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SERUM PROTEIN THIOL LEVELS IN PATIENT WITH HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY

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Abstract:

The basic purpose of this study is to analyze the antioxidants in acute kidney injury (AKI) patients and regulate whether the levels of serum protein thiols are linked with all-cause 90 days patient's mortality associated with hospital-acquired AKI.

As per the RIFLE (Risk, Injury, Failure, Loss, and ESRD) criteria hospital-acquired AKI 160 patients were registered in this research. As controls, from 160 patients 72 were critically ill patients without AKI and 72 sex and age-matched healthy subjects also registered. The levels of serum protein thiol were assessed in connection to all-cause AKI patients' mortality.

The levels of serum protein thiol in the patients of AKI were lesser than those in normal/healthy persons (p=0.010). Levels of protein thiol represented a weaker but important positive correlation with levels of serum albumin. The 90-day overall rate of mortality was elevated in the patients of AKI with high levels of serum protein thiol as compared with those with low (p=0.032 by the test of log-rank).

According to Cox regression multivariate analysis, levels of serum protein thiol (p=0.031) were impartially linked with an overall mortality of 90 days after adjustment of sex, age, sepsis, and Chronic Health Evaluation II scores.

It was found that hospital-acquired AKI patients have considerably low levels of serum protein thiol. Increased levels of protein thiol are linked with 90-day inclusive mortality in hospital-acquired AKI.

Keywords: *Serum Protein Thiols, Mortality, Acute Kidney Injury*

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1.0 INTRODUCTION:

In the recent past, some studies found that increased oxidative stress has a high mortality rate effect on AKI developed patients. The syndrome of systemic inflammatory response, multiple organ system failures and metabolic imbalance instigated by hyper-catabolism are predominant in the patients of AKI. A renal clearance hyper-catabolism decrease and reduction in inflammatory by-products may impair these systemic disorders. In stimulated phagocytic cells, specifically in inflammatory disorders, which generate additional cytokines are a major generator of responsive oxygen species. Renal failure also determined as an excessive stimulus for elevated oxidative stress (Chionh and Cruz, 2016).

It is believed that the most profuse plasma thiol is single thiol of serum albumin and it is decreased by 75%. It is generally recognized as an important target for oxidants and electrophiles due to its wide variety of species reactivity and its comparatively high concentration. However, the serum protein thiols are generally a kind of biomarker in oxidative stress. Thus, some other studies have analyzed the oxidative stress prevalence in AKI patients and there is no study to have analyzed the link between prognosis of AKI and serum protein thiols (Ahmad et al., 2017).

In this study, we struggle to investigate whether levels of protein thiol are increased or suppressed in the patients of AKI and whether they are linked with 90-day inclusive mortality in this populace.

2.0 METHODS:

2.1 Patients

This study was organized in Feb 2015 to Jan 2016, and we choose patients who are affected by hospital-acquired AKI. Total numbers of adult patients were 160 with age ≥ 18 years were specifically registered in this research as per RIFLE staging criteria. There was an exclusion criterion which contains:

1- Renal vasculitis etiology for AKI established glomerulonephritis and severe interstitial nephritis
2- Admission with AKI
3- Metastasis of tumors diagnosis
4- Pregnancy and registration in other studies
5- Antioxidants use
6- Premorbid elevation in the levels of serum creatinine forms any unknown reason (Chionh and Cruz, 2016).

There were 72 seriously ill patients without AKI, registered also for control subjects. These patients were matched in sex, age, and APACHE II scores, with the patients of AKI. Healthy subjects groups were based on 72 patients' who were registered as controls.

2.2 Study Definitions

RIFLE categorization criteria have been used in the determination of AKI and patients were classified and diagnosed based on an alteration in levels of serum creatinine from AKI diagnosis baseline, rather than the level of maximal creatinine in hospitalization period. The baseline level of serum creatinine was determined as the lowest level of serum creatinine in one week before the AKI diagnosis. Sepsis syndrome was associated to be offered in patients in whom the infection was escorted by two inflammatory response syndrome systemic criteria, as per the guidelines of consensus (Ahmad et al., 2017).

According to laboratory results, normal clinical syndromes and microbiological parameters infection were identified. Those patients who have a description of operations; as compared with a surgical operation maintain in a week before the AKI diagnosis (Jeeha et al., 2017).

2.3 Clinical evaluation and the primary outcome

There was a proper record of clinical evaluation at the diagnosis time of AKI in patients having AKI and at enrollment of control groups' time. Baseline demographics, comorbidities, sex, age and hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic hepatic disease, malignant tumors, chronic obstructive pulmonary disease were recorded. At the time of registration, we also record the possible AKI cause, the need for mechanical ventilation and presence of sepsis. We used APACHE II score to analyze the organ dysfunction degrees (Jeeha et al., 2017).

Table 1. Baseline demographic and clinical data of patients at the time of diagnosis of acute kidney injury stratified by RIFLE stages

Characteristic	No. (%)				
	Total (n=160)	Risk (n=70)	Injury (n=38)	Failure (n=52)	*p* value
Age (yr), mean (s.d.)	62.8±18.1	65.9±16.7	66.6±17.2	55.9±19.3	0.060
Sex(%female)	48(30.0)	20(28.6)	14(36.8)	14(26.9)	0.750
Baseline Scr (mg/dL)	0.70±0.25	0.75±0.23	0.67±0.17	0.64±0.33	0.300
Scr when AKI diagnosed (mg/dL)	1.53(1.21, 2.10)	1.25±0.39	1.63±0.39	3.82±3.3	<0.001
Comorbid conditions					
Hypertension (%)	76(47.5)	32(45.7)	21(55.3)	23(44.2)	0.715
CVD (%)	22(13.5)	11(15.7)	6(15.8)	5(9.6)	0.710
DM (%)	22(13.8)	12(17.1)	4(10.51)	6(11.5)	0.919
Chronic hepatic disease (%)	9(5.6)	4(5.7)	0(0)	5(9.6)	0.462
Malignant tumor (%)	15(9.4)	6(8.6)	4(10.5)	5(9.6)	0.962
COPD	6(3.8)	2(2.9)	2(5.3)	2(3.8)	0.906
CKD (%)	2(1.3)	0(0)	0(0)	2(3.8)	0.325
AKI etiology					
Ischemic (%)	59(36.9)	23(32.9)	18(47.4)	18(34.6)	0.534
Nephrotoxic (%)	51(31.9)	25(35.7)	12(31.6)	14(26.9)	0.788
Others (%)	50(31.2)	22(31.4)	8(21.0)	20(38.5)	
Operation (%)	83(51.9)	49(70.0)	18(47.4)	16(30.8)	0.008
Sepsis (%)	67(41.9)	29(41.4)	18(47.4)	20(38.5)	0.832
Mechanical ventilation (%)	65(40.6)	20(28.6)	18(47.4)	27(51.9)	0.149
MAP (mmHg)	89±18	91±15	86±17	88±22	0.608
WBC($\times 10^3/\mu L$)	12.8±6.6	12.3±6.3	15.1±6.9	12.0±6.6	0.237
Neutrophilic granulocyte (%)	82.5(76.2, 86.7)	81.5(73.2, 85.6)	82.4±9.45	79.6±16.4	0.361
Hemoglobin (g/dL)	11.0±2.7	11.4±2.0	11.1±2.8	10.5±3.5	0.405
Platelet ($\times 10^3/\mu L$)	138.4±89.8	148.7±88.6	138.4±77.3	124.5±100.4	0.588
ALT (U/L)	32.0(18.0, 63.0)	28.0(18.5, 58.5)	38.0(20.0, 73.0)	31.5(13.0, 98.0)	0.487
AST (U/L)	38.0(23.0, 91.0)	34.5(22.7, 71.0)	63.0(28.0, 145.0)	44.0(18.0, 113.7)	0.207
Serum albumin (g/dL)	3.2±0.7	3.5±0.7	3.3±0.7	2.9±0.7	0.001
Serum total calcium (mmol/L)	2.1±0.3	2.1±0.2	2.0±0.3	2.0±0.3	0.217
Serum phosphate (mmol/L)	1.3±0.7	1.1±0.6	1.4±0.8	1.7±0.8	0.062
Cholesterol (mmol/L)	3.5±1.5	3.4±1.4	3.5±1.8	3.5±1.4	0.925
Prealbumin (mg/dL)	14.4±6.0	15.5±6.4	14.7±6.8	12.7±4.8	0.212
CRP (mg/dL)	9.2±7.0	7.5±6.9	9.9±7.4	11.3±6.4	0.114
APACHE II	20.4±9.6	15.5±8.2	23.0±7.9	25.1±9.8	<0.001

Note: Data were obtained at the time of diagnosis of AKI, unless otherwise noted.
Abbreviations: RIFLE, Risk, Injury, Failure, Loss, or End-stage kidney disease staging criteria; CVD, cardiovascular disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; Scr, serum creatinine; AKI, acute kidney disease; MAP, mean arterial pressure; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II.

(Source: Jeeha et al., 2017)

All these patients were specifically followed up for 90 days and the basic result was in-hospital all-cause mortality. Not any respondents were using medications which known to delay or interfere with vitamin C/E, oxidative stress, reduced glutathione in the time period of 90 days follows up.

2.4 Blood samples for serum protein thiol

BD vacutainer serum-separating tubes have been used for the measurements, these tubes contained an activator for a clot at the time of AKI diagnosis in AKI affected patient and at the time of registration in the control groups. Protein separation has been done initially through centrifugal ultrafiltration. The performance of the quantification of serum protein thiols while utilizing a quantitation kit of thiol and sulfide (Invitrogen Life Technologies). The levels of serum protein thiol were expressed as µM as suggested by the manufacturer (Jeeha et al., 2017).

2.5 Statistical Analysis

Generally, distributed variables were expressed as a mean ± standard deviation and specifically analyzed through *t*-test and one way ANOVA. On the other hand, non-normally distributed variables are reflected as medians with quartile particularly compared utilizing the test of the rank sum. Finally, categorical variable further expressed by percentages and also compared utilizing the "Pearson Chi-squared Test and Fisher's Exact Test". Continuous data correlations were performed by Pearson Correlation Coefficients (Lee et al., 2017).

3.0 RESULTS:

3.1 Baseline Clinical Characteristics and demographics of AKI Cohort

We registered 160 patients with 112 men and 48 women in this study. The AKI cohort means age was

62.8±18.1 years. Seventy (which are 43.8%) patients grasped the stage of RIFLE, 23.7% (38 patients) reached the RIFLE stage of injury and 32.5% (52) reached the failure stage of RIFLE. The clinical characteristics and demographic features stratified by AKI patients' RIFLE stage as shown in Table 1. Accordingly, predominant comorbid AKI cohort patients' condition was; hypertension in 47.5% (76 patients), diabetes mellitus in 13.8% (22 patients), cardiovascular diseases in 13.8% (22 patients), chronic hepatic disease in 5.6% (09 patients), chronic obstructive pulmonary in 3.8% (6 patients), tumor of non-metastasis malignant in 9.4% (15 patients) and chronic kidney disease in 1.3% (2 patients). In between 160 patients of AKI 51.9% (83 patients) experienced surgery and 41.9% (67 patients) suffered from sepsis (Lee et al., 2017).

The level of median serum creatinine was 0.70 mg/dL at the time of registration and when AKI was diagnosed it was increased to 1.53 mg/dL. APACHE II mean score was 20.4±9.6. In healthy subjects the level of Thiol critically ill patients exclusive of AKI and with AKI patients. The healthy subjects mean ages, specifically for ill patients without AKI, and with AKI patients were "55.5±18.2, 60.0±12.7, and 62.8±18.1" years, accordingly the females proportion was 38.9%, 38.9%, and 30.0%, correspondingly. Basically, there are no important divergence in sex and age among the 3 groups (*p>0.05).* The score of APACHE II regarding severe ill patients without AKI was identical to those patients with AKI (*p>0.05) (Lee et al., 2017).*

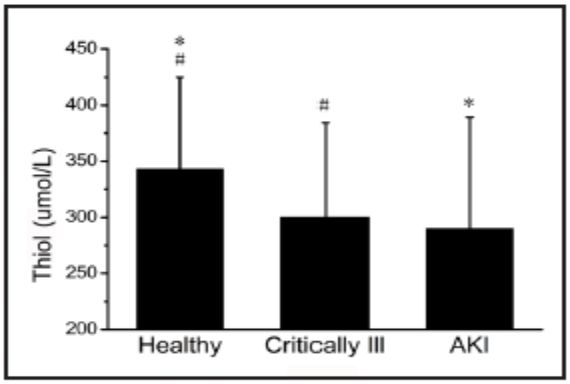

Fig. 1. Thiol levels among healthy subjects, critically ill patients without AKI, and patients with AKI. *t test (p =0.044), critically ill patients compared with healthy subjects; *t test (p =0.005), AKI patients compared with healthy subjects.

(Source: Lee et al., 2017)

In this Figure 1, level of serum protein thiol in between healthy subjects remains without AKI but critically ill patients and with those patients who have AKI. There was an important divergence in the level of serum protein thiol in healthy subjects with and without AKI patients (as per ANOVA *p=0.017).* Level of serum protein thiol in the patients of AKI (290.1±99.1 µmol/L) considered lesser as compared with healthy subjects (343.2±81.8 µmol/L), on the other hand, it seems identical to those of significantly ill patients (300.3±84.0 µmol/L) (Lee et al., 2017).

3.2 Levels of Thiol in AKI patients of several stages according to the RIFLE criteria of staging

There are three further categories for those patients with AKI by RIFLE criteria of staging (risk, injury, and failure) as per their alterations in the level of serum creatinine within one week. The size of the sample of every subgroup was 43.8% (70), 23.7% (38) and 35.5% (52) accordingly. No particular divergence in sex, age, and comorbid conditions was observed in the three subgroups. The operations percentage and levels of serum albumin were greatest in risk stage patients and lowest in failure stage (p=0.008, p=0.001). The score of APACHE II elevated with AKI severity (*p<0.001).* The clinical and demographic features of all three groups are also represented in Table 1. Levels of serum protein levels were "289.1±101.3, 333.6±103.5, and 260.1±85.8 µmol/L" in all three stages of risk, injury and failure and mentioned below the severity of AKI correlation (ANOVA, *p=0.008)* in Figure 2.

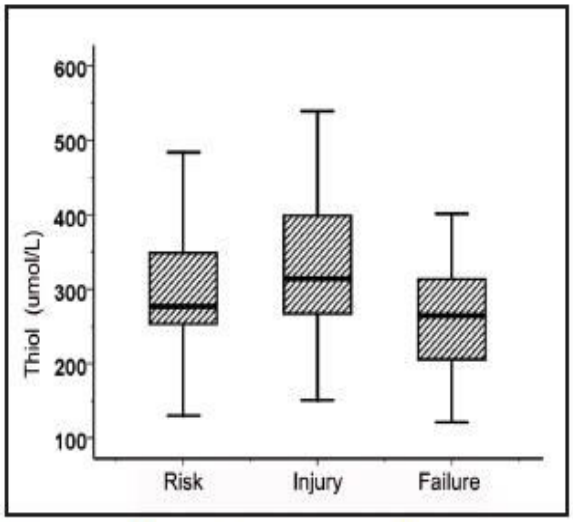

Fig. 2. Thiol levels in 160 patients with AKI stratified by RIFLE stages. p=0.088 by ANOVA.

3.3 Correlations of serum thiol levels with serum albumin and creatinine levels and the APACHE II score

The levels of serum protein thiol represented a feeble, but important, positive correlation with levels of

serum albumin (r=0.293, p=0.005). Thus, there was the important correlation of levels of serum protein thiol with levels of serum creatinine or APACHE II score(Sykes, Reed and Lamerton, 2017).

4.0 DISCUSSION:

Thiols are basically organic sulfur derivatives which are featured by sulfhydryl presence residues. According to biological systems, thiols are originated in cysteine and are high and low molecular weight's molecules. Mostly, in cysteine and proteins accounts for less than three percent of the amino acids composition. Therefore, the versatility chemical of thiol permits this residue to contribute to different processes, such as signaling, catalysis, metal complexing, antioxidant defense, and structural stabilization (Qian et al., 2015).

According to some researchers the protein thiols, specifically in albumin, establish the main defense against oxidative plasma stress. Plasma thiols basically have an impact on foraging free radicals and myeloperoxidase-produced oxidants. The compartment of plasma is featured by partaking relatively fewer meditations of thiols and by the serum albumin presence as the most copious thiols. In this study, we observed that levels of serum protein thiol in patients with AKI and in severely ill patients were particularly lesser than those in healthy subjects. Furthermore, the levels of serum protein thiol were completely correlated with levels of serum albumin in AKI patients. In this study, we did not further analyze the reason for the finding of levels of low thiol in AKI patients and in server ill patients. Levels of decreased serum albumin may have been the single significant cause for this observation (Qian et al., 2015).

Additionally, we also observed that the 90-day rate of mortality was elevated in the patients of AKI with high levels of serum thiol as compared with those who have levels of low serum thiol. Furthermore, levels of serum thiol in AKI affected patients were correlated with overall 90 days mortality rate, even APACHE II score and multivariable adjustment following for sepsis (Sykes, Reed and Lamerton, 2017).

5.0 CONCLUSION:

In concluding note, the AKI patients have curiously low levels of protein thiol, while increased level thiol are concerned with 90-day overall AKI population mortality. According to these findings, there is a need to further investigation for better results. There are basically few data on the connection between levels of plasma thiol and mortality, specifically in those patients who are affected with AKI. Finally, the connection between mortality and kinds of the levels of serum antioxidant in severely ill patients still persists controversial.

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