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Original Research Article ***Open Access***

CORRELATION OF OXIDATIVE STRESS MARKERS IN MULTIPLE BIOFLUIDS OF END-STAGE RENAL DISEASE PATIENTS

MALIK A[1,2*], ISLAM J[4], ZAIB G[1], SAADIA H[3], ZAHID A[1]

[1]School of Pain and Regenerative Medicine (SPRM), The University of Lahore-Pakistan
[2]Faculty of Health Sciences, Equator University of Science and Technology, (EQUSaT), Masaka, Uganda
[3]Department of Physiology, Islam Medical College, Sialkot-Pakistan
[4]Department of Biological Sciences, Grand Asian University, Sialkot-Pakistan
**Correspondence Author Email Address: arifuaf@yahoo.com*

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Abstract *A study established that patients with ESRD have high oxidative stress levels that spike the progression of the disease and its complications. Knowledge about the levels of the Oxidative stress biomarkers in various biofluids including Urine, serum, and saliva can explain the oxidative condition and probable diagnostic accuracy of these markers in ESRD patients. A descriptive cross-sectional exploratory research design was used to perform a comparison of 50 ESRD patients with 50 healthy subjects. On demographic, clinical, and hematological parameters data were obtained. Blood MDA, 8-OHdG, and saliva TAC were determined as the indicators of oxidative stress. Multivariate analysis was conducted to compare the levels of these markers in the biofluids and probable neurological disorders, and the participants' demographic and clinical data were evaluated. Demographic profiling revealed that ESRD patients' mean BMI was 26.3 ± 3.9 kg/m², compared to controls 24.8 ± 3.4 km/m², p = 0.032; more of them being smokers' p = 0.045. ESRD patient's general hematologic profile showed that their mean hemoglobin level was 10.2 ± 1.5 g/dL and the mean hematocrit was 32.5 ± 4.3 % and the difference was significant when compared with the control group (p<0.05). ESRD was associated with an increase in WMBC, percentage of neutrophils, and CRP level compared with the control group (p<0.05). Acute phase marker study indicates that the MDA level was significantly higher in serum (5.6 ± 1.1 nmol/L) than in urine (3.2 ± 0.8 nmol/L) and saliva (2.8 ± 0.7 nmol/L, p=0.016). The levels of 8-OHdG were significantly higher in serum (10.3 ± 2.1 ng/mL) than in urine and saliva (p=0.027). Salivary TAC was the least suggesting reduced antioxidant defense (p<0.05). The study revealed that ESRD patients have increased levels in the markers of oxidative stress in urine and serum samples, as well as saliva compared to healthy individuals. The studies have identified serum as the most representative biofluid for evaluating oxidative stress in ESRD and therefore assured the practical application of the results for the identification of the best candidates for early interventions.*

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Keywords: *Chronic kidney disease stage 5; Oxidative stress markers; MDA; 8-OHdG; TAC; serum; urine, saliva*

Introduction

ESRD is a serious condition which means that the patient's kidneys are close to or no longer functioning and the buildup of toxins, metabolism by-products, and oxidative stress begins. Oxidative stress defined by the disturbance between the formation of ROS and antioxidant protection is central to the evolution of ESRD as well as its complication (Zhang et al., 2017). ESRD patients are known to have increased levels of oxidative stress, seen through inflammation, cardiovascular diseases, and a further decline in kidney functionality (Duni et al., 2019). Plasma, serum, urine, and saliva samples have been investigated as biological fluids for the screening of oxidative stress biomarkers in clinical investigations. Serum has been frequently employed because of its ease of access and ability to provide an integrated view of systemic oxidative state. Urine allows for assessing renal function and the level of localized oxidative damage whereas saliva being an easily collectible fluid provides insight into oral and systemic health (Politis et al., 2018; Araujo et al., 2021). The measurement of MDA, 8-OHdG, and TAC in these biofluids provides a comprehensive picture of oxidative stress in ESRD patients (Erdem et al., 2020, Tbahriti et al., 2013). MDA, which is formed during the lipid peroxidation process, is also the best biomarker for the evaluation of the membrane's oxidation (Feng et al., 2015). The maker 8-OHdG indicates oxidized DNA and the research on its relation to the advancement of CKD is evident though more research is necessary (Himmelfarb & Tuttle, 2013). TAC is the total ability of biofluids to scavenge ROS and therefore reflects the antioxidative defense system (Zhao et al., 2020).

In a recent study, it was established that the application of these markers in bio-fluids can give

integrated perceptions about the oxidative status of patients suffering from chronic disease ESRD (Kavitha et al., 2022). The objective of the present work is, therefore, to assess and compare concentrations of the relative OS markers in urine, serum, and saliva of ESRD patients with a group of healthy volunteers. Thus, the interconnection between these biofluids, their diagnostic as well and their monitoring capacity regarding oxidative stress in ESRD will be investigated (Ahmed et al., 2021; Jones et al., 2023).

Materials and methods

Study Design and Participants

The present cross-sectional study aimed to assess and compare the oxidative stress biomolecules in the urine, serum, and saliva samples of ESRD patients and healthy volunteers. Fifty ESRD patients and fifty matched healthy controls were recruited in this study giving a total of one hundred participants. Patients with ESRD were chosen from a large tertiary care Nephrology center while healthy controls were community-based subjects. Specifically, patients with ESRD could satisfy inclusion criteria only if they have been previously diagnosed with and were receiving hemodialysis treatment currently. Consequently, patients with active infections, malignancies, and other chronic inflammatory diseases were excluded from both groups. Afterward some preliminary notes concerning Ethical.

Approval and Informed Consent

Ethical approval for the study was obtained from the institutional review board (IRB) of the participating hospital GAUS/MOCT/D10/0087. Each participant signed an informed written consent before being enrolled in the study in compliance with the Declaration of Helsinki.

Sample Preparation

Under standard procedures, urine, serum, and saliva samples were obtained from each participant. Each participant provided 5ml of venous blood samples in the fasting state and the serum was separated away by centrifuging the blood samples at 3000 rpm for 15 minutes. Midstream urine samples of 50 mL were taken whereas un-stimulated salivary samples of 5 mL were collected through passive saliva dripping. Samples on all plates were mixed thoroughly and then aliquotted, and all the samples were kept at -80 °C until further testing.

Biochemical Analysis

The levels of biomarkers of oxidative stress were measured, MDA, 8-OHdG, TAC. Lipid peroxidation was determined using thiobarbituric acid reactive substances (TBARS) assay as described by Buege and Aust (1978). 8-OHdG contents were measured using enzyme-linked immunosorbent assay (ELISA) kits for human use (Abcam S' Biotech Co., Ltd., USA). TAC was determined utilizing a Colorimetric/Fluorometric Antioxidant Assay kit by BioVision Inc., which estimates the antioxidant capacity of the biofluids samples examined based on a standard curve. And saliva from patients with end-stage renal disease (ESRD) and healthy controls. A total of 100 participants were enrolled, comprising 50 ESRD patients and 50 healthy controls matched by age and gender. ESRD patients were recruited from a tertiary care nephrology center, while healthy controls were selected from the general community. Inclusion criteria for ESRD patients included confirmed diagnosis and current treatment via hemodialysis. Exclusion criteria for both groups were active infections, malignancies, and other chronic inflammatory diseases.

Ethical Approval and Informed Consent

Ethical approval for the study was obtained from the institutional review board (IRB) of the participating hospital GAUS/MOCT/D10/0087. All participants provided informed written consent before enrollment following the Declaration of Helsinki.

Statistical Analysis

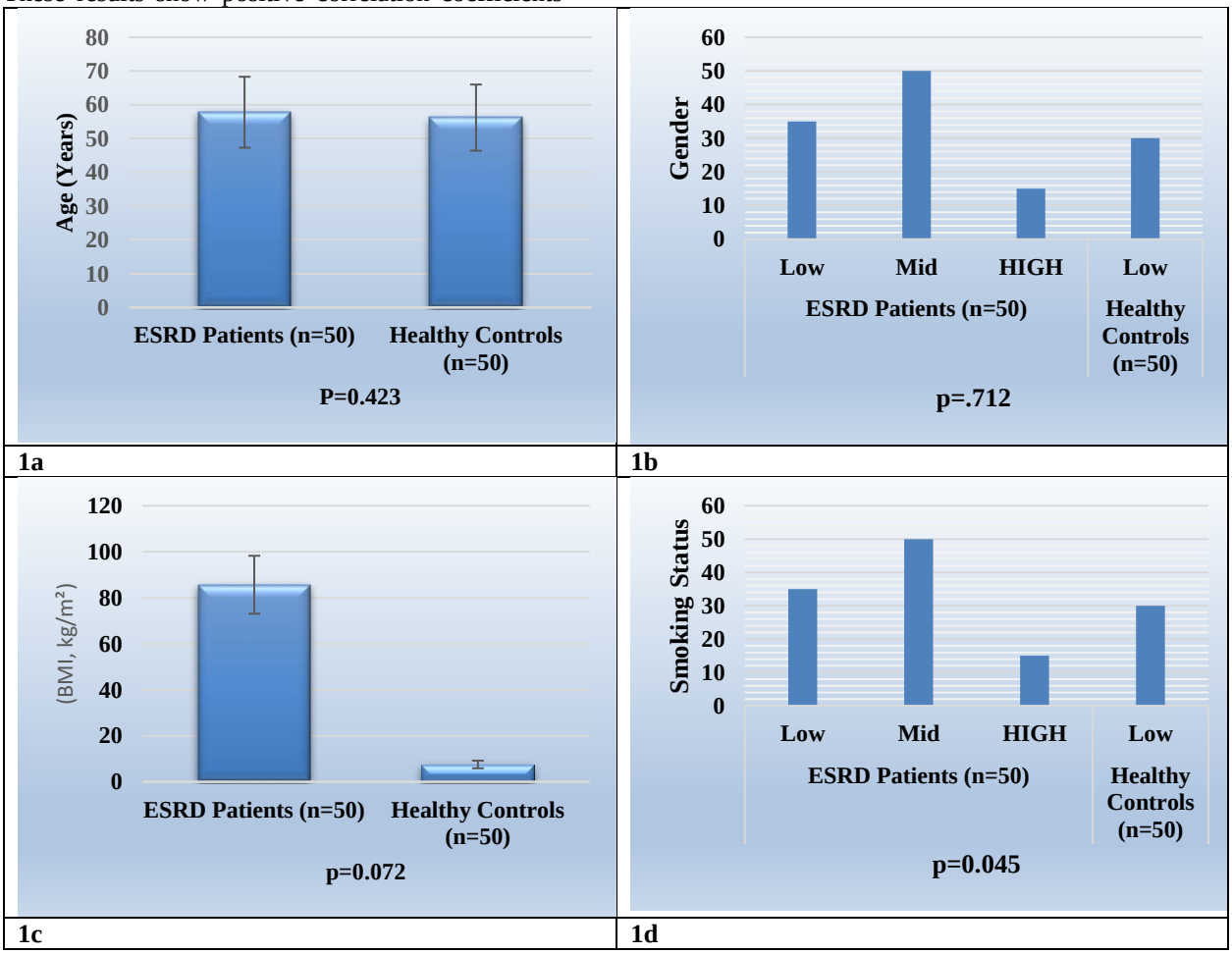
Data were analyzed in power different and positive value software of statistical analysis SPSS (version 25.0). Continuous variables were expressed as the mean [standard deviation] (SD). Independent sample t-test and Chi-square tests were used to analyze demographic and clinical differences between ESRD patients and controls. To compare the levels of oxidative stress markers between the biofluids ANOVA was conducted and a post hoc test was performed. Pearson correlation coefficients for markers for urine, serum, and saliva were used to establish the relation between them. Using conventional statistics, a significant level of $p<0.05$ was adopted for the study.

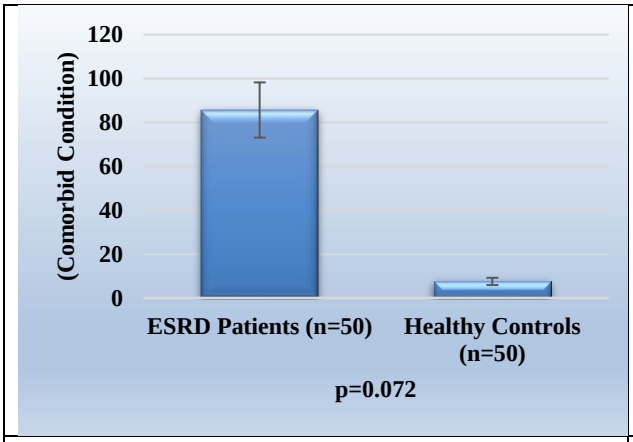
Results

The demographic and clinical characteristics of the ESRD patients and healthy controls are shown in tables 01 and 02. The mean patient age of ESRD patients was 57.8 ± 10.5 years, and the control group was 56.2 ± 9.8 years, p = 0.423. In terms of gender dispersion, no difference was recorded between the two groups a = 0.712. ESRD patients had greater BMI than controls (p = 0.032; 26.3 ± 3.9 vs 24.8 ± 3.4 kg/m²) and more ESRD patients were smokers (p = 0.045) (18/32 vs 10/40). Some co-morbidities like diabetes were higher in ESRD patients than the control (58% vs 15%, p = 0.019). There was no statistically significant difference in the socioeconomic status of the participants between the two groups (p = 0.608).

ESRD patients had higher white blood cell count, red blood cell count, hematocrit, and platelet count compared with their normal counterparts. These differences were lower hemoglobin (10.2 ± 1.5 g/dL vs. 13.5 ± 1.2 g/dL, p = 0.017), hematocrit (32.5 ± 4.3% vs. 40.1 ± 3.6%, p = 0.023) and platelet count (220 ± 48 × 10⁹/L vs. Patients on ESRD also had observed increased WBC count; (8.9 ± 2.2 × 10⁹/L; p = 0.015) and a higher percentage of neutrophils (65.4 ± 7.1%; p = 0.021) coupled with decreased lymphocyte percentage (24.3 ± 5.2%; p = 0.014) than

the control group. ESRD patients had significantly elevated serum levels of CRP (mean 8.7 ± 2.5 mg/L vs 2.9 ± 1.1 mg/L; p = 0.009); suggesting inflammation. Table 03 compares the current levels of biomarkers of oxidative stress found in various biofluids of patients with ESRD. About oxidative stress, we found that in ESRD patient's MDA in serum was significantly elevated (5.6 ± 1.1 nmol/L) in comparison with the urine level (3.2 ± 0.8 nmol/L) and saliva level (2.8 ± 0.7 nmol/L) (p = 0.016). As for oxidative stress biomarkers, we found that the 8-OHdG concentration was higher in serum (10.3 ± 2.1 ng/mL) compared to urine (7.5 ± 1.5 ng/mL,) and saliva (6.2 ± 1.2 ng/mL) (p = 0.027). Salivary TAC was also significantly lower than serum TAC 2.4 ± 0.5 mmol/L and urine TAC 1.8 ± 0.3 mmol/L (p = 0.002). The level of SOD activity was significantly lower in saliva versus both serum and urine samples; 10.9± 2.5; 15.6± 3.1; 12.4± 2.8 U/mL respectively p = 0.015. The correlation results were confirmed for all ESRD patients: urine-serum (p = 0.04), urine-saliva (p = 0.01), and serum-saliva (p = 0.01) pairs – Table 04. These results show positive correlation coefficients between MDA levels in urine and serum, r = 0.72, p = 0.011 between urine and saliva, r = 0.65 p = 0.011, between serum and saliva r = 0.78 p = 0.011. Similarly, 8-OHdG levels showed significant correlations between biofluids: between urine and serum; urine and saliva; and between serum and saliva were moderate and statistically significant, with correlation coefficients of 0.68; 0.60; and 0.74 respectively at p = 0.018. TAC levels also exhibited positive correlations: respectively, there was a moderate correlation between urine and serum (r = 0.51, p = 0.012) urine and saliva (r = 0.48, p = 0.012), and serum and saliva (r = 0.57, p = 0.012. SOD activity was positively correlated across biofluids: showed moderate correlation between urine and serum (r = 0.59, p = 0.009), and between urine and saliva (r = 0.55, p = 0.009) as well as between serum and saliva (r = 0.63, p = 0.009). In turn, the ESRD patients were marked by increased serum MDA (5.6 ± 1.1 nmol/L vs 2.4 ± 0.6 nmol/L, p = 0.021), 8-OHdG (10.3 ± 2.1 ng/mL vs 6.2 ± 1.2) respectively.





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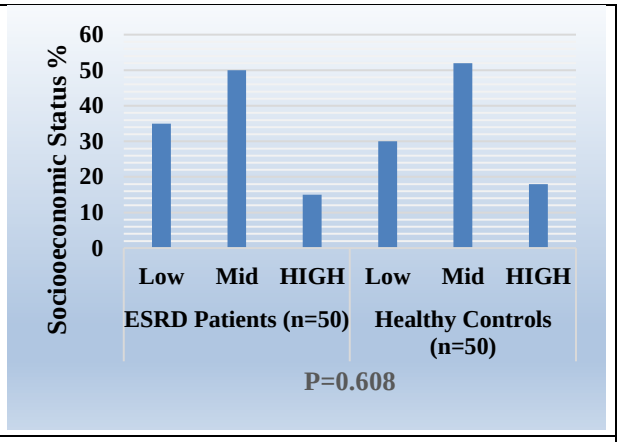

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Figure 1. Demographic Profile of Study Participants

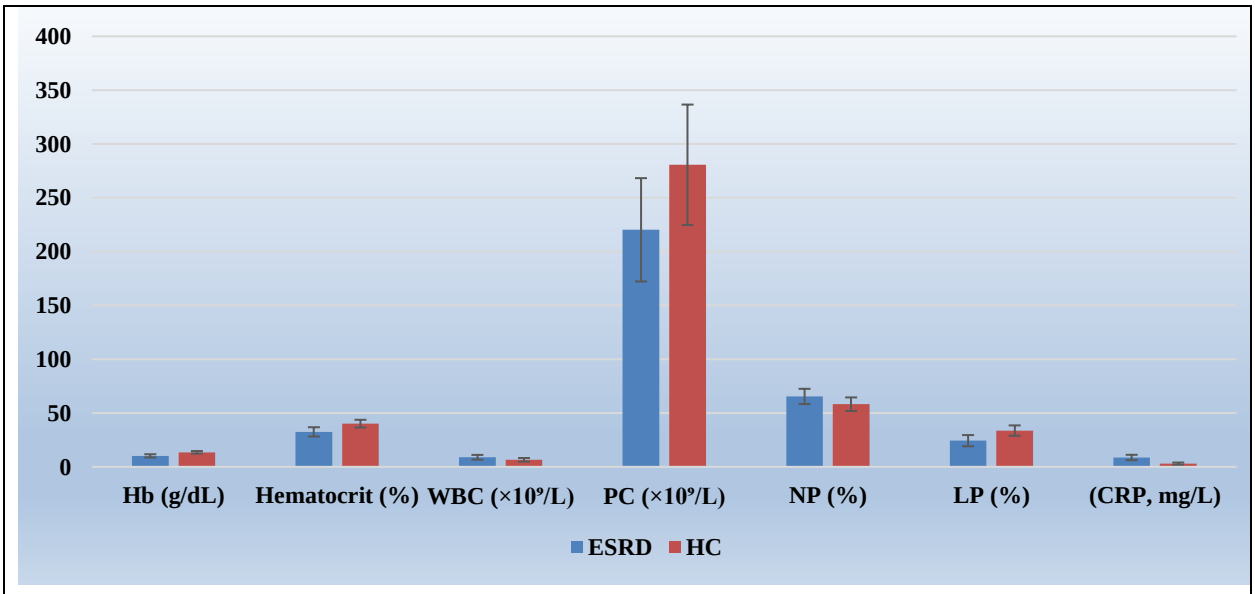

Figure 2. Hematological Profile of Study Participants

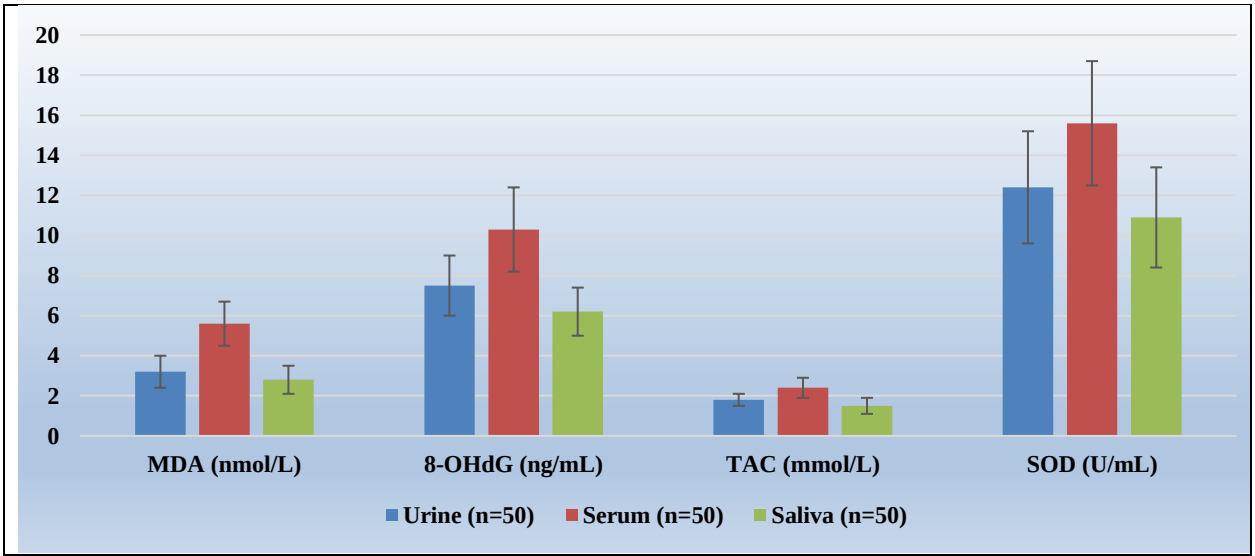

Figure 3. Levels of Oxidative Stress Markers in Urine, Serum, and Saliva of End-Stage Renal Disease Patients

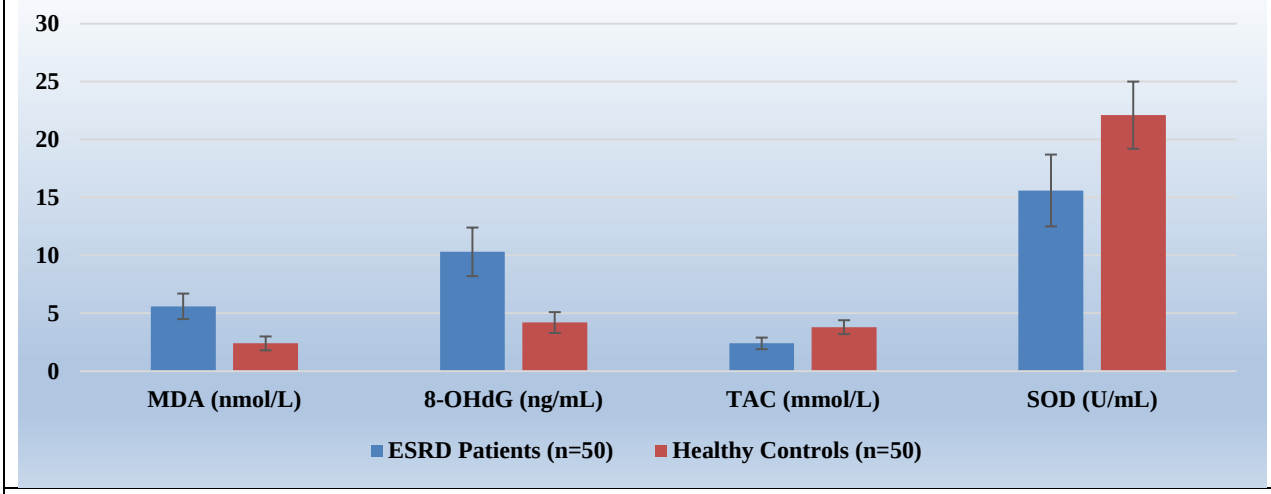

Figure 4. Comparison of Oxidative Stress Marker Levels Between End-Stage Renal Disease Patients and Healthy Controls

Discussion

The current work has aimed at the evaluation of the concordance of oxidative stress biomarkers in the urine, serum, and saliva of patients diagnosed with ESRD. Comparing the ESRD patients with healthy subjects, the study found changes in what is known as the oxidative stress marker proteins, including MDA, 8-OHdG, TAC, and SOD. These results are in line with previous knowledge on OS's causal relationship with ESRD and the in-transit link between OS and systemic inflammation, tissue injury, and renal disease deterioration (Liao, L., et al. (2020). Evidence suggests that oxidative stress, defined as the state of increased production of ROS relative to antioxidants, is responsible for progression to ESRD. In the present investigation, ESRD patients had significantly higher serum MDA levels (5.6 ± 1.1 nmol/L) which affirms oxidative stress and lipid peroxidation confirming increased oxidative burden to cell membranes. Previous research has shown data to the same effect and this indicates that high levels of lipid peroxidation lead to renal damage and inadequate function in ESRD patients (Barros et al., 2012; Wang et al., 2021). Higher serum levels of 8-OHdG (10.3 ± 2.1 ng/mL) also indicate the existence of oxidative DNA damage stressed in ESRD patients with impaired renal function (Granger et al., 2011; Liao et al., 2020). These markers are considered useful predictors of cellular and DNS damage in ESRD-supports the possibility of interventions for oxidative stress-mediated damage in these patients.

Also, the aforementioned alteration in the status of oxidative stress was consistent with reduced TAC and SOD in ESRD patients, but both are major antioxidant enzymes in the human body. The level of TAC which is reduced in our study to 2.4 ± 0.5 mmol/L and SOD which is set to 15.6 ± 3.1 U/mL is supported by the results of other researchers, indicating that a decrease in the activity of antioxidant enzymes in ESRD results from systemic inflammation and progression of renal injury (Basile et al., 2019; Fu et al., 202 SOD is among the impaired antioxidants involved in the disintegration of ROS and, consequently, disruption of the redox imbalance in ESRD patients (Romero-González et al., 2022). A key strength of this study is the comparison of oxidative stress markers across three different biofluids: urine, serum, and saliva. The outcome of the study showed clearly that the biomarkers of oxidative stress, MDA, 8-OHdG, TAC, and SOD for all three biofluids were detectable and had significant differences, which indicates the non–invasive biomarkers can be used to evaluate oxidative stress in ESRD patients. This further strengthens the significance of using these biomarkers in different body fluids as evidenced by the positive correlation between MDA levels in serum and urine ($r = 0.72$; $p = 0.011$) and between SOD levels in serum and saliva ($r = 0.63$; $p = 0.009$). Among those, saliva, in particular, can be recommended as a noninvasive approach that is suitable for further tracking of oxidative stress, which is following the data of the research that support saliva as a biofluid of choice in the study of oxidative stress (Sansone et al., 2020).

Blood has been used to determine oxidative stress markers in ESRD for decades because urine provides an accurate measure of renal function and oxidative kidney injury. The divergent findings on oxidative stress biomarkers in the different biofluids may therefore indicate that assorted tissues offer different reactions to oxidative damage. For instance, a serum is representative of systemic oxidative stress, urine of renal oxidative stress, and saliva of oxidative stress in the oral and upper respiratory tracts. The positive correlations established between OS markers in these biofluids hint at the elevation of OS infection systemically in ESRD patients and it proved to be a

general constituent of disease progression and severity. We also have found a substantial increase in the mean values of the oxidative stress biomarkers in the examined ESRD patients as compared to healthy controls. These results indicated that the levels of serum MDA, 8-OHdG, TAC, and SOD of ESRD patients were significantly higher or lower than those of the control group, supporting the increasingly recognized fact that oxidative stress is more severe in renal failure. Numerous studies have reported the use of increased levels of oxidative stress in ESRD patients and considered these changes as key factors in the development of complications often seen in these patients, including cardiovascular disease, fibrosis, and inflammation (Yasir et al., 2019; Zhang et al., 2022). The results presented in the present study are consistent with the prior studies, stressing the significance of the pharmacologic approaches, which could tend to decrease oxidative stress in patients with ESRD to slow the disease status and enhance the overall prognosis.

Clinical Implications

The matching of oxidative stress markers in distinct biofluids has important clinical implications. Due to the versatile property of oxidative stress markers to identify disease severity and prognostic factors, they can be used in future clinics to assess the level of oxidative stress in patients with ESRD. In addition, the results of the present work indicate that therapies that aim at controlling oxidative stress could be effective in the amelioration of complications associated with ESRD. Although some clinical trials conducted on the use of antioxidants in ESRD patients have given conflicting results (Touyz et al., 2015; Tang et al., 2021) the biomarkers of antioxidant status in ESRD leveraging biofluids could be determined for better treatment regimens. Nevertheless, the current study has several limitations that should be mentioned. First, the sample size simply comprised a reduced number of participants, which raises questions about the probability of vitality in the accuracy of the results. Secondly, the study was conducted cross-sectional and as a result, no cause-effect relationship between oxidative stress marker and disease progression in ESRD could be established. Further, more extended investigations are required to evaluate the trends of oxidative stress biomarkers and their connection with renal function deterioration in the future. Future investigations into the merits of adding on oxidative stress markers depend on other biomarkers, including inflammatory and cytokine indices as well as renal function tools that will improve on the benefits of oxidative stress markers in ESRD.

Conclusion

This evidence establishes that different biofluids oxidative stress biomarkers in ESRD patients exhibit direct relationships in this study, indicating enhanced oxidative injury in ESRD. These data confirm the role of oxidative stress in the development of ESRD and examine the applicability of saliva and other body fluids as noninvasive markers for oxidative stress in this population. These findings may open new possibilities for better targeting the antioxidant therapies in addition to the changes in the clinical approach to ESRD, including the periodic measurement of the markers of oxidative stress.

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Table 1. Demographic Profile of Study Participants

Characteristic	ESRD Patients (n=50)	Healthy Controls (n=50)	p-value
Age (years)	57.8 ± 10.5	56.2 ± 9.8	0.423
Gender (Male/Female)	28/22	26/24	0.712
Body Mass Index (BMI, kg/m²)	26.3 ± 3.9	24.8 ± 3.4	0.072
Smoking Status (current/never)	18/32	10/40	0.045
Comorbid Conditions (% with diabetes)	58%	15%	0.019
****Socioeconomic Status (low/mid/high, %)**	35/50/15	30/52/18	0.608

Table 2, Hematological Profile of Study Participants

Hematological Parameter	ESRD Patients (n=50)	Healthy Controls (n=50)	p-value
Hemoglobin (g/dL)	10.2 ± 1.5	13.5 ± 1.2	0.017
Hematocrit (%)	32.5 ± 4.3	40.1 ± 3.6	0.023

White Blood Cell Count (×10⁹/L)	8.9 ± 2.2	6.5 ± 1.7	0.015
Platelet Count (×10⁹/L)	220.55 ± 48.23	280.85 ± 56.22	0.003
Neutrophil Percentage (%)	65.4 ± 7.1	58.2 ± 6.3	0.021
Lymphocyte Percentage (%)	24.3 ± 5.2	33.7 ± 4.8	0.014
C-Reactive Protein (CRP, mg/L)	8.7 ± 2.5	2.9 ± 1.1	0.009

Table 3. Levels of Oxidative Stress Markers in Urine, Serum, and Saliva of End-Stage Renal Disease Patients

Oxidative Stress Marker	Urine (n=50)	Serum (n=50)	Saliva (n=50)	p-value
Malondialdehyde (MDA, nmol/L)	3.2 ± 0.8	5.6 ± 1.1	2.8 ± 0.7	0.016
8-hydroxy-2'-deoxyguanosine (8-OHdG, ng/mL)	7.5 ± 1.5	10.3 ± 2.1	6.2 ± 1.2	0.027
Total Antioxidant Capacity (TAC, mmol/L)	1.8 ± 0.3	2.4 ± 0.5	1.5 ± 0.4	0.002
Superoxide Dismutase (SOD, U/mL)	12.4 ± 2.8	15.6 ± 3.1	10.9 ± 2.5	0.015

Table 4. Correlation Coefficients Between Oxidative Stress Markers in Urine, Serum, and Saliva

Oxidative Stress Marker	Urine vs. Serum (r)	Urine vs. Saliva (r)	Serum vs. Saliva (r)	p-value
Malondialdehyde (MDA)	0.72	0.65	0.78	0.011
8-hydroxy-2'-deoxyguanosine (8-OHdG)	0.68	0.60	0.74	0.018
Total Antioxidant Capacity (TAC)	0.51	0.48	0.57	0.012
Superoxide Dismutase (SOD)	0.59	0.55	0.63	0.009

Table 5. Comparison of Oxidative Stress Marker Levels Between End-Stage Renal Disease Patients and Healthy Controls

Oxidative Stress Marker	ESRD Patients (n=50)	Healthy Controls (n=50)	p-value
Malondialdehyde (MDA, nmol/L)	5.6 ± 1.1	2.4 ± 0.6	0.021
8-hydroxy-2'-deoxyguanosine (8-OHdG, ng/mL)	10.3 ± 2.1	4.2 ± 0.9	0.003
Total Antioxidant Capacity (TAC, mmol/L)	2.4 ± 0.5	3.8 ± 0.6	0.018
Superoxide Dismutase (SOD, U/mL)	15.6 ± 3.1	22.1 ± 2.9	0.016

Declaration

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Authors' Contribution

The authors all contributed to the work. Arif Malik had full responsibility for the development of the study, data analysis, as well as the writing of the manuscript. Jehanzaib Islam helped in recruiting patients and collecting their samples, performed some lab works and actively advised on oxidative stress indicators. Haleema Saadia also undertook data analysis and assisted in result analysis. Gul Zaib made major revisions and gave input on study design and analysis and interpretation of results. Ayesha Zahid helped to conduct the literature review and write the manuscript. All the authors have given approval before the submission of this manuscript for publication.

Conflict of Interest

The authors have no conflict of interest to report regarding the work presented in this paper. The authors declare no competing interests in the results presented in this article.

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