

# Estimation of antioxidant enzymes in hemodialysis patients

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## Background

Oxidative stress in hemodialysis (HD) is a critical concern in the management of patients. HD, a life-sustaining renal replacement therapy, exposes individuals to various factors that promote the production of harmful reactive oxygen species within the body. These reactive oxygen species, including free radicals, can overwhelm the body's antioxidant defenses, leading to oxidative stress.

## Objective

This study aimed to evaluate the activities of superoxide dismutase (SOD), glutathione peroxidases (GPx) and catalase (CAT), and serum malondialdehyde (MDA) levels with dyslipidemia in HD patients and compare them with control groups.

## Patients and methods

The case–control study was conducted on 75 patients undergoing HD and 75 age-matched healthy controls. Oxidative stress markers include CAT, SOD, GPx, and MDA. Serum electrolytes including potassium ion (K<sup>+</sup>), phosphate (PO<sub>4</sub>), calcium (Ca<sup>+</sup>), urea, and creatinine (Cr) were measured for each group.

## Results

Our results show a significant difference between patients and the control group in each of the oxidative stress markers, which are CAT, GPx, and SOD, showing a decrease that is statistically significant in patients in comparison to the controls. The level of MDA shows an increase that is statistically significant in patients in comparison to the controls. Serum electrolyte levels, which are K<sup>+</sup>, PO<sub>4</sub>, urea, and Cr, show a statistically significant increase in patients in comparison to the controls. Ca<sup>+</sup> shows a decrease that is statistically significant in patients in comparison to the controls.

## Conclusions

From the results, we could conclude that oxidative stress plays a role in HD patients and can affect the management of end-stage renal failure patients.

## Keywords:

electrolytes, hemodialysis, kidney, oxidative stress

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## Introduction

Hemodialysis (HD) is defined as a decline in renal function over 3 months, as measured by a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m<sup>2</sup> or the presence of kidney damage markers [1]. HD indirectly affects worldwide health outcomes and mortality by increasing the odds of at least five other leading causes of death. Diabetes mellitus, malaria, HIV, hypertension, and cardiovascular disease using the Global Burden of Disease as an illustration, are estimated to cause 1.2 million deaths each year, 19 million DALYs, and about the same number of years lost to reduced GFR. In addition, renal failure was the cause of death for 1.2 million people in 2015, up by 32% from 2005. An estimated 2.3–7.1 million HD patients died in 2010 due to a lack of access to chronic dialysis [2]. Also, 1.7 million people are thought to die annually as a result of acute renal impairment [3]. As a result, it is estimated that 5–10 million individuals per year die from renal disease [4]. Renal HD is a treatment option for people with end-stage renal

disease [5]. Renal failure that has persisted for a long time (HD patients) is characterized by functional and structural kidney abnormalities from a variety of causes. A decrease in kidney function is indicated by a higher GFR [6]. Oxidative stress, characterized by increased intracellular reactive oxygen species (ROS) and/or reactive nitrogen species, is frequent in various renal disorders [7]. The antioxidant enzyme reduces the production of ROS by converting them into less harmful forms of ROS, thereby protecting cells from ROS. People whose CAT activity levels are low have a greater risk of developing conditions associated with oxidative stress, including dyslipidemia and related diseases [8]. Catalase (CAT) is a type of antioxidant enzyme that also plays the role of a catalyst in the

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process of converting hydrogen peroxide into oxygen and water [9]. Because most CAT is destroyed during tissue manipulation, determining the exact amount of CAT present in the cytoplasm is impossible [10]. Superoxide dismutase (SOD) is a family of metalloproteases that prevents oxidative damage by promoting the disassembly of the superoxide anion radical into hydrogen peroxide and water. The enzyme SOD catalyzes the disassembly of superoxide and is found throughout the body. Hydrogen peroxide is produced as a byproduct of this reaction and plays a role in the propagation of free radical-induced damage [11]. Hydrogen peroxide, superoxide, and hydroxyl radicals are just some of the many reactive oxidants that the human body generates. Hydroxyl radicals are the most damaging because they kill neighboring cells. Manganese (SOD) is found in the mitochondria, while copper-containing and zinc-containing enzymes predominate in the cytoplasm [12]. Glutathione peroxidases (GPx) are a type of antioxidant enzyme that is responsible for catalyzing the breakdown of lipid peroxides. A high activity is demonstrated by GPx with both hydrogen peroxide and organic hydroperoxides [13]. These enzymes help the mechanism of detoxification [14]. One type of antioxidant enzyme is GPx, the oxidized form of glutathione is not protective, while the reduced form can be used for defense. These enzymes are essential components in the defense against an increase in oxidative stress levels [15]. Glutathione becomes an effective free radical scavenger as a result of its frequent oxidation and reduction states [16]. Malondialdehyde (MDA) is commonly used as an indicator of peroxidation because it is a product with a low molecular weight that results from lipid peroxidation [17]. These products penetrate the body, where they can harm lipids, brain cells, DNA, and other biomolecules. MDA has been widely used for many years as a handy biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids (TBA) [18]. HD is the form of renal replacement therapy that is used most frequently for patients who have end-stage renal disease. Patients who are undergoing HD may be at an elevated risk of experiencing an excessive amount of oxidative stress [19]. The purpose of this study was to assess the oxidative stress and dyslipidemia roles in HD patients in Basrah Governate, Iraq.

### Patients and methods

A case-control study that included 75 healthy people who served as controls and 75 patients who attended the HD patient center in Basrah Teaching Hospital, Basrah City, Southern Iraq, from November 2022 to

May 2023. All patients were diagnosed and confirmed by a specialist physician. Those with other diseases that can cause a similar clinical picture to chronic kidney disease (CKD), such as sepsis infected immunocompromised individuals, critical catheter-related issues, chest infections, hepatitis C, B infectious disease, hepatitis, and chronic liver disease, were excluded. Patients and controls in this study ranged in age from 17 to 67 years. Participants' demographic data, including age, sex, and clinical findings were collected using a standardized questionnaire. Collecting measure of 5 ml of venous blood from each of the 150 participants (75 patients and 75 controls) was collected. The blood was centrifuged to obtain serum for the measurement of oxidative stress markers and other tests. For ELISA kits, CAT and SOD are from BTLAB (#1008 Junjiang Inter. Bldg 228 Ningguo Rd, Yangpu Dist, Shanghai 200090, China) Company in China, and GPx and MDA are from Elabscience in the USA. Cobas C111 from Roche/Germany was used to estimate PO<sub>4</sub>, Cr, Ca<sup>+</sup>, and urea. K<sup>+</sup> was tested using the ABL 800 Flex in Japan. A spectrophotometer was used to test the lipid profile using the BIOLABO Kit in France.

### Ethical approval

All enrolled patients signed a written illustrative consent form. The Declaration of Helsinki (1964) ethical principles for medical research involving human volunteers were followed in this investigation. The Ethics and Research Committee of the Department of Medical Laboratory Technology, College of Health and Medical Technology, Southern Technical University, Basrah, Iraq, approved the study.

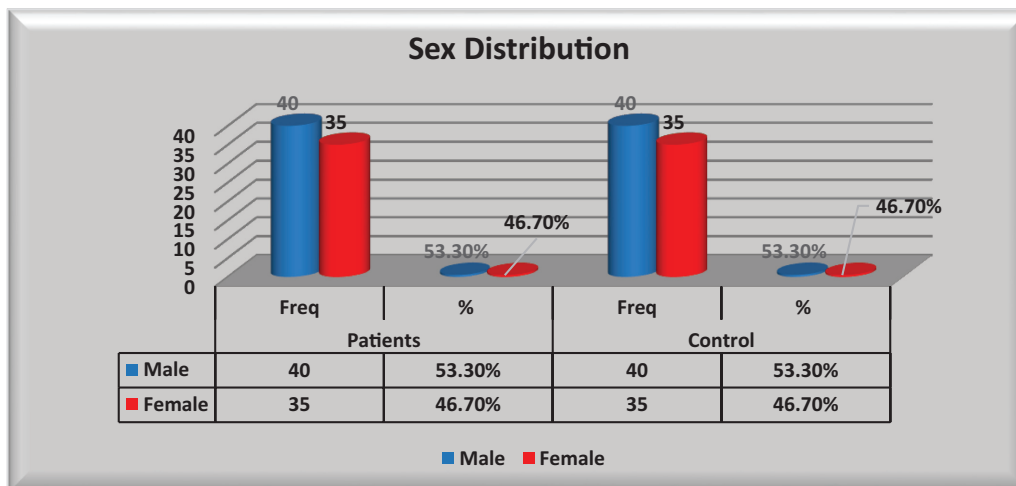
### Statistical analysis

The data was analyzed using the Statistical Package for the Social Sciences (SPSS, 14780 Memorial Drive, Suite 105, Houston, Texas, 77079, USA), version 22 (2013), developed by IBM, SPSS Inc., USA. The study used an independent sample *t* test for parametric variables and a Mann-Whitney *U* test for nonparametric variables. Pearson's correlation coefficient analysis was used to evaluate the correlation between dependent variables. The outcome was deemed statistically significant based on a *P* value of less than or equal to 0.05.

### Results

The total number of samples is 150, divided mainly into 75 patients and 75 healthy people. In terms of sex distribution, the patient group study included 40

Figure 1



The sex distribution of study groups.

(53.3%) males and 35 (46.7%) females. The control group included 75 (53.3%) males and 35 (46.7%) females, as shown in Fig. 1.

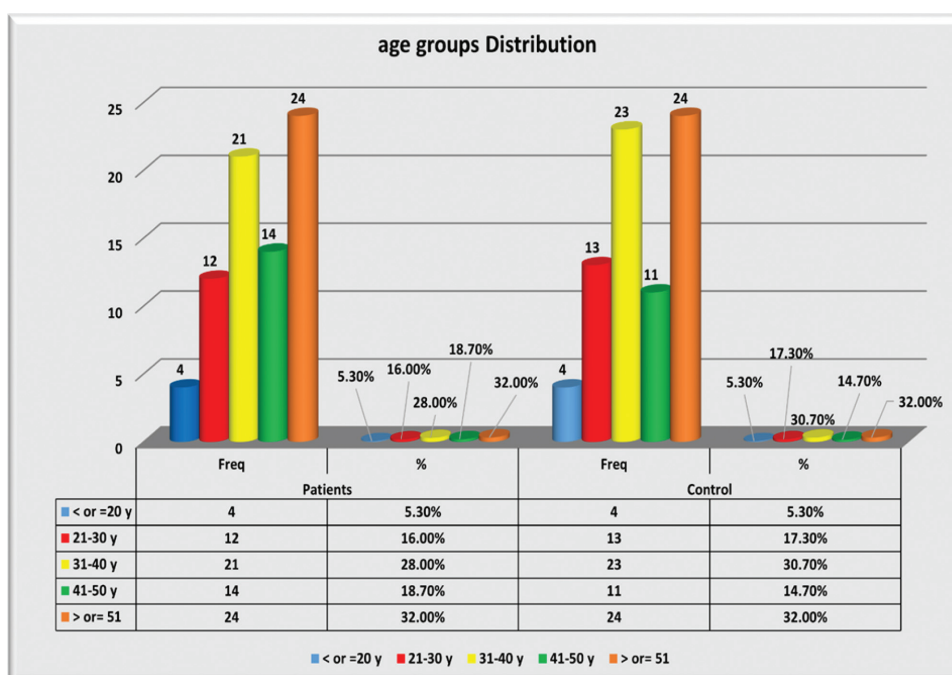
The classification of both study groups according to age shows that most patients are aged more than 51 years, and another detail is shown in Fig. 2.

According to Table 1, there is no statistically significant difference observed between the healthy and patient groups in relation to age and sex ( $P=0.778$ ,  $P=1.0$ ), respectively.

Table 2 shows a comparison between the control and HD patients according to oxidative stress, which showed a statistically significant increase in MDA in the patient compared with the control ( $P=0.000$ ), while tests of CAT, GPx, and SOD showed a statistically significant decrease in HD patients compared with the control ( $P=0.000$ ).

Table 3 includes study electrolytes ( $PO_4$ ,  $K^+$ , and  $Ca$ ) and renal function tests (urea and creatinine). The study showed a statistically significant increase in phosphate and potassium in patients ( $P=0.000$ ),

Figure 2



Study group distribution according to the age group.

**Table 1** Statistical distribution of study groups by their age, sex, and duration of the study

	Sex		Total	Mean±SD
	Male	Female	Age (years)	
Study groups				
Patients				
Frequency	40	35	75	41.84±12.86
%	53.3	46.7	100.0	
Control				
Frequency	40	35	75	41.24±13.1
%	53.3	46.7	100.0	
<i>P</i> value	1.000	0.778		

\*Chi-square and independent *t*-test was used.

**Table 2** Comparison of oxidative markers among the control and hemodialysis patients' groups

Variables	Study group	Mean±SD	<i>P</i> value
Catalase	Patients	159.33±35.39	0.000
	Control	194.71±53.89	
GPx	Patients	16.367±3.93	0.000
	Control	31.227±9.04	
SOD	Patients	7.6020±2.52	0.000
	Control	10.0659±1.61	
MDA	Patients	244.29±27.53	0.000
	Control	136.27±24.73	

GPx, glutathione peroxidases; MDA, malondialdehyde; SOD, superoxide dismutase. \*Independent *t* test or Mann–Whitney *U* test were used.

while decreasing calcium in patients. Referring to urea and creatinine showed a statistically significant increase in patients ( $P=0.000$ ).

Table 4 includes the test of lipid profile [total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL)] between patient and control. It shows a statistically significant increase of cholesterol, TG, VLDL, and LDL in the patient ( $P=0.000$ ), while a significant decrease in HDL ( $P=0.000$ ).

**Table 3** Comparison of electrolyte, urea, and creatinine among the control and hemodialysis patient groups

Variables	Study group	Mean±SD	<i>P</i> value
Phosphate	Patients	6.1252±1.37	0.000
	Control	3.9321±0.45	
Potassium	Patients	4.8493±1.11	0.000
	Control	3.8284±0.29	
Calcium	Patients	6.8672±0.77	0.000
	Control	8.8013±0.57	
Urea	Patients	97.4959±15.48	0.000
	Control	25.9880±3.68	
Creatinine	Patients	8.1877±1.03	0.000
	Control	0.8039±0.09	

\*Independent *t* test or Mann–Whitney *U* test was used.

**Table 4** Comparison of lipid profile among the control and hemodialysis patient groups

Variables	Study group	Mean±SD	<i>P</i> value
Cholesterol	Patients	206.29±14.68	0.000
	Control	183.69±15.05	
Triglyceride	Patients	185.65±23.06	0.000
	Control	140.68±18.03	
LDL	Patients	136.321±15.21	0.000
	Control	109.527±12.05	
HDL	Patients	32.841±6.27	0.000
	Control	47.309±6.17	
VLDL	Patients	37.131±4.61	0.000
	Control	28.187±3.66	
HDL/VLDL	Patients	69.972±8.01	0.000
	Control	75.496±6.54	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein. \*Independent *t* test or Mann–Whitney *U* test were used.

#### Correlations of oxidative stress markers with lipid profile in hemodialysis patients

The cholesterol marker shows a strong positive relationship with LDL and a weak negative relationship with VLDL. The TG marker shows a strong positive relationship with VLDL and the HDL/VLDL ratio. For the LDL marker, a moderately negative relationship between HDL and the HDL/VLDL ratio was indicated. HDL and VLDL have a strong positive relationship with the HDL/VLDL ratio. According to Table 5, there was no correlation between lipid profile markers and oxidative stress markers. It showed the correlation between the studied parameters (cholesterol, TG, HDL, LDL, VLDL, CAT, SOD, GPx) as significant correlations.

There is a significant positive correlation between cholesterol measurements and a significant negative correlation between cholesterol measurement and VLDL. There was also a positive and significant correlation between TG measurement and VLDL and a positive and significant correlation between TG measurement and HDL/VLDL. There was a negative correlation between LDL measurements and HDL. A negative correlation between LDL measurement and HDL/VLDL, a positive and significant correlation between HDL measurement and HDL/VLDL, and a positive and significant correlation between VLDL measurement and HDL/VLDL were noted, as shown in Table 5.

Correlations of oxidative stress markers with electrolytes, urea, and creatinine in HD patients showed no statistically significant correlation between biomarkers.

**Table 5 Correlations of oxidative stress markers with lipid profile in hemodialysis patients**

Study group	Cholesterol	Triglyceride	LDL	HDL	VLDL	HDL/VLDL
Patients						
SOD						
Pearson	0.104	0.061	0.093	-0.027	0.061	0.014
Significant	0.375	0.605	0.427	0.819	0.605	0.906
Catalase						
Pearson	-0.098	-0.001	-0.070	-0.059	-0.001	-0.047
Significant	0.404	0.991	0.552	0.616	0.991	0.690
MDA						
Pearson	0.187	0.147	0.140	-0.011	0.147	0.076
Significant	0.108	0.208	0.230	0.926	0.208	0.517
GPx						
Pearson	0.110	-0.016	0.140	-0.070	-0.016	-0.064
Significant	0.348	0.892	0.233	0.552	0.892	0.587
Cholesterol						
Pearson	1	0.274*	0.857**	0.062	0.274*	0.206
Significant		0.017	0.000	0.599	0.017	0.077
Triglyceride						
Pearson		1	-0.065	0.064	1.000**	0.625**
Significant			0.579	0.588	0.000	0.000
LDL						
Pearson			1	-0.372**	-0.065	-0.328**
Significant				0.001	0.579	0.004
HDL						
Pearson				1	0.064	0.819**
Significant					0.588	0.000
VLDL						
Pearson					1	0.625**
Significant						0.000
HDL/VLDL						
Pearson						1
Significant						

GPx, glutathione peroxides; high-density lipoprotein; LDL, low-density lipoprotein; MDA, malondialdehyde; SOD, superoxide dismutase; VLDL, very low-density lipoprotein. \*Only lipid profile shows significant relation with each other's. \*\*P value highly significant.

It was noted from our results that the relationship of oxidative stress with electrolytes, urea, and creatinine is as follows:

- (1) The positive correlation between SOD, CAT, and GPx measurement with urea and creatinine,  $PO_4$ ,  $K^+$ , and negative correlation with  $Ca^{+}$ .
- (2) The negative correlation between MDA measurement with urea, creatinine,  $PO_4$ , and  $K^+$ , and there is a positive correlation with  $Ca^{+}$  (Table 6).

## Discussion

The phenomenon of oxidative stress has garnered significant attention from researchers. The presence of an imbalance between free radicals and antioxidants results in the occurrence of oxidative damage to proteins, fats, nucleic acids, and carbohydrates. Antioxidants play a crucial role in safeguarding the body against the detrimental impact of free radicals [13]. CAT is an enzyme with antioxidant properties

that functions as a catalyst in the conversion of hydrogen peroxide into oxygen and water. It negates the intracellular presence of hydrogen peroxide, thereby removing its effect. HD patients had significantly decreased plasma CAT activity [20]. The increased CAT activity in these groups may represent a compensating mechanism of the body to minimize tissue damage from free radicals, as other antioxidant enzyme activities did not increase [21]. The significantly decreased activity of CAT in the present study is in agreement with a previous study that found a lower activity of the antioxidant enzyme [22]. The endogenous defense mechanisms against ROS are enhanced by natural antioxidants, which reinforce and recover the optimal balance by neutralizing ROS [14]. An intracellular antioxidant enzyme is responsible for the enzymatic reduction of hydrogen peroxide to water, thereby reducing its detrimental effects. Its primary function is to safeguard hemoglobin from the damaging effects of oxidative stress. Further research has indicated that the

**Table 6 Correlations of oxidative stress markers with electrolytes, urea, and creatinine in hemodialysis patients show no significant relationship**

Study group	Phosphate	Potassium	Calcium	Creatinine	Urea
Patients					
SOD					
Pearson	-0.128	0.140	0.135	-0.128	0.050
Significant	0.275	0.233	0.248	0.274	0.670
Catalase					
Pearson	0.035	0.031	0.014	-0.144	-0.060
Significant	0.765	0.795	0.907	0.219	0.606
MDA					
Pearson	0.026	-0.009	-0.043	0.162	0.026
Significant	0.826	0.939	0.717	0.166	0.827
GPx					
Pearson	0.136	-0.057	0.192	-0.106	0.179
Significant	0.245	0.625	0.100	0.365	0.124
Phosphate					
Pearson	1	0.010	0.009	0.020	-0.079
Significant		0.935	0.938	0.868	0.502
Potassium					
Pearson		1	0.051	0.043	0.068
Significant			0.666	0.712	0.561
Calcium					
Pearson			1	-0.003	-0.143
Significant				0.978	0.223
Creatinine					
Pearson				1	-0.051
Significant					0.664
Urea					
Pearson					1
Significant					

GPx, glutathione peroxidases; MDA, malondialdehyde; SOD, superoxide dismutase. \*No significant relation.

presence of the mineral selenium is crucial for the proper functioning of GPx1 activity [23]. The significant decrease in plasma GPx is because reduced eGPx activity is consistent with the hypothesis that the renal tubule is the primary location of eGPx production and may be a result of active nephron mass reduction. Loss in enzyme activity may also be attributable to other factors, such as a lack of selenium, which leads to less efficient inactivation of ROS, and a defect in the kidneys that reduces their clearance [24]. Reduced GPx detoxifies hydrogen peroxide and lipid peroxides [25]. The GSH-Px that contains selenium is responsible for reducing organic lipid peroxide. This reduction process relies on GSH to donate hydrogen. Renal failure disrupts the antioxidant system, which in turn causes ROS to attack cell membranes and lead to the development of lipid peroxidation products such as MDA [26]. Independent of the treatment of erythropoietin, there is evidence of increased lipid peroxidation [27]. It plays an important part in cellular energy by reducing cellular degradation and neutralizing SOD, a prevalent and highly hazardous free radical [28]. The enzyme

catalyzes the dismutation or partitioning of the superoxide radical into molecular oxygen and hydrogen peroxide. Superoxide is generated during oxygen metabolism and can lead to various forms of cellular damage if not properly controlled [23]. A recent study found that SOD1 controls oxidative stress in renal damage [29]. The oxidative degradation of lipids refers to the biochemical process where free radicals extract electrons from lipids present in cell membranes, leading to cellular damage. One of the results of the peroxidation of polyunsaturated fatty acids is observed in cellular processes. The overproduction of MDA is caused by an increase in free radicals. The measurement of MDA levels is widely recognized as a reliable indicator of oxidative stress [30]. Serum MDA increased significantly, which may be because the production of free radicals and antioxidant enzymes are both important for maintaining cellular health. An imbalance between the two can lead to oxidative damage [13]. Elevated levels of MDA may have resulted from a delay in the removal of free radicals [31]. Our results agree with the results of several other

studies that had been done previously [32,33]. Blood urea levels were found to be significantly higher in the CKD group compared with the control group ( $P<0.000$ ). In the HD patients' group, the levels of blood urea are significantly higher ( $P<0.000$ ) than in the control group, as shown in Table 3 stating the rise in urea levels in patients with HD. This study agrees with several previous studies [34,35]. This may be related to disrupted transport activities of the epithelial cells of the collecting tubules and diffuse impairment in the functions of the proximal convoluted tubules. Urea levels are markedly increased in HD patients', reaching predialysis concentrations that can reach 10 times or more the upper limit of the normal range in patients with end-stage renal disease. It is used as a marker of uremic retention in HD patients and the adequacy of intradialytic solute removal [36]. Our study results are consistent with the findings of the researchers [35,37]. High levels of Cr indicate kidney problems, while low levels may indicate muscular mass and low levels may indicate liver or muscle dysfunction. The current study found that CKD patients had a highly significant elevation ( $P>0.000$ ) in blood levels when compared with the control group, which was one of the findings of the study. An elevated level beyond the normal range may be attributed to factors such as kidney damage or failure, infection, or diminished blood flow. Dehydration, which refers to the reduction of bodily fluids, and muscle-related issues, such as the degeneration of muscle fibers, aligns with the findings of the researcher [35]. Recent research found a substantial decrease ( $P<0.000$ ) in blood  $\text{Ca}^+$  levels in CKD patients compared with the control group. The present study's findings also indicate that the levels of blood  $\text{Ca}^+$  in HD patients are significantly lower ( $P<0.000$ ). This finding agrees with Wan *et al.* [38], who found that serum  $\text{Ca}^+$  concentrations are lower in renal failure patients and that this decrease in serum  $\text{Ca}^+$  could be due to an increase in serum  $\text{PO}_4$  because serum  $\text{Ca}^+$  and  $\text{PO}_4$  concentrations have an inverse relationship and any increase in one will result in a decrease in the other [39]. Another possible cause for the decrease in serum  $\text{Ca}^+$  is a disturbance in vitamin D synthesis due to renal failure, which is caused by the kidney's failure to synthesize the active form of vitamin D (1,25-dihydroxycholecalciferol). It is very important for calcium absorption in the patient's intestine [40]. The study found a significant increase ( $P<0.000$ ) in blood potassium levels in HD patients compared with the control group. The kidney has the primary responsibility for maintaining total body  $\text{K}^+$  levels [41]. Tubular necrosis in CKD may cause significant damage to the late distal tubule and

collecting duct, causing direct injury to cells that perform  $\text{K}^+$  secretion, resulting in the retention of  $\text{K}^+$  in the blood. Due to an adaptively increased rate of  $\text{K}^+$  secretion in the remaining nephrons, the capacity to maintain a reasonably normal plasma  $\text{K}^+$  concentration despite a substantial decrease in kidney mass is possible. This adaptation is thought to be similar to what happens to healthy people who consume a lot of  $\text{K}^+$  in their diet. Long-term  $\text{K}^+$  loading increases the secretory capacity of the distal nephron in animal models, resulting in increased kidney  $\text{K}^+$  excretion independent of plasma  $\text{K}^+$  concentration. The study did not agree with the previous study [42]. The current research discovered that HD patients had a very significant rise ( $P<0.000$ ) in blood phosphorus levels when compared with the control group, this finding is consistent with a previous study [43]. There are many valid factors for chronic hyperphosphatemia in dialysis patients such as phosphate elimination during a single HD session is only 800–1,000 mg. As a result, dialyzing three times a week is insufficient to eliminate the required daily intake of phosphorus (1000 mg/d) for dialysis patients. In large cross-sectional population studies, mean blood phosphorus (or inorganic phosphate) in individuals with normal renal function stays fairly stable at about 3.8 mg/dl. It works the same way in those who have poor kidney function until their GFR drops below 30 ml/min/1.73 m<sup>2</sup>, which indicates stage 4 CKD. Serum phosphorus levels begin to increase at this time, and they continue to climb as these individuals progress to end-stage renal disease [43]. Dyslipidemia, a significant outcome of CKD and lipoprotein metabolism change, is linked to GFR loss; therefore, the lipid profile depends on renal function and proteinuria [44]. Hypercholesterolemia in CKD is primarily attributed to the acquired deficiency of LDL receptors, which is a result of renal insufficiency. In addition, it can be further exacerbated when combined with heavy proteinuria [45]. As renal function declines, there is an increase in oxidative stress, which results in the heightened oxidation of lipids in the bloodstream. Lipid metabolism is an intricate process that encompasses various organs, cells, and tissues, such as the liver, intestine, plasma, macrophages, and the vascular endothelium. It is important to note that impaired kidney function can have an impact on all of these components [46]. The most common reason for an increased concentration of TG-rich lipoproteins in patients with CKD is delayed catabolism. This is likely due to a decrease in the activity of hepatic TG lipase and peripheral lipoprotein lipase. The presence of lipase inhibitors may potentially affect the

breakdown of TG-rich lipoproteins, leading to a delay in their catabolism [47,48].

## Conclusion

Oxidative stress, driven by the generation of ROS during HD sessions, poses a substantial threat to the health of individuals with end-stage renal disease. This oxidative burden contributes to the development of various complications, including cardiovascular disease, inflammation, and cellular damage, thereby worsening the already compromised condition of these patients. Effective management and mitigation of oxidative stress are paramount to improving the overall well-being and quality of life of HD patients. Further research into novel therapeutic approaches and personalized interventions is warranted to address this critical issue and enhance patient outcomes in the long term.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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