


RESEARCH ARTICLE

Increased lipid peroxidation, depleted non-enzymatic antioxidant, and variability in trace elements concentration in serum are correlated with Bangladeshi end-stage renal disease population

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Abstract

Introduction: End-stage renal disease (ESRD) is an abnormality where the kidneys are not usually working. This case-control study was planned to determine the extent of serum lipid peroxidation, non-enzymatic antioxidant (vitamin c), and trace elements in 50 patients with ESRD as cases and 50 normal healthy individuals as controls.

Methods: Determination of lipid peroxidation was carried out by ascertaining concentration of malondialdehyde (MDA) and vitamin C in serum using UV spectrophotometry whereas atomic absorption spectroscopy was used for trace elements estimation. The statistical analysis was conducted via the independent *t*-test samples and Pearson correlation test.

Results: The blood serum study has shown substantially higher MDA values than the control level and lowers vitamin C levels in the patient population ($P < .001$). A negative correlation was found between the vitamin C in serum with BMI and MDA for both patients ($r = -0.017$ and $r = -0.132$, respectively) and the control group ($r = -0.014$ and $r = -0.229$, respectively) after Pearson's correlation analysis. Regarding trace elements, significantly ($P < .001$) lower concentrations of zinc, copper, and manganese were found in the patient group than control subjects. Inter-element-relationship established a strong positive harmonization between these studied elements in both the cases of patients and control subjects.

Conclusion: Our results indicate strong associations of the pathogenesis of ESRD with depleted non-enzymatic antioxidant, increased lipid peroxidation, and inconsistency in trace elements concentration in serum, which may provide a prognostic tool for the treatment of this concerning the disease.

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KEYWORDS

antioxidants, ESRD, lipid peroxidation, MDA, trace elements

1 | INTRODUCTION

The kidneys are two bean-shaped organs of the body, an essential organ that regulates the body's urinary system. They remove water-soluble wastes from the body, being a natural filtration system of the blood transported to the bladder to excrete as urine. They also maintain body homeostasis by balancing the acid-base level of the body and regulating electrolytes and blood pressure. The kidneys act as a filter and produce hormones such as calcitriol, erythropoietin, and the enzyme renin, which play a significant role in maintaining blood calcium level and regulating blood pressure.^{1,2} Acute renal failure (ARF) or End-stage renal disease (ESDR) is a state when the kidneys permanently disable to work and the glomerular filtration rate (GFR) is reduced to <15 mL/min/1.73 m² or dialysis is becoming mandatory. Usually, complete loss of kidney function is occurred at this stage due to progressive chronic kidney disease (CKD). Several diseases like hypertension, poor nutritional health, anemia, and bone weakness due to mineral abnormalities such as calcium and nerve damage develop due to ESDR.³ Diabetes and high blood pressure are found to be the causative factors responsible for up to two-thirds of the cases of ESRD. In ESRD, the kidneys' function is reduced to such an extent where the kidney loses its standard capacity. When ARF occurs, and no other option remains, either kidney dialysis is done using a machine or transplanting a new healthy kidney that will perform the work of the two kidneys.⁴

Lipid peroxidation is a chain reaction that continues due to free radicals known as oxidative degradation of lipid, which results from extensive cell damage. It mainly affects polyunsaturated fatty acids, which possess reactive hydrogen. The most common free radical for initiation of lipid peroxidation is reactive oxygen species (ROS). ROS can be produced in our body endogenously or exogenously. ROS's endogenous sources are cell metabolism or hypoxia, apoptosis, pro-inflammatory cytokines (like TNF- α), and oncogenic cancer intermediates (like ROS) and exogenous source is ionizing radiation like UV or heat exposure.⁵ Body has its own free radical scavenging mechanisms known as antioxidants. These scavengers include catalase, superoxide dismutase, glutathione peroxidase, and cofactors (factors that allow enzymes to fully function) such as glutathione and vitamins as vitamin A, C, and E. The imbalance between these ROS and antioxidants gives rise to free radicals, consequently oxidative stress. Several research reveals that CKD has a positive correlation with oxidative stress and treatment of kidney patients with hemodialysis has been recommended to significantly contribute to oxidative stress and decreased antioxidant concentrations in these patients.⁵ In recent years, several studies illustrated signs of improved oxidative stress in patients with renal diseases.⁵ Lipid peroxidation creates several types of free radicals; Malondialdehyde (MDA) is prevalent among them. This aldehyde is a highly toxic molecule used as a biomarker to measure the level of oxidative stress in the human body.⁶

Trace elements or micro-minerals are essential for the proper functioning of biological processes by providing antioxidant defense in the human body and developing the immune system. Trace elements regulate a significant number of metabolic reactions in human body.⁷ Copper (Cu) as a trace element has antioxidant and pro-oxidant properties. As an antioxidant, Cu prevents cell damage by scavenging or neutralizing free radicals.^{8,9} Manganese (Mn) has a vital role in forming enzymes and activation. It works as an antioxidant and heals wounds by increasing collagen productions. Maintaining the proper dietary balance with essential elements like Cu, along with other minerals such as Zn (Zinc) and Mn, is essential.¹⁰ Zn is another remarkable component, which is directly involved in antioxidant defense mechanism and protects the immunological and vascular systems from the damaging effects of ROS. Thus, it plays an important role as an antioxidant.¹⁰

No research with serum samples with Bangladeshi ESRD patients is found to explore the blood concentration of lipid peroxidation (MDA), non-enzymatic antioxidant, and trace elements, namely Zn, Cu, and Mn. Therefore, the present study attempted to evaluate the changes in the serum levels of above mentioned parameters in ESRD patients relative to normal individuals, to hypothesize about their changes, and to relate their altered statuses to the pathogenesis and progression of ESRD.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

In this study, analytical chemical and reagent grades were used and bought from well-known companies available on the market. 2-thiobarbituric acid (TBA), Hydrochloric acid (37% HCl), Sulfuric acid (97% H₂SO₄), Phosphoric acid, Sodium nitrite (NaNO₂), Sulphanilamide, Sodium sulfate, n-butyl alcohol, and Dinitrophenyl hydrazine was purchased from Merck, Germany. Trichloroacetic acid (TCA) [Guangdong, China], Copper sulfate [Uni-chem, China], Metaphosphoric acid, and N-(1-naphthyl) ethylene diamine dihydrochloride [LobaChemie, India], 1,1,3,3-tetraethoxy-propane [Sigma, Aldrich], Zn, Cu, Mn [Buck Scientific, USA] were purchased for conducting experiment. Ascorbic acid was provided as a gift from Globe Pharmaceuticals, Noakhali, Bangladesh. In the whole study, distilled water was used as a solvent.

2.2 | Research design and study population

This case-control study was conducted in the Urology Department, Prime Hospital Ltd., Noakhali; from June 2019 to December 2019. For the study purpose, 50 patients of more than 18 years old with

ESRD (End Stage Renal Disease) were selected as positive cases, with 50 healthy volunteers selected as a control. All patients were evaluated clinically as per exclusion criteria. Several parameters such as personal information, family history, socio-economic data, and illness history were taken by a designed questionnaire filled up by individual subjects.

The exclusion criteria included patients with any other complications other than ESRD like systemic diseases and other chronic diseases that might interfere with the study. For this purpose, subjects had to undergo a routine physical checkup, including their weight, nutritional condition, organ activity, blood pressure, chest X-ray, and electrocardiogram. Furthermore, blood urea, creatinine, nitrogen, glucose, and liver enzyme tests were also performed for all subjects to find out their actual pathological conditions. Individuals with antioxidant and nutrition supplementation were also excluded.

2.3 | Ethical consideration

Ethical Committee of Noakhali Science and Technology University approved and reviewed the research protocol (number: PHRM_1204053/2019). In this study, some personal and family affairs were necessary to ask, which was very much sensitive. Strict measures were taken to ensure privacy, and no financial involvement of the patient or respondents was encouraged. Scope and limitation of the study were clearly defined to subjects or their key relatives. Written consent was taken from the issues and their critical relatives before study. No medication was given to the patient for trial except therapeutic measures and precautions were taken not to produce any environmental hazards.

2.4 | Data collection

A well-designed questionnaire was designed to collect detailed patient history by regularly attending Prime Hospital Ltd., Noakhali, Bangladesh. Data of the following parameters such as body mass index (BMI), age, systolic blood pressure (SBP) (mm Hg), and diastolic blood pressure (DBP) were collected from patients with ESRD and healthy volunteers. After explaining the purpose of the research, the questionnaires were given to patients, and they had assured about the study's confidentiality. Data were collected from the participating patient through a face-to-face interview by the author.

2.5 | Blood sample collection and storage

A plastic syringe with a stainless steel needle was used to draw 5 mL venous blood in a metal-free plastic tube out of each patient and control group. Each blood sample was centrifuged at 3000 for 15 minutes to extract serum, which takes 30 minutes to coagulate and serum was stored at -80°C in an Eppendorf tube for further study. To avoid potential interference in the test readings, all of the measures were completed in a dust-free environment.

2.6 | Biochemical analysis

2.6.1 | Determination of serum MDA and vitamin C

Determination of lipid peroxidation was performed through measuring serum MDA level according to Nahar et al with some modification.¹¹ A mixture was prepared by mixing 100 μL of serum with 900 μL of 0.9% saline solution. A total of 2 mL of TBA reagent and 30 μL of 50 mM butylated hydroxyl toluene (BHT) had been added. After that, the prepared mixture was incubated for 15 minutes at 60°C and kept in ice water for another 5 min. Then, the samples were centrifuged for 10 minutes at 5000 rpm. Finally, the absorbance of the supernatant was determined spectrophotometrically at 535 nm using 1,1,3,3-tetraethoxy-propane as standard.

In order to determine serum vitamin C (ascorbic acid), 5% TCA was mixed with isolated serum sample in a test tube and centrifuged for 10 min at 3000 rpm. The obtained supernatant was then preserved at -80°C for further study. UV spectrophotometer (UV-1201, Shimadzu, Kyoto, Japan) was applied to determine the concentration of ascorbic acid.¹²

2.6.2 | Determination of minerals

Serum concentration of Zn, Cu, and Mn was determined by flame atomic absorption spectrometry (Varian Spectra AA 220) with the graphite analysis.¹³ Study population have been diluted 10 times with deionized water. For the calibration of standard graphics, different amounts of trace elements were used (0.5, 1.0, 2.0, 5.0, and 10.0 mg/L). Absorbances were recorded at 213.9, 224.8, and 279.8 nm for zinc, copper, and manganese, respectively, in the atomic absorption spectrometer. Standard solutions were used to maintain quality control and assay accuracy for every 10 test samples.

2.7 | Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, IL) was used to carry out statistical analysis. All results were expressed as mean \pm SE mean (mean \pm SEM) with corresponding *P* values. A non-parametric and independent t-test sample was used to compare the patient and the control groups' parameters, where a correlation was established between the different study parameters by Pearson's correlation analysis.

3 | RESULTS

3.1 | Anthropometric and clinical characteristics of the study population

This study encircled 50 ESRD patients as cases as well as 50 healthy individuals as the control group. The anthropometric, clinical, and

biochemical characteristics of the patients and controls are tabulated in Table 1. The result showed that the patient and control group's mean age was 47.90 ± 2.06 and 48.12 ± 2.24 , respectively. Clinical parameters result revealed that the mean-variance of SBP between the patients (155.40 ± 2.99 mm Hg) and controls (142.38 ± 1.17 mm Hg) was statistically significant ($P < .001$). The average DBP and BMI were 86.60 ± 1.89 mm Hg and 24.42 ± 0.44 kg/m² for the patient group and 82.72 ± 0.63 mm Hg and 24.14 ± 0.24 kg/m² for the control group, respectively.

3.2 | Lipid peroxidation and antioxidant status

In this study, MDA was 3.29 ± 0.61 and 1.79 ± 0.72 $\mu\text{mol/mL}$, while the amount of vitamin C was 14.38 ± 4.83 and 17.95 ± 5.14 $\mu\text{mol/L}$ in patient and control groups, respectively (Table 2). Statistical analysis revealed that serum MDA level was significant in ESRD patients than in the control group. It had also been found that the concentration of vitamin C was lower in the serum of the patients when compared to controls.

3.3 | Correlation analysis of the variables

In our experiment, we tried to find a mechanistic way of lipid peroxidation with the anthropometric and clinical features of ESRD, and the observed results are represented in Table 3. No significant correlation was found among different socio-demographic factors and MDA or vitamin C ($P > .05$). But BMI and MDA were negatively or inversely with vitamin C in both the patients ($r = -0.017$ and $r = -0.132$, respectively) and control ($r = -0.014$ and $r = -0.229$, respectively) group.

TABLE 1 Anthropometric and clinical characteristics of the study population

Parameters	Values (Mean \pm SEM)		P value
	Patients	Control	
Age	47.90 ± 2.06	48.12 ± 2.24	.942 ^{NS}
BMI (kg/m ²)	24.42 ± 0.44	24.14 ± 0.24	.582 ^{NS}
SBP (mm Hg)	155.40 ± 2.99	142.38 ± 1.17	.000 ^{***}
DBP (mm Hg)	86.60 ± 1.89	82.72 ± 0.63	.054 ^{NS}

***Indicates $P < .001$ when compared to control; NS, non-significant.

TABLE 2 Serum level of MDA and vitamin C in the study population

Parameters	Values (Mean \pm SEM)		P value
	Patients	Control	
MDA ($\mu\text{mol/ml}$)	3.29 ± 0.61	1.79 ± 0.72	.000 ^{***}
Vitamin C ($\mu\text{mol/L}$)	14.38 ± 4.83	17.95 ± 5.14	.000 ^{***}

***Indicates $P < .001$ when compared to control.

3.4 | Serum trace elements concentration

Trace elements determination in blood serum exhibited that the mean Zn level in patient groups was 10.13 ± 2.35 mg/L (mean \pm SEM), though average Zn concentrations in the controls were 19.71 ± 14.03 mg/L. Minimum Zn levels were 1.12 mg/L, and maximum Zn levels were 32.62 mg/L, which was usually lower ($P < .001$) in the ESRD patients compared to that of healthy volunteers. For Cu, the mean serum levels in the patients with ESRD were 6.01 ± 8.63 mg/L (mean \pm SD) with a range of 1.5–14.25 mg/L while lower in the control group (5.78 ± 10.76 mg/L). The difference was distinguished as statistically significant ($P < .001$), having higher values in patients than the controls. Mn levels in the patient group (20.99 ± 7.53 mg/L) (mean \pm SD) were almost the same as that of the control group (20.37 ± 2.34 $\mu\text{g/dL}$), and the results were statistically less significant ($P > .001$) (Table 4).

TABLE 3 Correlation study between various research parameters in the study population

Correlation Parameters	Patient group		Control group	
	r	P	r	P
Age and BMI	0.381 ^{**}	.006	0.260	.068
Age and SBP	0.062	.667	0.137	.342
Age and DBP	-0.082	.573	0.279 [*]	.049
Age and MDA	0.149	.301	0.085	.556
Age and Vitamin C	0.058	.689	-0.014	.941
BMI and SBP	-0.061	.674	0.145	.316
BMI and DBP	-0.138	.339	0.025	.863
BMI and MDA	0.130	.367	0.072	.621
BMI and Vitamin C	-0.017	.905	-0.014	.940
SBP and DBP	0.545 ^{**}	.000	0.549 ^{**}	.000
SBP and MDA	-0.431 ^{**}	.002	0.206	.152
SBP and Vitamin C	0.166	.251	0.200	.290
DBP and MDA	-0.185	.197	0.077	.597
DBP and Vitamin C	0.217	.130	-0.005	.980
MDA and Vitamin C	-0.132	.359	-0.229	.224

Note: r, Correlation co-efficient; P, significance; values with negative sign indicate an inverse correlation; ^{**} $P < .01$, ^{*} $P < .05$ indicates correlation is significant at .01 and .05 level (two-tailed).

TABLE 4 Serum levels of Zn, Cu, and Mn in the study population

Parameters	Values (Mean \pm SEM)		P value
	Patients group	Control group	
Zn (mg/L)	10.13 ± 2.35	19.71 ± 14.03	$P < .001$
Cu (mg/L)	6.01 ± 8.63	5.78 ± 10.76	$P < .001$
Mn (mg/L)	20.99 ± 7.53	20.37 ± 2.34	$P > .001$

4 | DISCUSSION

People suffer from ESRD because of ignorance, illiteracy, poverty, and apathy toward health problems. The prevalence of ESRD has been rising over the past few decades.^{14,15} Severe ESRD can be more challenging to treat. However, medicines can help to prevent or control ESRD.¹⁴ This study aimed to determine the status of many biochemical parameters that may contribute to ESRD progression by analyzing the anthropometric, clinical, and biochemical characteristics of the targeted patients and tried to establish the relevance of these parameters with the disease process for the improvement of our knowledge about ESRD.

Differences found in SBP between ESRD patients and the control group were significant. Many studies suggest that SBP is the most common reason for ESRD, and the prevalence increases with decreasing GFR.^{16,17}

Although oxidative stress is generated as part of the body's defense mechanisms, it takes part in the pathogenesis of atherosclerosis, malnutrition, dialysis-related amyloidosis, anemia, and coronary heart disease. The study suggests that oxidative stress results from excessive free radicals production coupled with defective anti-oxidant defense mechanisms. An inverse relationship was reported between vitamin C with MDA in our study ($r = -0.132$). A highly significant level ($P < .001$) of MDA and lower level of vitamin C in ESRD patients than control groups was found in this study. Our finding was in agreement with the results found by several authors.¹⁸⁻²¹ MDA is the biomarker of lipid peroxidation, and ROS is the causative reason for lipid peroxidation. To maintain cellular physiology, ROS is produced in many areas of the kidneys, especially non-phagocytic cells. But overproduction of ROS results in loss of redox homeostasis, leading to pro-inflammatory and pro-fibrotic pathways in the kidney.²² To counteract the deleterious effects of ROS, the body has natural anti-oxidant pathways. Several studies suggest that defective anti-oxidant defense mechanisms decrease vitamin C levels due to low dietary intake of vegetables that contain vitamin C due to diseases like hyperkalemia and loss of vitamins during dialysis.^{23,24}

As a part of enzymes, hormones, and cells, trace elements are crucial in maintaining normal body physiology although required in a minute amount. In this research work, we determined the serum concentrations of zinc (Zn), copper (Cu), and manganese (Mn) in both ESRD patients and healthy control subjects. We found no significant differences ($P > .05$) in Cu and Mn level in patient subjects than in control subjects. However, we found a significantly ($P < .001$) lower Zn level in ESRD patients compared to control. Our finding complies with previously conducted studies.²⁵⁻²⁷ Cu, Zn, and Mn have a good role in reducing oxidative stress. 60% of the copper occurs as part of copper-zinc metallo-enzyme superoxide dismutase and plays a crucial role in protecting the cell from free radicals harmful effects. Cu/Zn-SOD converts the superoxide anion into hydrogen peroxide, which is the most important antioxidant mechanism in the body. Thus this is an important marker for the progression of kidney diseases.^{28,29} The activity of SOD enzymes depends on the release of ROS. In ESRD patients, the high level of ROS produces enzyme deficiency, and

finally, the activity of this enzyme is thoroughly compromised by low zinc concentrations.²⁹⁻³¹ Reduced level of Zn may have a contribution in the activation of monocytes and macrophages for generating different inflammatory cytokines and increasing oxidative stress.³² Several studies revealed that Zn's low concentration in ESRD patients is due to dietary restrictions and low absorption of Zn by the gut wall.^{30,31}

5 | LIMITATIONS OF THE STUDY

Apart from the significance of our current study, we should note some limitations. We did not include the effect of dietary supplementation and social classes in our study criteria. Therefore, further research is required to see whether a nutritional intervention can improve the quality of ESRD patients or not. The study was also conducted on a small number of subjects, so it lacks the exact severity of disease scores. A large-scale study with a larger number of samples from different parts of Bangladesh could better represent the condition of this population. Although this study still has some shortcomings, we believe that our research would contribute significantly to the development of new pathological tools for ESRD patients in Bangladesh.

6 | CONCLUSIONS

ESRD is a significant concern in the present day due to its high treatment cost and poor outcomes. This research study concluded that SBP and oxidative stress contribute to the worse condition of ESRD patients. A study of trace elements level in patients group reveals that Zn level was decreased in ESRD patients, which has a correlation to cause oxidative stress. Further studies are recommended to ascertain whether Zn and antioxidant supplements can reduce oxidative stress to improve ESRD patients' condition. Therefore, we have conducted an analysis only for non-enzymatic antioxidants (Vitamin-C). Further studies are recommended for enzymatic antioxidants.

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CONFLICT OF INTEREST

The author reports no conflict of interest in this work.

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TRANSPARENCY STATEMENT

The lead author (Mohammad Safiqul Islam, one of the corresponding authors) confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

All data and materials are contained and described in the manuscript. The data set was deposited in the Department of Pharmacy, Noakhali Science and Technology University, Noakhali-3814, Bangladesh.

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