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Original Research

Evolution of Oxidative Stress in Renal Failure Patients Undergoing Hemodialysis: Progressive Impairment of Antioxidant Defenses

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Abstract

Background: Hemodialysis, an essential renal replacement therapy for patients with end-stage renal disease, is known to induce a marked redox imbalance that contributes to the cardiovascular and metabolic burden in this population.

Methods: This study assessed the evolution of major oxidative stress biomarkers, malondialdehyde (MDA), reduced glutathione (GSH), total antioxidant capacity (FRAP), and catalase (CAT), in hemodialysis patients in Togo stratified by dialysis vintage (< 1 year, [1 – 2 years[, [2 – 3 years, [3 – 4 years[, [4 – 5 years[, and ≥ 5 years).

Findings: A progressive and statistically significant increase in MDA concentrations (from 2.10 ± 0.18 to 3.68 ± 0.33 µmol/L) was observed, concomitant with a continuous decline in GSH (8.7 ± 0.6 to 5.4 ± 0.3 µmol/g Hb), FRAP (690 ± 35 to 470 ± 25 µmol/L), and CAT activity (55.2 ± 2.8 to 38.2 ± 1.9 U/mg protein) as treatment duration increased.

Conclusion: These trends reflect an intensification of oxidative stress and a gradual depletion of antioxidant defenses, indicating a cumulative oxidative load associated with repeated dialysis sessions and the loss of water-soluble antioxidants. From a pathophysiological perspective, these alterations may be explained by increased production of reactive oxygen species (ROS), oxidative carbamylation of proteins, chronic inflammation, and the limited biocompatibility of certain dialysis membranes. The resulting chronic oxidative stress plays a pivotal role in endothelial dysfunction and cardiovascular complications among long-term dialysis patients. These findings highlight the need for regular monitoring of redox biomarkers and the implementation of tailored nutritional or pharmacological antioxidant strategies to improve prognosis and quality of life in patients undergoing prolonged hemodialysis.

Keywords: Hemodialysis; Oxidative stress ; MDA, Glutathione, FRAP and Catalase.

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Introduction

Chronic kidney disease (CKD) is a major global public health concern, affecting nearly 850 million individuals and ranking among the leading causes of cardiovascular morbidity and mortality[8]. When residual renal function declines below 10 - 15%, renal replacement therapy particularly hemodialysis becomes essential for patient survival[7]. However, despite its life-saving role, hemodialysis promotes a profound redox imbalance characterized by excessive production of reactive oxygen species (ROS) and a reduction in antioxidant defenses[9].

Oxidative stress corresponds to an imbalance between free radical generation and the antioxidant capacity of biological systems[12]. In hemodialysis, this imbalance arises from several mechanisms, including leukocyte activation by dialysis membranes, exposure to free iron and endotoxins, accumulation of pro-oxidant uremic toxins, and the loss of water-soluble antioxidants during treatment[3]. This chronic oxidative environment leads to lipid peroxidation, protein carbonylation, and oxidative DNA damage, thereby contributing to endothelial dysfunction, inflammation, and cardiovascular complications commonly observed in long-term dialysis patients[11].

Assessment of redox status relie on several key biomarkers: malondialdehyde (MDA), reflecting lipid peroxidation; reduced glutathione (GSH), a major intracellular antioxidant; total antioxidant capacity (FRAP), which evaluates global plasma reducing potential; and catalase activity (CAT), essential for hydrogen peroxide detoxification[2]. Numerous studies have shown increased MDA levels associated with reduced GSH and FRAP in hemodialysis patients, supporting the central role of oxidative stress in dialysis-related tissue injury, anemia, and cardiovascular disease[1,5].

Despite these findings, few studies have systematically explored how the duration of hemodialysis influences the evolution of oxidative stress biomarkers, even though this variable may reflect the cumulative oxidative load induced by repeated sessions[13]. Understanding this dynamic could guide preventive strategies, particularly through nutritional or pharmacological antioxidant modulation[6].

This study therefore aims to evaluate the evolution of major oxidative stress biomarkers (MDA, GSH, FRAP, and CAT) in chronic kidney disease patients undergoing hemodialysis in several hospitals in Togo, according to treatment duration. The goal is to determine whether prolonged exposure to hemodialysis is associated with a progressive deterioration of antioxidant status, thereby improving the understanding and monitoring of oxidative stress in this vulnerable population.

Material and Methods

1. Study population

This cross-sectional and analytical study was conducted from June to August 2024 and included 132 chronic hemodialysis patients recruited from nephrology and hemodialysis units in Lomé. The participating centers were: Sylvanus Olympio University Hospital (CHU), Nadouvi Lawson Body Hospital, Unidial Clinic, Martin Luther King Clinic, and CMS Maison du Hadj.

The distribution of participants according to the duration of hemodialysis is presented in Table 1.

Table 1. Distribution of Participants According to Dialysis Vintage

	Length of time on hemodialysis (years)	Number of people n (%)
	< 1 years	27
	[1 – 2[	26
	[2 – 3[	19
	[3 – 4[	23
	[4 – 5[	16
	≥ 5	21
Total	-	**132**

2. Inclusion Criteria

Participants were eligible for inclusion if they met the following conditions: Were undergoing maintenance hemodialysis for at least three (03) months and provided written informed consent to participate in the study.

3. Exclusion Criteria

Patients undergoing hemodialysis for less than 3 months and who have not consented to participate in the study are not included in this study.

3. Exclusion Criteria

Participants were excluded from the study if they met any of the following conditions : Hemodialysis duration less than three (03) months, presence of acute or severe infection, inflammatory flare, or recent surgery during the study period, current use of oral or parenteral nutritional supplements or antioxidant supplementation, major physical disabilities preventing accurate anthropometric measurements, severe psychiatric, cognitive, or hearing impairment interfering with data collection and refusal or inability to provide informed consent.

4. Ethical Considerations

The study protocol was approved by the Bioethics Committee for Health Research of the Togolese Ministry of Health, under approval number 034/2023/CBRS, issued on 30 September 2022.

5. Blood Collection and Sample Preparation

Five milliliters of venous blood were collected from each participant into lithium heparin anticoagulant tubes under aseptic conditions. Samples were immediately placed on ice and transported to the laboratory within one hour. Blood was centrifuged at 3000 rpm for 10 minutes at 4 °C, and the plasma obtained was aliquoted into cryogenic tubes to avoid repeated freeze–thaw cycles. Plasma samples were stored at -20 °C until biochemical analysis, which was performed within two weeks. All procedures were carried out in accordance with international pre-analytical standards for oxidative stress biomarkers.

6. Measurement of Oxidative Stress Biomarkers

6.1. Malondialdehyde (MDA)

Lipid peroxidation was quantified using the thiobarbituric acid reactive substances (TBARS) assay described by Ohkawa et al.[14]. Plasma was mixed with a reaction mixture containing 0.375% thiobarbituric acid (TBA), 15% trichloroacetic acid (TCA), and 0.25 N hydrochloric acid (HCl). The mixture was heated at 95 °C for 15 minutes, cooled, and centrifuged. The absorbance of the supernatant was measured at 532 nm, and MDA concentration (nmol/mL) was calculated using the molar extinction coefficient $\varepsilon = 1.56 \times 10^5$ $M^{-1} \cdot cm^{-1}$.

6.2. Reduced Glutathione (GSH)

GSH was quantified using the Ellman method[15]. Samples were incubated with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), forming a yellow-colored chromophore measured at 412 nm. Results were expressed in µmol/mL, based on a standard calibration curve prepared from reduced glutathione standards.

6.3. Catalase Activity (CAT)

Catalase activity was determined using the kinetic method of Aebi[16], based on the decomposition rate of hydrogen peroxide (H_2O_2). The assay mixture consisted of 50 mM phosphate buffer (pH 7.0) and 10 mM H_2O_2. The reduction in absorbance at 240 nm was monitored for 1 minute. Activity was expressed in U/mL, where one unit corresponds to the degradation of 1 µmol of H_2O_2 per minute.

6.4. Total Antioxidant Capacity (FRAP)

Total antioxidant capacity was assessed using the FRAP assay, following Benzie and Strain[17]. The reagent comprised 300 mM acetate buffer (pH 3.6), 10 mM TPTZ, and 20 mM $FeCl_3 \cdot 6H_2O$. A volume of 100 µL of plasma was incubated with the FRAP reagent at 37 °C for 10 minutes, and absorbance was measured at 593 nm. Results were expressed as µmol Fe^{2+}/L, using a ferrous sulfate calibration curve.

7. Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Normality of distributions was

assessed using the Shapiro–Wilk test. Comparisons between duration-of-dialysis groups were performed using one-way ANOVA with Welch's correction to account for heterogeneity of variances. When significant, comparisons were followed by the Games–Howell post hoc test. A p-value < 0.05 was considered statistically significant. All analyses were performed using GraphPad Prism version 9.0.

Results

Evolution of MDA Content

MDA levels show a progressive increase with the duration of hemodialysis, rising from 2.10 ± 0.18 µmol/L in patients undergoing dialysis for less than one year to 3.68 ± 0.33 µmol/L in those treated for more than five years (Figure 1). This trend suggests a gradual intensification of oxidative stress and a sustained accumulation of lipid peroxidation products over time. The elevation in MDA may be attributed to the oxidation of membrane lipids induced by free radicals generated during hemodialysis, particularly through leukocyte activation and the limited biocompatibility of certain dialysis membranes. Overall, these findings indicate that prolonged exposure to the dialysis procedure is associated with increased oxidative damage affecting both cellular membranes and circulating plasma proteins.

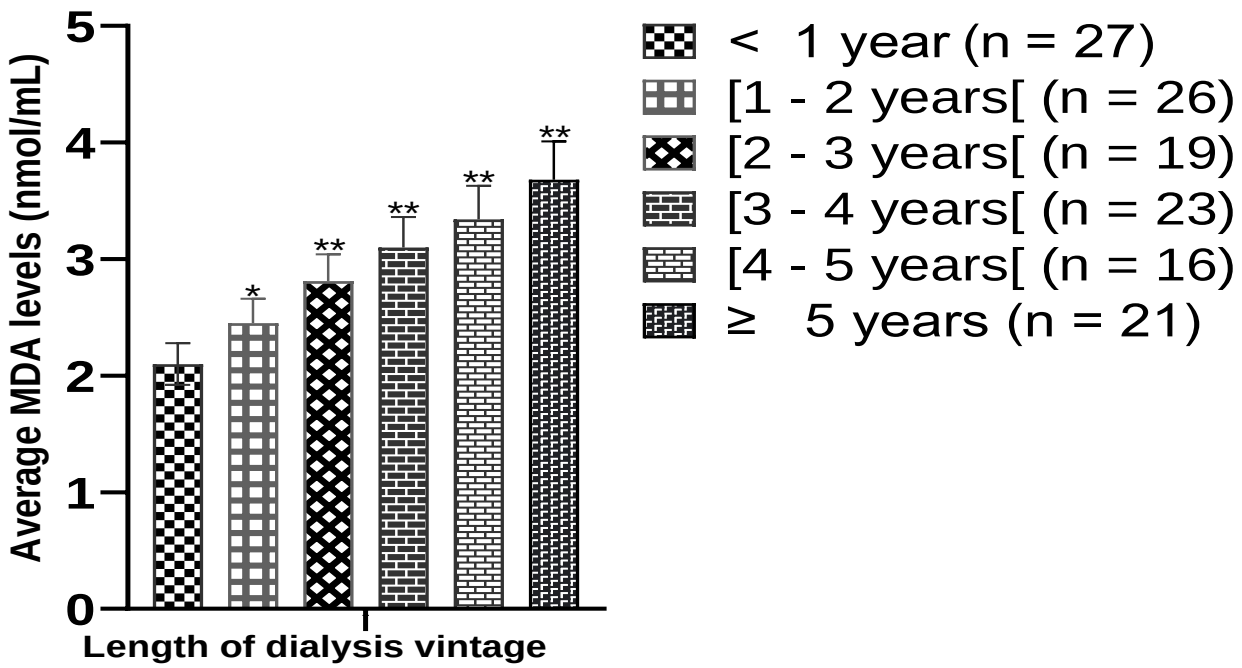

Figure 1. Evolution of MDA Content According to Duration of Hemodialysis
MDA: Malondialdehyde. Data are expressed as mean ± SEM; significantly different from control (< 1 year): *$p < 0.05$; **$p < 0.01$.

Evolution of GSH Content

GSH concentrations exhibit a progressive decrease, from 8.7 ± 0.6 µmol/g Hb in patients on dialysis for 0 – 1 year to 5.4 ± 0.3 µmol/g Hb in those undergoing dialysis for five years or more (Figure 2). This reduction may reflect the depletion of non-enzymatic antioxidant reserves in response to the sustained production of reactive oxygen species (ROS). As GSH serves as a crucial cofactor for glutathione peroxidase (GPx) and glutathione reductase, its decrease could impair peroxide neutralization and enhance cellular susceptibility to oxidative damage. These findings suggest that patients receiving long-term hemodialysis experience a significant redox imbalance, which may contribute to the progression of cardiovascular and inflammatory complications associated with chronic dialysis.

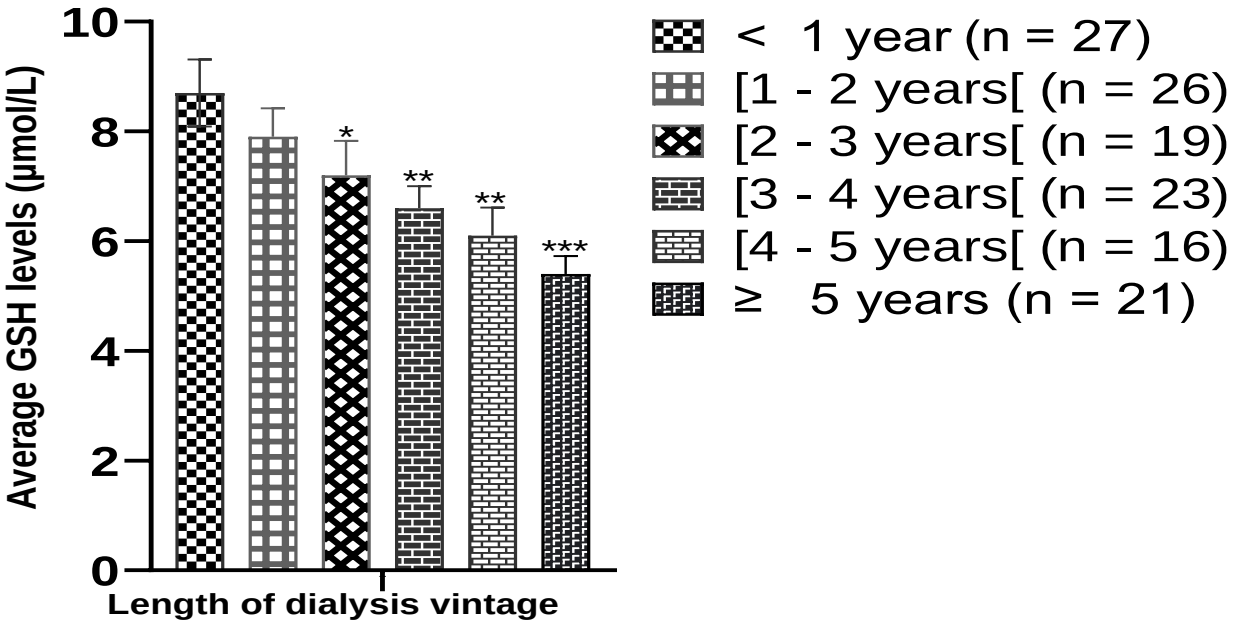

Figure 2. Evolution of GSH Content According to Duration of Hemodialysis

GSH: Reduced glutathione. Data are expressed as mean ± SEM; significantly different from control (< 1 year): *p < 0.05; **p < 0.01 and ***p < 0.001.

Evolution of Total Antioxidant Power (FRAP)

Ferric Reducing Antioxidant Power (FRAP) decreases progressively over the years, from 691.33 ± 35.28 µmol/L to 505.71 ± 26.16 µmol/L in patients undergoing hemodialysis for more than five years (Figure 3). This decline reflects a reduction in the overall plasma reducing capacity, suggesting a gradual depletion of both water-soluble antioxidants (vitamins C and B9, uric acid, GSH) and fat-soluble antioxidants (vitamin E, carotenoids). While hemodialysis efficiently removes toxic metabolites, it also contributes to the loss of plasma antioxidants through diffusion and adsorption onto the dialysis membrane. Consequently, the total antioxidant capacity of the plasma diminishes over time, which may exacerbate systemic oxidative stress in long-term dialysis patients.

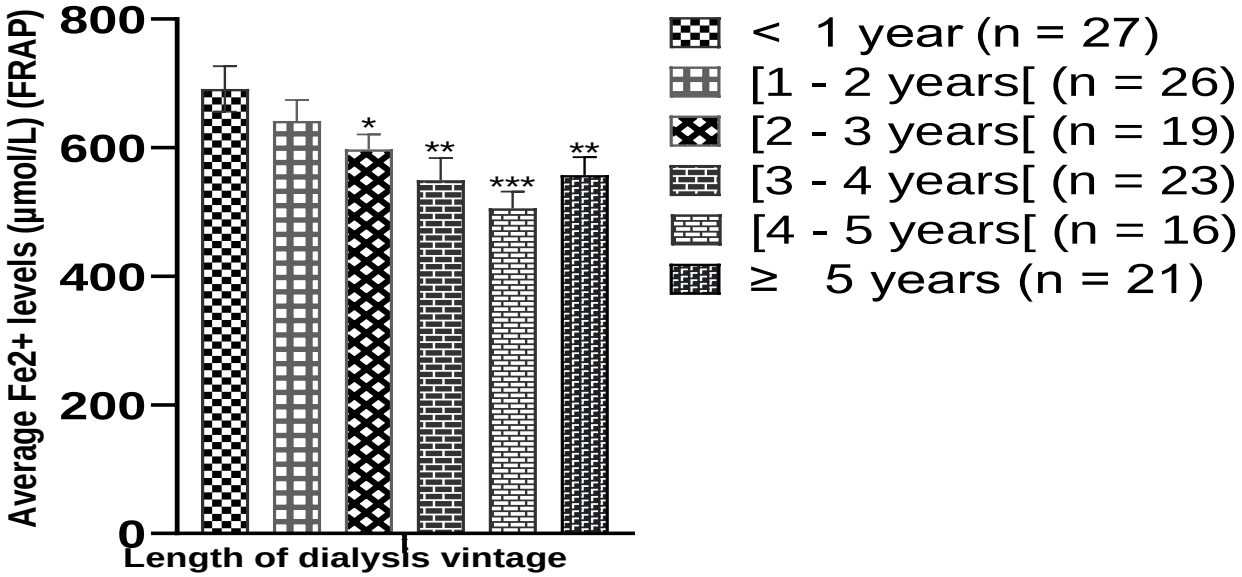

Figure 3. Evolution of Fe^{2+} ion Content (FRAP) According to Duration of Hemodialysis

FRAP: Ferric Reducing Antioxidant Power. Data are expressed as mean ± SEM; significantly different from the control (< 1 year): *p < 0.05; **p < 0.01 and ***p < 0.001.

Evolution of Catalase (CAT) Activity

Catalase (CAT) activity declines progressively from 55.2 ± 2.8 U/mL in patients on dialysis for 0–1 year to 38.2 ± 1.9 U/mL in those treated for five years or more (Figure 4). This reduction reflects cumulative enzymatic dysfunction in red blood cells and tissues chronically exposed to reactive oxygen species (ROS). Catalase plays a central role in the detoxification of hydrogen peroxide (H_2O_2), and its decline compromises the cellular antioxidant defense system. Chronic oxidative stress, protein carbamylation, and the presence of catalytic metal ions (Fe^{2+}, Cu^{2+}) may contribute to enzyme inactivation. As a result, the reliance on other antioxidant systems, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD), increases; however, these systems are often also impaired in long-term hemodialysis patients.

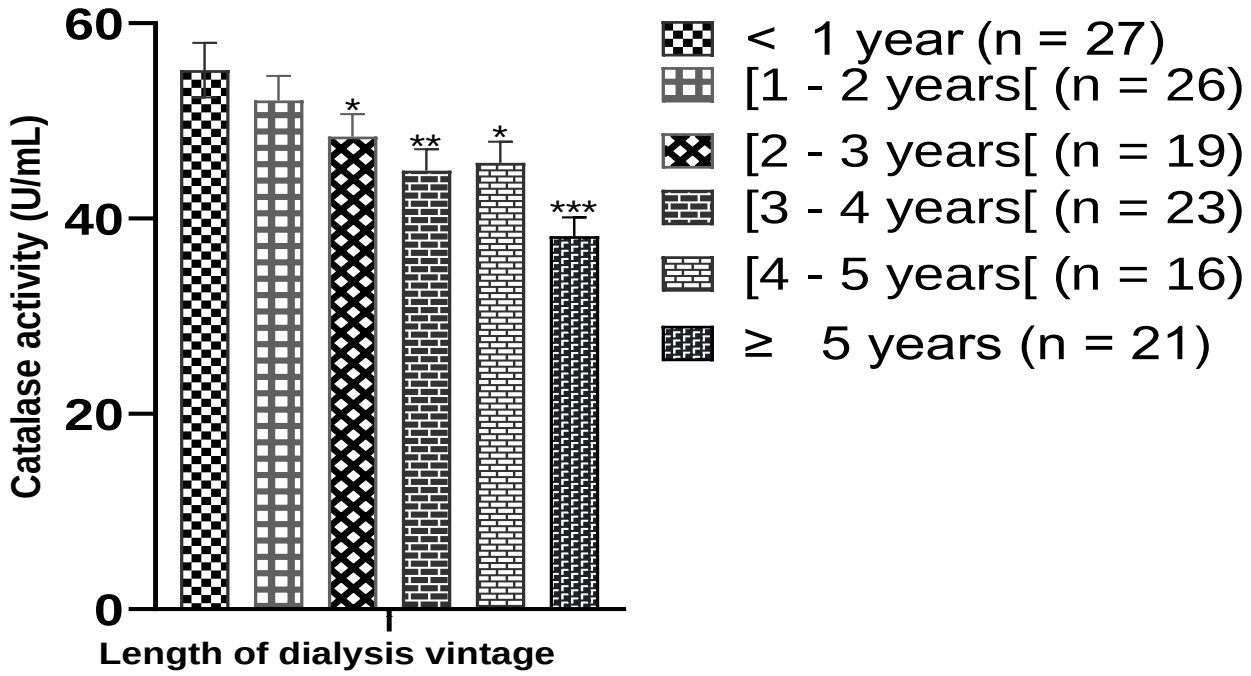

Figure 4. Evolution of Catalase Activity According to Duration of Hemodialysis
Data were expressed as mean ± SEM; significantly different from control (< 1 year): *$p < 0.05$; **$p < 0.01$ and ***$p < 0.001$.

The combination of observed changes elevated MDA, decreased GSH, reduced FRAP, and lowered catalase activity, indicates an oxidative profile that progressively worsens with the duration of hemodialysis (Figures 1 - 4). The increase in MDA reflects enhanced lipid peroxidation, whereas the reductions in GSH and FRAP reveal a general weakening of non-enzymatic antioxidant defenses. The decline in catalase activity demonstrates enzymatic vulnerability to oxidative stress. Overall, patients undergoing long-term hemodialysis exhibit a state of chronic oxidative stress, resulting from recurrent free radical production and the cumulative depletion of antioxidant capacity. This redox imbalance may contribute to systemic inflammation, atherosclerosis, cellular oxidative damage, and the progression of cardiovascular and metabolic comorbidities.

Discussion

Analysis of oxidative stress biomarkers in chronic kidney disease patients undergoing hemodialysis reveals a progressive deterioration in redox status with increasing treatment duration. This evolution is characterized by elevated malondialdehyde (MDA) levels alongside reductions in reduced glutathione (GSH), total antioxidant capacity (FRAP), and catalase activity (CAT), confirming a growing oxidative/antioxidant imbalance during hemodialysis follow-up.

Intensification of Lipid Peroxidation

The significant increase in MDA over time reflects ongoing membrane lipid peroxidation due to excessive production of reactive oxygen species (ROS) during dialysis. Mechanisms include leukocyte activation, blood-membrane interactions, and the use of partially biocompatible dialyzers[1]. Superoxide anions ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2) generate hydroxyl radicals (•OH) via the Fenton reaction, which oxidize polyunsaturated fatty acids in cell membranes[4]. Consequently, MDA serves as a sensitive biomarker of oxidative damage in end-stage renal disease[11]

Depletion of Glutathione and Non-Enzymatic Defenses

GSH decreases progressively with dialysis duration, reflecting the depletion of intracellular antioxidant reserves. GSH is a major scavenger of free radicals and a cofactor for glutathione peroxidase (GPx) and glutathione reductase (GR), essential for peroxide neutralization[9]. Factors contributing to GSH depletion include diffusion loss across dialysis membranes, direct ROS oxidation, and impaired regeneration due to NADPH deficiency induced by chronic metabolic stress[2]. This depletion exacerbates cellular vulnerability and sustains a pro-oxidant, pro-inflammatory state.

Decreased Total Antioxidant Potential (FRAP)

FRAP declines in parallel with GSH, reflecting the loss of both endogenous (urates, bilirubin, ascorbic acid) and exogenous (vitamins C and E, carotenoids) antioxidants during dialysis[6]. This reduction underscores the failure of the antioxidant network due to increased free radical production and excessive clearance of protective molecules.

Alteration of Enzymatic Defenses (Catalase)

Catalase activity diminishes with dialysis duration, likely due to oxidative carbamylation of proteins, denaturation by free metal ions, and loss of essential cofactors (iron, copper)[3]. Reduced catalase activity compromises H_2O_2 detoxification, increasing exposure to hydroxyl radicals and contributing to mitochondrial and cellular oxidative stress[10].

Physiopathological Integration and Clinical Implications

Collectively, these alterations indicate a cumulative oxidant load that worsens with dialysis duration. Chronic oxidative stress contributes to endothelial dysfunction, accelerated cellular aging, and cardiovascular complications, the leading causes of mortality in hemodialysis patients[11]. These findings support integrated interventions, including optimized dialyzer biocompatibility, targeted antioxidant supplementation (vitamin E, α-lipoic acid, N-acetylcysteine), and dietary reinforcement with natural antioxidants (fruits, vegetables, polyphenols), which have been shown to improve plasma antioxidant status and reduce oxidative damage[1,].

The observed results highlight a direct correlation between the duration of hemodialysis and the deterioration of antioxidant status. Chronic oxidative stress is therefore a major component of the pathophysiology of complications related to prolonged hemodialysis. These observations reinforce the need for regular monitoring of redox biomarkers and targeted nutritional and pharmacological interventions to limit oxidative damage in this vulnerable population.

Conclusion

The assessment of oxidative stress biomarkers in chronic kidney disease patients undergoing hemodialysis demonstrates a progressive and measurable deterioration of redox balance with increasing treatment duration. The rise in malondialdehyde (MDA), reflecting enhanced lipid peroxidation, together with the decline in reduced glutathione (GSH), total antioxidant capacity (FRAP), and catalase (CAT) activity, indicates a sustained imbalance between oxidant production and antioxidant defenses over the years of dialysis. This cumulative oxidative burden is likely driven by repeated leukocyte activation,

partial biocompatibility of dialysis membranes, loss of circulating antioxidants during treatment, accumulation of catalytic transition metals, and persistent uremic inflammation. Uncompensated chronic oxidative stress contributes to endothelial dysfunction, vascular remodeling, tissue damage, and the development of cardiovascular complications the leading cause of morbidity and mortality in long-term hemodialysis patients.

These findings support the need for routine monitoring of redox biomarkers in the clinical management of dialysis patients and justify targeted preventive strategies. Such strategies may include improving membrane biocompatibility, optimized antioxidant supplementation (vitamins E and C, alpha-lipoic acid, N-acetylcysteine, selenium), and nutrition strategies emphasizing polyphenol- and micronutrient-rich foods. From a scientific standpoint, this study strengthens the understanding of the pathophysiological continuum linking hemodialysis duration to oxidative stress intensity and highlights avenues for future interventional research. Longitudinal studies integrating inflammatory, nutritional, and metabolic markers will be essential to further elucidate mechanisms and identify effective approaches for modulating oxidative stress in this population.

In summary, controlling oxidative stress represents a major challenge for improving prognosis and quality of life in chronic hemodialysis patients and constitutes a key step toward safer, more sustainable, and more personalized dialysis care.

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