, Analysis and interpretation: OÖ, ÖE, HE, FT, SN, Literature search: OÖ, ÖE, HE, FT, Writing: OÖ, HE, Critical review: OÖ, HE, FT, SN, ÖE

REFERENCES

1. Böger RH. The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor. Cardiovasc Res 2003;59 (4): 824-33. https://doi.org/10.1016/s0008-6363(03)00500-5.
2. Sugimoto M, Yamaoka Y. Review of Helicobacter pylori infection and chronic renal failure. Therapeutic Ther Apher Dial. 2011;15(1):1-9. https://doi.org/10.1111/j.1744-9987.2010.00851.x.
3. Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, et al. Chronic kidney disease. Nat Rev Dis Primers. 2017;3(1): 1-24. https://doi.org/10.1038/nrdp.2017.88.
4. Özcan O, Erdal H, Çakırca G, Yönden Z. Oksidatif stress ve hücre içi lipit, protein ve DNA yapıları üzerine etkileri. J Clin Exp Invest. 2015;6(3):331-6. https://doi.org/10.5799/ahinjs.01.2015.03.0545.
5. Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative stress in hemodialysis patients: a review of the literature. Oxid Med Cell Longev. 2017;2017: 3081856.https://doi.org/10.1155/2017/3081856.
6. Modaresi A, Nafar M, Sahraei Z. Oxidative stress in chronic kidney disease. Iran J Kidney Dis. 2015; 9(3):165 -79.
7. Zhang J, Li X, Han X, Liu R, Fang J. Targeting the thioredoxin system for cancer theraphy. Trends Pharmacol Sci. 2017;38(9): 794-808.https://doi.org/10.1016/j.tips.2017.06.001.
8. Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr. 2000;72(2):653-69. https://doi.org/10.1093/ajcn/72.2.653S.
9. Ates I, Ozkayar N, Inan B, Yılmaz FM, Topcuoğlu C, et al. Dynamic thiol/disulphide homeostasis in patients with newly diagnosed primary hypertension. J Am Soc Hypertens. 2016;10(2):159-66. https://doi.org/10.1016/j.jash.2015.12.008.
10. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47(18):326-32. https://doi.org/10.1016/j.clinbiochem.2014.09.026.
11. Williams CH, Arscott LD, Müller S, Lennon BW, Ludwig ML, Wang PF, et al. Thioredoxin reductase: two modes of catalysis have evolved. Eur J Biochem. 2000;267(20):6110-7. https://doi.org/10.1046/j.1432-1327.2000.01702.x.
12. Zagrodzki P. Thioredoxin reductase--a new target for molecular medical investigations. Postepy Hig Med Dosw. 2002;56(2):155-67.
13. Holmgren A. Thioredoxin and glutaredoxin systems. J Biol Chem. 1989;264 (24):139636. https://doi.org/10.1016/S0021-9258(18)71625-6.
14. Gromer S, Gross JH. Methylseleninate is a substrate rather than an inhibitor of mammalian thioredoxin reductase Implications for the antitumor effects of selenium. J Biol Chem. 2002;277(12):9701-6. https ://doi.org/10.1074/jbc.M109234200.
15. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem. 2005;38(12):1103-11. https://doi.org/ 10.1016/j.clinbiochem.2005.08.008.
16. Bar-Or D, Curtis G, Rao N, Bampos N, Lau E. Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. Eur J Biochem. 2001;268(1):42-7. https://doi.org/10.1046/j.1432-1327.2001.01846.x.
17. Coşkun C, Emre HÖ, Gümüş A, Uzun S, Karadağ S, Behlül A, et al. Diyabetik ve Diyabetik Olmayan Kronik Böbrek Yetmezliğinde Dinamik Tiyol Disülfit Homeostazı ve İleri Protein Oksidasyon Ürünleri (AOPPs). Deneysel Tıp Araştırma Enstitüsü Dergisi.6(12):1-9.
18. Ateş İ, Özkayar N, Yılmaz FM, Bayrakçı N, Neşelioğlu S et al. Oxidative stress level in patients with chronic kidney disease. Ortadogu Medical Journal/Ortadogu Tıp Dergisi. 2018;10(1). https://doi.org/10.21601/ortadogutipdergisi.308443.
19. Turell L, Radi R, Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. An Introduction to a Special Issue of Free Radical Biology and Medicine - "Reactive Oxygen Species and Musculoskeletal Aging". McArdle A, Jackson MJ. Free Radic Biol Med. 2013; 65:244-53. https://doi.org/10.1016/j.freeradbiomed.2013.05.050.
20. Carbonell LF, Nadal JA, Llanos MC, Hernandez I, Nava E, Diaz J. Depletion of liver glutathione potentiates the oxidative stress and decreases nitric oxide synthesis in a rat endotoxin shock model. Crit Care Med. 2000; 28(6):2002-6. https://doi.org/10.1097/00003246-200006000-00054.
21. Ayar G, Sahin S, Yazici MU, Neselioglu S, Erel O, Bayrakcı US. Effects of Hemodialysis on Thiol-Disulphide Homeostasis in Critically Ill Pediatric Patients with Acute Kidney Injury. BioMed Research International. 2018;2018. https://doi.org/10.1155/2018/1898671.
22. Fanti P, Giustarini D, Rossi R, Cunningham SE, Folli F, Khazim K, et al. Dietary intake of proteins and calories is inversely associated with the oxidation state of plasma thiols in end-stage renal disease patients. J Ren Nutr. 2015;25(6):494-503. https://doi.org/10.1053/j.jrn.2015.06.003.
23. Simons AL, Parsons AD, Foster KA, Orcutt KP, Fath MA, Spitz DR. Inhibition of glutathione and thioredoxin metabolism enhances sensitivity to perifosine in head and neck cancer cells. J Oncol. 2009;2009. https://doi.org/10.1155/2009/519563.
24. Otal Y, Dermican S, Sener A, Alisik M, Tanriverdi F, Güllü Ercan Haydar F. Acute renal failure and thiol-disulfide homeostasis. J Nephrol Ther. 2018;8: 312. https://doi.org/10.4172/2161-0959.1000312.
25. Turedi S, Cinar O, Yavuz I, Mentese A, Gunduz A, Karahan SC, et al. Differences in ischemia-modified albumin levels between end stage renal disease patients and the normal population. J Nephrol. 2010;23(3):335-40.