Acute Renal Failure and Thiol-Disulfide Homeostasis

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Introduction

Thiols are best known as mercaptans and contain the -SH group [1]. The plasma thiol pool mostly consists of thiols such as albumin and low molecular weight cysteinylglycine, cysteine (Cys), homocysteine, glutathione and γ-glutamylcysteineprotein [2]. Thiol-disulphide balance is of vital importance. Thiol-disulphide rate (TDR) plays a critical role in the process of detoxification, its efficiency in antioxidant protection, signal transduction, enzymatic regulation, apoptosis and cellular signal mechanisms has also been shown [3,4]. Thiol-disulphide balance was investigated in a number of disorders, yet while this balance could be measured unilaterally until 2014, it can now be determined bilaterally through the use of a new method developed by Erel and Neselioglu [5,6].

We also investigated the clinical importance of thiol-disulphide balance in the patients with acute renal failure in the emergency department. This is the first known study in the literature in which thiol-disulphide balance in acute renal failure has been investigated.

Acute renal failure (ARF) is a disorder resulting in the accumulation of toxic wastes and the loss of inner homeostasis, which then leads to the failure of renal functions within hours and days. This disorder is the most common cause of complaint in emergency departments. ARF is classified as prerenal, renal and postrenal failures. During the initial stages, the disease courses in an asymptomatic fashion. Oxidative changes can also be seen in patients with ARF. The thiol level drops down in patients with ARF.

MDRD used for evaluating the renal functions in acute renal failure is a formula commonly used in calculating eGFR [8]. In this calculation, no result can be achieved when age, gender and race are unidentified. In ARF creatinin level not stable and in ARF should be used 24-hours urine collation methods for measurement GFR. 24-hours urine is collected in our study and then GFR was calculated by device automatically.

In this study, a new method referred to as "thiol based GFR (tGFR)", which can only be calculated by using thiol and creatinine values, was studied.
identified. We are of the opinion that this new method can be an alternative to eGFR calculation.

Materials and Methods

42 patients diagnosed with acute renal failure in the emergency department were incorporated into the study. Separately, the cases likely to have another additional disease that might cause an oxidative stress were excluded from the study. The patients who have medical treatment and without hemodialysis were excluded from the study. Generally there is no need dialysis in ARF. Dialysis indications in ARF is uremia, asidicis, hyperkalemia and anuric ARF. Our patients also had uremi, acidosis and anuria. Causes of ARF were 32 case prerenal and 10 case renal. The blood samples of 42 cases on whom hemodialysis therapy was performed due to the diagnosis of acute renal failure were taken. Thiol-disulphide levels were studied by using Erel's method without keeping the blood samples waiting. Separately, the other biochemical tests and the arterial blood gas samples of all the cases were also studied. The demographic characteristics of 42 cases and 45 control groups incorporated into the study have been shown in Table 1.

The statistical results were analyzed by using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) program. In the distribution sample of the variables, Kolmogorov-Smirnov Test was used. In inter-group comparisons showing a normal distribution, LSD (least significant difference) test and the groups were compared with one another through Mann-Whitney U test. In comparing the numeric variables not showing a normal distribution, Kruskal-Wallis Test was used, another through Mann-Whitney U test. The relationships between numeric variables were analyzed through Pearson's correlation or Sperman's correlation test.

The study protocol was approved by the local ethics committee, and the written informed consent forms of all the participants were received.

Results

There were no significant differences between the groups in terms of mean age and gender. A hemodialysis support was also provided in the treatment of all the patients. The results obtained from the patients and the data regarding the controls have been given in Table 1.

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Table 1: Results obtained from the patients and controls data.

As seen in Figures 1 and 2, native thiol levels in the patient population were significantly lower than those of the healthy controls both before and after the dialysis (233.35 ± 65.15; 247.17 ± 68.76; 394.82 ± 46.50; <0.001, respectively). The total thiol levels in the patient population were also significantly lower than those of the healthy controls both before and after the dialysis (265.65 (104.03); 266.45 (107.23); 439.00 (50.95), p<0.001 respectively). Disulphides/native thiol and Disulphides/total thiol rates, however were found to be significantly higher in the patient population when compared with those of the control group both before and after the hemodialysis (p<0.001).

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While eGFR (ml/min/1.73 m²) values were being calculated, MDRD (Modification of Diet in Renal Disease) formula was used. The formula we used in calculating tGFR (thiol based GFR), which we claimed had the potential of being used as an alternative to eGFR which was tGFR=(SH/creatinine) xk. As seen in Figure 3, quite a significant relationship was found between eGFR and tGFR values. (r=0.975; p<0.001 respectively).

Discussion and Conclusion
Dynamic thiol-disulphide homeostasis has a critical role within the organism. The changes in the thiol-disulphide balance serve as the antioxidant protection, detoxification, regulation of enzymatic activity and the components of the cellular signal mechanism [3,4]. Thiol-disulphide balance has been associated with a number of disorders such as DM, cancer, migraine, hyperemesis gravidarum and chronic renal failure [7-14].

Cysteine and the components of cysteine are the main thiol-disulphide structures within the plasma. Ultimately, cysteine plays a role both in structural functioning and in redox systems like thiol-disulphide changes [15]. Disulphides like cysteine are the members of thiol-based regulatory redox systems [16].

Thiols are organic sulphur derivatives, on the active side of which sulphhydryl group is found. In some studies, it was shown that the albumin-related thiols in particular posed a major defense against the oxidative stress within the plasma. In these studies was the plasma thiol-disulphide balance identified unilaterally [17-20]. In our study, thiol-disulphide balance was measured bilaterally. The results are seen in Figure 1 and 2. In our study, we found out that we could form an opinion over the interpretation of the measurements of plasma thiol-disulphide balance and the severity of the disease as well as the condition of the oxidative stress. Therefore, we are of the opinion that this test is of a high clinical value.

Patients with acute renal failure are commonly seen in emergency departments, and the disease may cause mortality due to various factors. In this process, the oxidative stress plays a major role. Inflammation and unstable metabolism increase the oxidative stress in the patients with ARF. The plasma thiol levels drop down along with the increasing oxidative stress [17]. However, there is no information as to disulphide levels. We also saw that the oxidative stress increased in the patients with ARF and that this condition could be identified bilaterally through the method we used in our study. Again, in our study, we found that there was a significant relationship between high urea and high creatinine levels and thiol-disulphide balance in the patients with acute renal failure. Determining the thiol-disulphide balance, which is an indicator of oxidative stress in patients with ARF which can serve as a biomarker in clinics.

Also in our study, thiol and disulphide amounts per albumin in the patients with ARF were found to be high. While albumin levels were low, thiol levels increasingly dropped down, which indicates the fact that the balance shifted towards the oxidative direction as the result of extreme oxidation as well as thiol deficiency. In some studies, there is this view that administering antioxidant agents may change the oxidative stress in a positive way; hence, we are of the opinion that administering N-acetylcysteine, an antioxidant agent can boost the balance in favour of disulphide by meeting the deficit of native thiol [21-23].

eGFR is a parameter used in the evaluation of renal functions, and MDRD formula is commonly used in its calculation [8]. In this complex formula are age, gender, race and serum creatinine values. With this study, we suggest that this simple, useful tGFR index easily calculable only through serum thiol and creatinine values is of clinical importance in terms of being an alternative to eGFR. We also think that this formula which we consider as statistically very significant can be developed, as well. In our study, we saw that the correlation between tGFR and eGFR was quite powerful. tGFR index may have the potential of being used in clinics.

Thiol-sulphide balance in the patients with acute renal failure weaken, and this balance shifted in the direction of disulphide. The decrease in native thiol and total thiol levels is associated with the severity of the disease. Administering thiol-donor agents like N-acetylcysteine can be of use in meeting the deficit of homeostasis. tGFR index has the potential to be used as an alternative to eGFR, particularly in the emergency patients whose age, gender and race cannot be identified.

Declaration of Conflicting Interests
The Authors declare that there is no conflict of interest

References
1.   Sen CK, Packer L (2000) Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr 72: 653-669.
2.   Turell L, Radi R, Alvarez B (2013) The thiol pool in human plasma: The central contribution of albumin to redox processes. Free Radic Biol Med 65: 244-253.
3.   Biswas S, Chida AS, Rahman I (2006) Redox modifications of protein-thiols: Emerging roles in cell signaling. Biochem Pharmacol 71: 551-64.
4.   Circu ML, Aw TY (2010) Reactive oxygen species, cellular redox systems and apoptosis. Free Radic Biol Med 48: 749-762.
5.   Erel O, Nesioloğlu S (2014) A novel and automated assay for thiol/disulfide homeostasis. Clin Biochem 47: 326-332.
6.   Ellman G, Lyso H (1979) A precise method for the determination of whole blood and plasma sulphhydryl groups. Anal Biochem 93: 98-102.
7.   Ates I, Kaplan M, Inan B, Alısık M, Erel O, et al. (2015) How does thiol/disulfide homeostasis change in prediabetic patients? Diabetes Res Clin Pract 110: 168-171.
8.   Levey AS, Bosch JP, Lewis JB, Rogers N, et al. (1999) A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461-470.
9.   Matteucci E, Giampietro O (2010) Thiol signalling network with an eye to glioblastoma. J Nephrol Ther 8: 312.
10.  Prabhu A, Sarcar B, Kahali S, Yuan Z, Johnson JJ, et al. (2014) Cysteine catabolism: A novel metabolic pathway contributing to glioblastoma growth. Cancer Res 74: 787-796.
11. Rodrigues SD, Batista GB, Inghberman M, Pecotts-Filho R, Nakao LS (2012) Plasma cysteine/cystine reduction potential correlates with plasma creatinine levels in chronic kidney disease. Blood Purif 34: 231-237.

12. Kundi H, Ates I, Kiziltunc E, Çetin M, Cicekcioglu H, et al. (2015) A novel oxidative stress marker in acute myocardial infarction: Thiols/disulfide homeostasis. Am J Emerg Med 33: 1567-1571.

13. Eren Y, Dirik E, Neşelioğlu S, Erel Ö (2015) Oxidative stress and decreased thiol level in patients with migraine: Cross-sectional study. Acta Neurol Belg 115: 643-649.

14. Ergin M, Cendek BD, Neselioglu S, Avsar AF, Erel O (2015) Dynamic thiol-disulfide homeostasis in hyperemesis gravidarum. J Perinatol 35: 788-792.

15. Hansen RE, Østergaard H, Winther JR (2005) Increasing the reactivity of an artificial dithioldisulfide pair through modification of the electrostatic milieu. Biochem 44: 5899-5906.

16. Wouters MA, George RA, Haworth NI (2007) Forbidden disulfides: their role as redox switches. Curr Protein Pept Sci 8: 484-495.

17. Himmelfarb J, McMonagle E, Freedman S, Klenzak J, McMenamin E, et al. (2004) Oxidative stress is increased in critically ill patients with acute renal failure. J Am Soc Nephrol 15: 2449-2456.

18. Hu ML, Louie S, Cross CE, Motchnik P, Halliwell B (1993) Antioxidant protection against hypochlorous acid in human plasma. J Lab Clin Med 121: 257-262.

19. Halliwell B, Gutteridge JM (1990) The antioxidants of human extracellular fluids. Arch Biochem Biophys 280: 1-8.

20. Frei B, Stocker R, Ames BM (1992) Small molecule antioxidant defenses in human extracellular fluids. In: The Molecular Biology of Free Radical Scavenging. Cold Spring Harbor Laboratory Press.

21. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, et al. (2003) Oxidative stress in end-stage renal disease: An emerging threat to patient outcome. Nephrol Dial Transplant. 18: 1272-1780.

22. Rodrigues SD, França KC, Dallin FT, Fujihara CK, Nascimento AJ, et al. (2015) N-acetylcysteine as a potential strategy to attenuate the oxidative stress induced by uremic serum in the vascular system. Life Sci 121: 110-116.

23. Heller AR, Groth G, Heller SC, Breitkreutz N, Nebe T, et al. (2001) N-acetylcysteine reduces respiratory burst but augments neutrophil phagocytosis in intensive care unit patients. Crit Care Med 29: 272-276.