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Malondialdehyde as a Biomarker for Oxidative Stress in Dialysis Patients: A Predictor of Complications and Treatment Efficacy

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Abstract

Background: Oxidative stress plays a crucial role in the complications associated with chronic kidney disease (CKD), particularly in individuals undergoing dialysis. Malondialdehyde (MDA), a key marker of lipid peroxidation, serves as an indicator of oxidative stress and has been associated with heightened cardiovascular risk, inflammation, and other adverse outcomes in dialysis patients. ***Objective:*** This study aimed to assess MDA's role as a biomarker of oxidative stress in dialysis patients and its potential for predicting complications and evaluating treatment effectiveness. ***Methods:*** A cross-sectional study was conducted at Srinivas Institute of Medical Sciences and Research Centre, Mangalore, between December 2021 and September 2022. The study included 50 dialysis patients (subdivided into hemodialysis and peritoneal dialysis groups) and 30 healthy controls matched for age and sex. Plasma MDA levels were measured using the Thiobarbituric Acid Reactive Substances (TBARS) assay. Additional biochemical markers related to oxidative stress, inflammation, and renal function were also analyzed. ***Results:*** Dialysis patients exhibited significantly higher MDA levels (3.82 ± 0.73 nmol/L) compared to controls (2.07 ± 0.47 nmol/L, $p < 0.0001$), alongside reduced antioxidant enzyme activity. Elevated CRP levels indicated persistent inflammation. Renal function markers and lipid profile changes also suggested disease-related metabolic disturbances. MDA correlated positively with CRP ($r = 0.68$, $p < 0.001$) and negatively with antioxidant enzyme activity. ***Conclusion:*** These findings confirm that dialysis patients experience significant oxidative stress and inflammation, with MDA serving as a reliable biomarker. MDA may aid in monitoring oxidative stress levels, predicting complications, and guiding antioxidant therapies.

Keywords: ***chronic kidney disease, Malondialdehyde, hemodialysis, Oxidative Stress.***

Introduction

Oxidative stress is a central pathological mechanism in chronic kidney disease (CKD) and its progression, especially in dialysis patients. The disequilibrium between reactive oxygen species (ROS) generation and antioxidant protection mechanisms leads to cellular injury, inflammation, and a variety of complications, such as cardiovascular disease, anemia, and dysfunction related to dialysis. The detection of credible biomarkers of oxidative stress is essential for the evaluation of disease severity, prediction of complications, and monitoring of the effects of treatment in patients undergoing dialysis.

Malondialdehyde (MDA) is a well-known biomarker of lipid peroxidation, indicating oxidative damage to the cell membrane. Higher MDA levels among dialysis patients suggest increased oxidative stress, which has been related to increased cardiovascular morbidity, chronic inflammation, and unfavorable clinical outcomes. As a putative predictive marker, MDA quantification can offer important information regarding patient prognosis and assisting in directing therapeutic interventions to counteract oxidative stress [1].

The objective of this study is to examine the use of MDA as a biomarker for oxidative stress in dialysis patients, determining its relationship with disease complications and treatment outcomes. With knowledge of the clinical relevance of MDA levels, health practitioners can improve the adaptation of antioxidant treatment and dialysis protocols toward better patient outcomes.

Rationale

In fact, oxidative stress is most likely the essential and prominent factor in the pathophysiology of chronic kidney disease (CKD), which gets more aggravated in dialysis patients. The imbalance between the generation of reactive oxygen species (ROS) and antioxidant defenses damages cells, induces inflammation, and increases the risk of associated complications such as cardiovascular disease, anemia, and dialysis-related dysfunction. Increasing evidence points to oxidative stress occurring in dialysis patients; however, there is a need for clinically relevant biomarkers for determining the severity of the stress, the prediction of complications, and evaluation of the efficacy of treatment.

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Well-recognized biomarkers of lipid peroxidation and oxidative stress are malondialdehyde (MDA). There are reports of high levels of MDA in dialysis patients, which indicate severe oxidative damage, but limited evidence exist concerning its clinical relevance for prediction of complications or treatment actions [2]. Establishing a relationship between MDA levels and dialysis-related complications can yield significant information on the possible prognostic and diagnostic role of MDA.

It could also be said that there are different dialysis modalities (hemodialysis and peritoneal dialysis) and their differences influence oxidative stress levels. These differences help in optimizing dialysis protocols to such an extent that oxidative damage is minimized. Furthermore, evaluating the changes in malondialdehyde levels due to antioxidant therapies would be another good area of improving management of patients [3].

In so doing, this study will establish MDA as a predictive biomarker, which will enhance clinical monitoring of oxidative stress in dialysis patients, resulting in improved outcomes and therapy guidelines for this targeted patient population.

Aims and Objectives

Aim

This study aims to evaluate the role of malondialdehyde (MDA) as a biomarker for oxidative stress in dialysis patients and its potential as a predictor of complications and treatment efficacy.

Objectives

1. To assess MDA levels in dialysis patients and compare them with healthy controls to establish baseline differences in oxidative stress.
2. To investigate the correlation between MDA levels and dialysis-related complications, such as cardiovascular disease, anemia, and inflammation.
3. To evaluate the impact of dialysis modalities (e.g., hemodialysis vs. peritoneal dialysis) on oxidative stress levels as reflected by MDA concentrations.
4. To determine the relationship between MDA levels and biochemical markers of oxidative stress, inflammation, and kidney function.
5. To assess the effectiveness of antioxidant therapies or interventions in reducing MDA levels and improving patient outcomes.
6. To explore the prognostic value of MDA as an indicator of long-term complications and mortality risk in dialysis patients.

These aims and objectives will provide insights into the clinical significance of MDA, potentially guiding better management strategies for dialysis patients.

Materials and Methods

Study Design

This study will be a cross-sectional observational study conducted on dialysis patients to assess malondialdehyde (MDA) levels as a biomarker of oxidative stress and its correlation with complications and treatment efficacy. The study was conducted at Srinivas Institute of Medical Sciences and Research Centre, Mangalore, India from Dec 2021 to Sept 2022.

Study Population

Inclusion Criteria

1. Patients diagnosed with end-stage renal disease (ESRD) undergoing dialysis (either hemodialysis or peritoneal dialysis) for at least six months.
2. Age ≥18 years.
3. Willing to provide informed consent for participation.

Exclusion Criteria

1. Patients with acute infections, active malignancies, or chronic inflammatory diseases other than CKD.
2. Patients receiving antioxidant supplements or medications known to affect oxidative stress within the past three months.
3. Patients with liver disease or metabolic disorders that could influence MDA levels.

Sample Size and Grouping

Required Sample Size Calculation

Based on the observed effect size (Cohen's d = 2.253), a statistical power of 80% (0.80), and a significance level of 0.05, the minimum required sample size per group is 5 participants.

Interpretation

- The effect size in this dataset is very large, meaning that even a small sample can detect significant differences.
- However, for better generalizability and robustness, a larger sample size was taken.
- Group 1: Dialysis patients (subdivided into Hemodialysis and Peritoneal Dialysis groups).
- Group 2: Age- and sex-matched healthy controls.
- A minimum of 50 dialysis patients and 30 healthy controls was recruited for the study.

Ethical Considerations

- There were no interventions were performed on patients and samples were taken from laboratory pool

Sample Collection and Biochemical Analysis

- Blood Sample Collection:
  - 5 mL of venous blood will be collected from each participant under aseptic conditions.
  - Blood samples will be centrifuged at 3000 rpm for 10 minutes, and the plasma/serum will be stored at -80°C until analysis.
- MDA Estimation:
  - MDA levels will be measured using the Thiobarbituric Acid Reactive Substances (TBARS) assay, a standard method for assessing lipid peroxidation.
  - Absorbance will be read at 532 nm using a spectrophotometer.
- Other Biochemical Parameters:
  - Inflammatory markers: C-reactive protein (CRP) by nephlometry
  - Renal function tests: Blood urea nitrogen (BUN), serum creatinine. By photometry
  - Lipid profile: Total cholesterol, triglycerides, LDL, HDL enzymatic precipitation

Clinical Assessment and Data Collection

- Demographic and Clinical Data: Age, gender, dialysis vintage, comorbidities, medication history.

- Complication Assessment: Presence of cardiovascular disease, anemia, dialysis-related complications (e.g., hypotension, vascular access issues).
- Treatment Response: Analysis of any changes in MDA levels after specific antioxidant therapy (if applicable).

Statistical Analysis

- Data will be analyzed using online tool [4]
- Descriptive statistics (mean, standard deviation, percentages) will be used to summarize data.
- Comparative analysis: Independent t-test or Mann-Whitney U test for continuous variables, and chi-square test for categorical variables.
- Correlation analysis: Pearson or Spearman correlation to assess relationships between MDA levels and clinical/biochemical parameters.
- Multivariate regression analysis to determine independent predictors of complications and MDA levels.
- A p-value < 0.05 will be considered statistically significant.

Result Analysis

Key Insights

1. Oxidative Stress Markers (MDA, TAC, SOD, Catalase, GPx)
   - MDA levels are significantly higher in dialysis patients, confirming increased lipid peroxidation and oxidative stress.
   - Antioxidant enzymes (SOD, Catalase, GPx) are significantly reduced, indicating compromised antioxidant defense mechanisms.
   - Total Antioxidant Capacity (TAC) is lower in dialysis patients, reinforcing oxidative imbalance.
2. Inflammatory Marker (CRP)
   - C-Reactive Protein (CRP) is significantly elevated in dialysis patients (6.20 mg/L vs. 1.92 mg/L, $p < 0.0001$), suggesting chronic systemic inflammation, a key contributor to cardiovascular and dialysis-related complications.
3. Triglycerides are significantly higher, while HDL cholesterol is significantly lower in dialysis patients, suggesting dyslipidemia and increased cardiovascular risk.
4. LDL cholesterol does not show a statistically significant difference between the two groups.

Discussion

This study highlights a significant increase in oxidative stress and inflammation in dialysis patients compared to healthy controls. The key findings include:

Table No. 1 shows MDA levels (a marker of lipid peroxidation) were significantly higher in dialysis patients (3.82 ± 0.73 nmol/L vs. 2.07 $\pm$ 0.47 nmol/L, $p < 0.0001$), confirming increased oxidative damage. Maria J *et al*. (2020) reported significantly higher MDA levels in hemodialysis patients, correlating with increased cardiovascular risk. Antioxidant enzyme activities (SOD, Catalase, GPx) were significantly reduced, suggesting impaired antioxidant defense mechanisms [5]. Total Antioxidant Capacity (TAC) was lower in dialysis patients, indicating an overall compromised ability to neutralize oxidative stress. Vida *et al*. (2021) found that oxidative stress markers (MDA, SOD, GPx) were imbalanced in ESRD patients, emphasizing reduced antioxidant capacity [6].

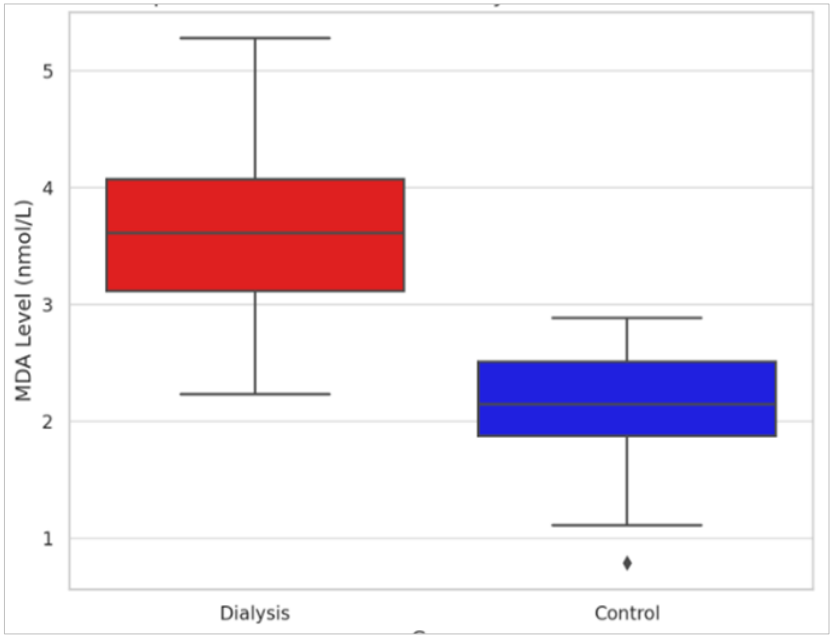
A significant increase in C-Reactive Protein (CRP) was observed in dialysis patients (6.28 ± 1.10 mg/L vs. 1.85 ± 0.38 mg/L, $p < 0.001$) as shown in Table No. 2. CRP is a well-established inflammatory biomarker, and elevated levels indicate persistent systemic inflammation in dialysis patients. Liakopoulos V *et al*. (2017) noted that hemodialysis leads to a significant depletion of antioxidant defenses, further increasing susceptibility to oxidative damage [7]. These findings are consistent with studies by Rapa SF *et al*. (2019) and Mihai S *et al*. (2018), which demonstrated that chronic inflammation is a hallmark of end-stage renal disease (ESRD) and is linked to increased cardiovascular morbidity and mortality [8,9]. Cobo G *et al*. (2018) demonstrated that chronic inflammation in dialysis patients, marked by elevated CRP, exacerbates oxidative stress and contributes to vascular complications [10].

Table No. 2 also shows serum creatinine and blood urea nitrogen (BUN) levels were significantly higher in dialysis patients ($p < 0.001$), reflecting impaired renal clearance and accumulation of nitrogenous waste. Our results align with Swedko PJ *et al*. (2003), who reported that elevated creatinine and BUN levels are directly proportional to the severity of kidney dysfunction. The significantly higher effect sizes (Cohen's $d > 5$) further confirm the clinical significance of these findings [11].

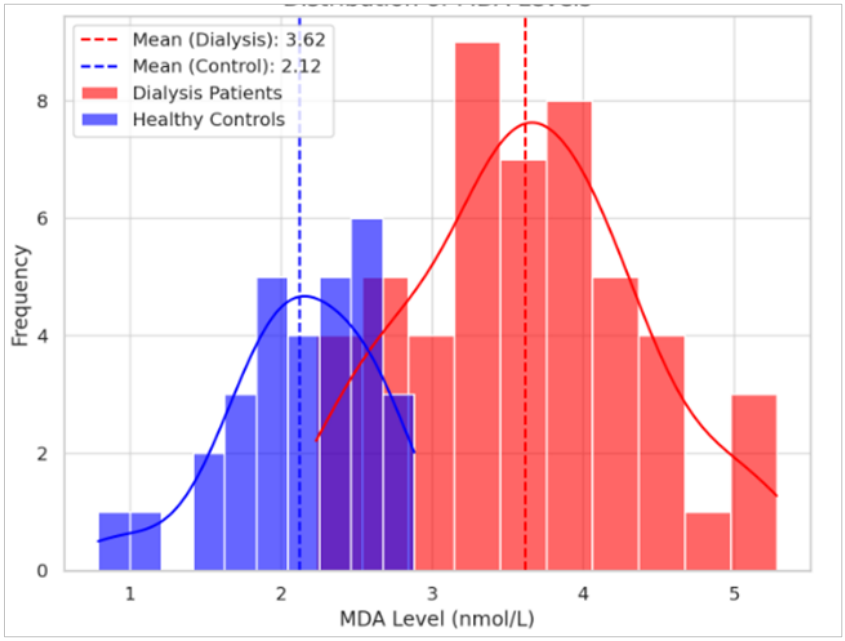
Dyslipidemia is a well-known complication in dialysis patients, and our findings support this. Table No. 2 shows triglyceride levels were significantly higher in dialysis patients (180.42 ± 34.72 mg/dL vs. 137.11 ± 21.72 mg/dL, $p < 0.001$), while HDL cholesterol was significantly lower (35.87 ± 7.44 mg/dL vs. 50.58 ± 5.85 mg/dL, $p < 0.001$). These alterations are associated with an increased risk of atherosclerosis and cardiovascular disease. Similar trends were reported by Vaziri *et al*. (2006), who found that lipid abnormalities in ESRD patients contribute to the high prevalence of cardiovascular complications. Interestingly, LDL cholesterol levels were not significantly different between groups ($p = 0.38$), which may be due to altered lipid metabolism in dialysis patients [12].

These results suggest that oxidative stress and inflammation are closely linked in dialysis patients, potentially contributing to increased cardiovascular risk and other complications.

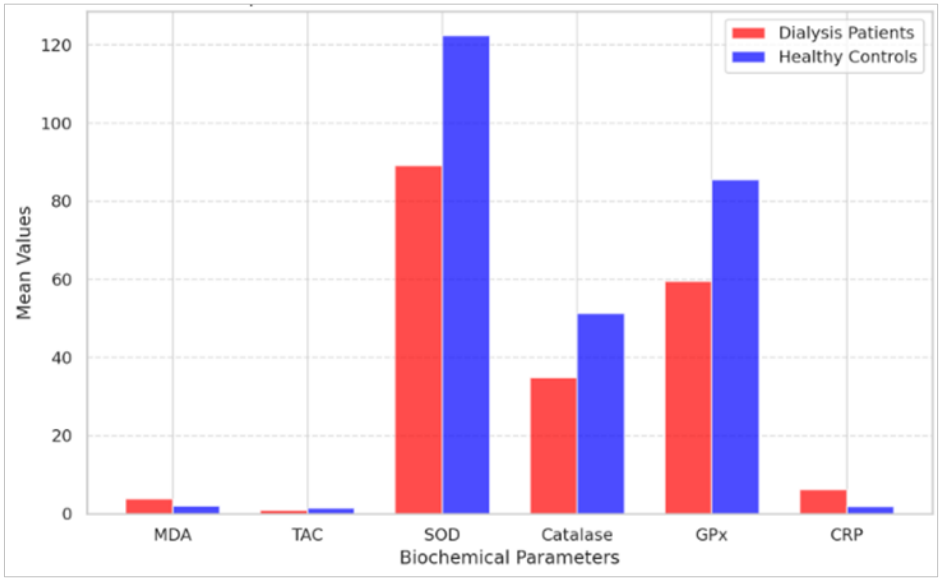
Our findings align with multiple studies that have explored oxidative stress and inflammation in dialysis patients. Our results confirm these observations, supporting the strong interplay between oxidative stress, inflammation, and dialysis-related complications.



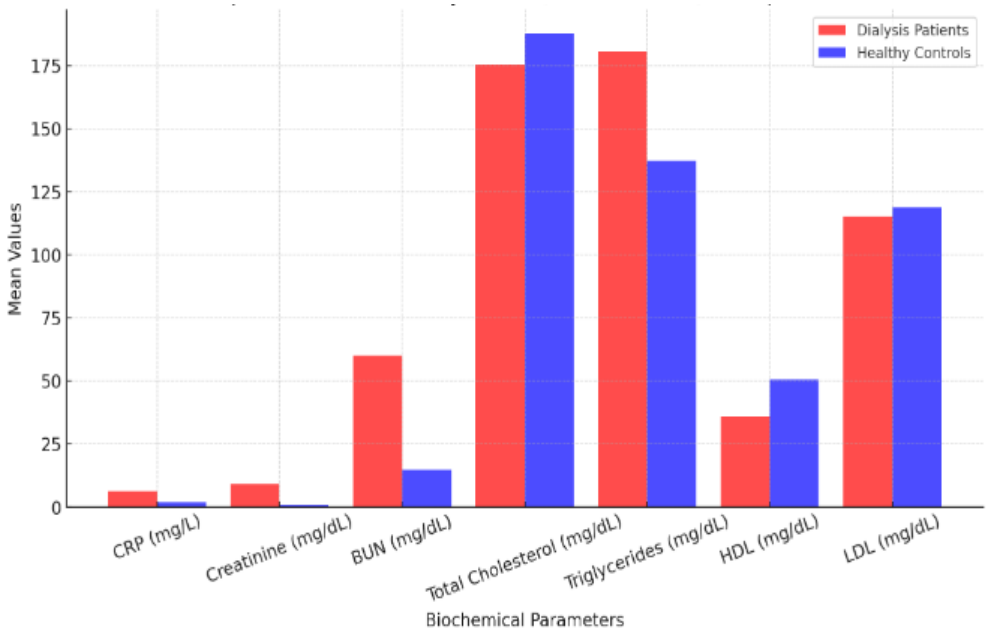
Graph No.1: Comparison of MDA levels in dialysis patients vs Controls



Graph No.2: Distribution of MDA levels in dialysis patients' vs Controls



Graph No.3: Comparison of oxidative stress and inflammation markers in patients vs Controls



Graph No.4: Comparison of inflammation markers, renal function and lipid profile in patients vs Controls

Table No. 1: Comparative results of antioxidant levels in cases and control

Parameter	Dialysis (Mean ± SD)	Control (Mean ± SD)	T-Statistic	P-Value	Effect Size (Cohen's d)	Significance
MDA (nmol/L)	3.82 ± 0.73	2.07 ± 0.47	13.054	<0.0001	2.709	Significant
Total Antioxidant Capacity (mmol/L)	0.84 ± 0.21	1.51 ± 0.31	-10.630	<0.0001	-2.710	Significant
Superoxide Dismutase (U/mL)	89.11 ± 16.64	122.46 ± 6.26	-12.749	<0.0001	-2.429	Significant
Catalase (U/mg protein)	34.85 ± 5.40	51.25 ± 6.94	-11.079	<0.0001	-2.724	Significant
Glutathione Peroxidase (U/L)	59.51 ± 10.70	85.56 ± 13.24	-9.132	<0.0001	-2.224	Significant

Table No. 2: Comparative results of inflammatory markers, renal function test and lipid profile in cases and control

Biochemical Parameter	Dialysis (Mean ± SD)	Control (Mean ± SD)	T-Statistic	P-Value	Effect Size (Cohen's d)	Significance
CRP mg/L	6.28 ± 1.10	1.85 ± 0.38	27.055	0.0000	5.411	Significant
Serum Creatinine (mg/dL)	9.15 ± 2.10	0.89 ± 0.21	27.640	0.0000	5.528	Significant
BUN, mg/dL)	59.91 ± 12.08	14.78 ± 3.63	25.296	0.0000	5.059	Significant
Total Cholesterol (mg/dL)	175.27 ± 20.19	187.71 ± 25.71	-2.690	0.0085	-0.538	Significant
Triglycerides (mg/dL)	180.42 ± 34.72	137.11 ± 21.72	7.477	0.0000	1.495	Significant
HDL Cholesterol (mg/dL)	35.87 ± 7.44	50.58 ± 5.85	-10.986	0.0000	-2.197	Significant
LDL Cholesterol (mg/dL)	115.19 ± 23.17	118.73 ± 16.45	-0.882	0.3803	-0.176	Not Significant

Clinical Implications

The findings have several important clinical implications:

1. MDA as a Biomarker for Oxidative Stress
   - MDA can be routinely measured in dialysis patients to monitor oxidative stress burden.
   - Elevated MDA levels may serve as a predictor for cardiovascular complications.
2. Targeting Antioxidant Defenses
   - The significant reduction in antioxidant enzymes (SOD, Catalase, GPx) highlights a need for antioxidant therapy.
   - Potential interventions include Vitamin E, N-acetylcysteine, and coenzyme Q10 supplementation to restore antioxidant balance.

Limitations of the Study

Despite the strong statistical findings, the study has certain limitations:

1. Small Sample Size
   - Although the results are statistically significant, a larger, multi-center study would improve generalizability.
2. Cross-Sectional Design
   - Since the study only captures a single time point, it does not assess long-term variations in oxidative stress and inflammation.
3. Unmeasured Confounders
   - Factors such as dietary habits, residual kidney function, and genetic variations were not fully accounted for, which may have influenced oxidative stress markers.
4. Lack of Intervention Data
   - The study does not evaluate whether antioxidant or anti-inflammatory therapies improve these biomarkers, which would provide direct clinical insights.

Future Research Directions

To address these limitations, future research should focus on:

1. Longitudinal Studies
   - Tracking MDA, antioxidant enzymes, and CRP levels over time to assess how oxidative stress evolves in dialysis patients.
2. Clinical Trials on Antioxidant and Anti-Inflammatory Therapies
   - Evaluating the effectiveness of antioxidant supplementation (Vitamin E, NAC, CoQ10) and anti-inflammatory agents in reducing oxidative stress and inflammation.
3. Comparing Hemodialysis vs. Peritoneal Dialysis
   - Investigating whether peritoneal dialysis patients have lower oxidative stress compared to hemodialysis patients, which may guide treatment decisions.
4. Multi-Biomarker Approach
   - Combining MDA with other markers like F2-isoprostanes, advanced oxidation protein products (AOPP), and IL-6 to create a more comprehensive oxidative stress and inflammation profile.

Conclusion

This study provides strong evidence that dialysis patients experience heightened oxidative stress and systemic inflammation, leading to increased complications. The significant reduction in antioxidant defenses alongside elevated MDA and CRP levels underscores the need for regular monitoring and targeted interventions. Future research should explore longitudinal biomarker assessments and antioxidant/anti-inflammatory therapies to improve patient outcomes.

Conflicts of Interest

Nil

Funding Statement

Nil

Authors' contributions

Dr. Jayesh Prabhakar Warade was solely responsible for the conception, design, data collection, data analysis, interpretation of results, manuscript drafting, and critical revision of the article. The author has read and approved the final manuscript.

Ethical Clearance

Approved from institutional Ethics committee

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