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Acute Renal Failure and Thiol-Disulfide Homeostasis

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Abstract

Aims: Investigating the thiol-disulphide balance in the patients with acute renal failure and evaluating the potential of using tGFR (thiol based GFR) index as a new parameter, alternative to the parameter called estimated Glomerular Filtration Rate (eGFR).

Study design: The serum thiol-disulphide levels in the predialysis and postdialysis blood samples of 42 patients diagnosed with acute renal failure in the emergency department and hemodialyzed right after were measured through the novel method.

Methods: The acute renal failure was detected through the clinical and laboratory findings, and a hemodialysis procedure was performed. The obtained results were statistically evaluated. While eGFR (ml/min/1.73 m^2) values were being calculated, MDRD (Modification of Diet in Renal Disease) formula was used. To calculate tGFR as an alternative to eGFR, tGFR=(SH/creatinine) xk formula was used.

Results: Disulphides/native thiol and Disulphides/total thiol rates in the patient population were found to be significantly lower after the hemodialysis when compared with those before the hemodialysis process ($p<0.001$). A significantly negative relationship was found between the creatinine values and the native and total thiol values ($r=-0.732$; $r=-0.739$; $p<0.001$ respectively). There was also a significantly negative relationship between the urea values and the native and total thiol values ($r=-0.722$; $r=-0.739$; $p<0.001$ respectively). Quite a significant relationship was also found between eGFR values and tGFR values ($r=0.98$; $p<0.001$).

Conclusion: The thiol-disulphide balance in the patients with acute renal failure weakened, in addition to which the balance in question shifted towards the direction of disulphide. Native thiol and total thiol levels are associated with the severity of the disease. There is the potential of using tGFR index as an alternative to eGFR for the emergency department patients (ER-patients) whose age, gender and race cannot be identified.

Keywords: Acute renal failure; Thiol-disulphide balance; eGFR

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. The condition of the renal functions can be estimated through eGFR calculation [7]. 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 24hours urine collation methods for measurement GFR. 24hours 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

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 endications in ARF is uremia, asidicis, hyperkalemia and anuric ARF. Our patients also had üremi, 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, fisher LSD (least significant difference) test and the groups were compared with one another after using the one-way ANOVA test. In comparing the numeric variables not showing a normal distribution, Kruskal-Wallis Test was used, after which the groups were compared with one 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.

	Pre-dialysis (n=42)	Post-dialysis (n=42)	Control (n=45)	p value*
Age (year)	75.1 ± 12.09	75.1 ± 12.09	71.4 ± 7.98	0.183
Urea mg/dl	244.3 ± 87.9[a]	143.4 ± 48.1[a-b]	37.8 ± 13.0	<0.001
Creatinine mg/dL	5.95 (5.13)[a]	3.60 (2.74)[a-b]	0.82 (0.37)	<0.001
Total protein g/dL	6.40 ± 0.71[a]	6.40 ± 0.71[a]	7.09 ± 0.49	<0.001
Albumin g/dL	3.48 ± 0.52[a]	3.48 ± 0.52[a]	4.34 ± 0.28	<0.001
Native thiol μmol/L	233.35 ± 65.15[a]	247.17 ± 68.76[a]	394.82 ± 46.50	<0.001
Total thiol μmol/L	265.65 (104.03)[a]	266.45 (107.23)[a]	439.00 (50.95)	<0.001
Disulfides μmol/L	18.64 ± 7.67	17.18 ± 7.14	19.48 ± 6.78	0.326
Disulfides/ Native thiol %	7.55 (5.06)[a]	6.90 (4.92)[a]	5.02 (2.47)	<0.001
Disulfides/Total thiol %	6.56 (3.78)[a]	6.06 (3.70)[a]	4.57 (2.07)	<0.001
Native thiol/ Total thiol %	86.37 (7.56)[a]	87.87 (7.40)[a]	90.87 (4.13)	<0.001
eGFR (MDRD)	8.57 (9.71)[a]	14.99 (16.25)[a-b]	79.96 (46.14)	<0.001
tGFR arbitrary unit**	10.6 (6.66)[a]	14.88(9.96)[a-b]	82.26 (38.15)	<0.001

a: Differs from control, b: Diffres from pre-dialysis group
Values are expressed as mean ± SD or median
*p value<0.05, obtained from One-Way ANOVA or Kruskal-Walls test, is considered as significant
**results were obtained by the linear regression formula (y: 0.161x+4.794)

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; p<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).

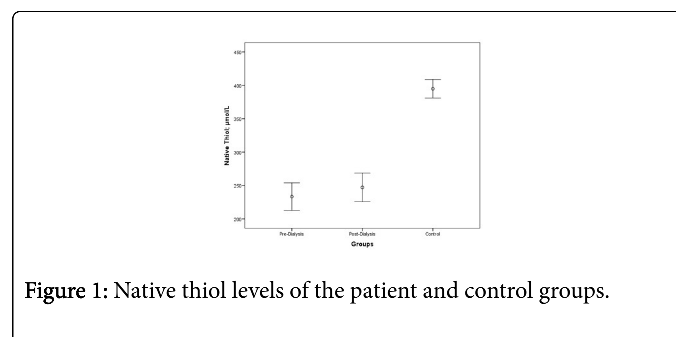

Figure 1: Native thiol levels of the patient and control groups.

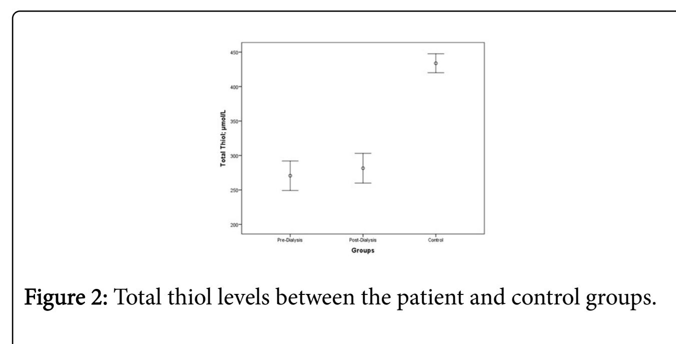

Figure 2: Total thiol levels between the patient and control groups.

While eGFR (ml/min/1.73 m^2) 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).

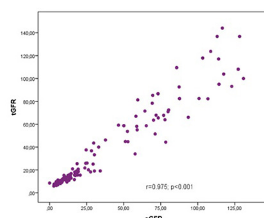

Figure 3: The relationship between eGFR and tGFR.

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 functionings 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 sulfhydryl 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 course mortally 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

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