

Comparative Analysis of Protein Fractions and Oxidative Stress Markers in Patients with Chronic Kidney Disease: Clinical and Biochemical Implications

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KEYWORDS

chronic kidney disease, total protein, albumin, total oxidant status, ceruloplasmin ferroxidase

Received: 17/05/2025
Accepted: 22/06/2025
Available online 30/06/2025

ABSTRACT

This study showed the effect of chronic kidney disease (CKD) on serum protein balance and redox homeostasis through a comparative analysis of serum protein fractions and oxidation markers. The results showed a significant reduction in total protein, albumin, and ceruloplasmin ferroxidase activity coupled with marked elevation in globulin levels and total oxidant status (TOS), also a decline in catalase activity compared with the first (healthy) group. These alterations connected with a dual disturbance in nutritional and immune status: tubular damage, malnutrition, and protein loss which cause a decreased in proteins serum. While the increase in globulin levels indicates a chronic inflammatory response. The increase in (TOS) with reduced antioxidant defenses confirms the role of oxidative stress in (CKD) progression. Furthermore, the decrease in ceruloplasmin ferroxidase activity is caused by impaired iron and copper metabolism and the accumulation of labile iron, which promotes Fenton reactions and the generation of reactive oxygen species. Overall these results suggest that assessment of serum proteins and oxidative stress biomarkers provides important diagnostic and prognostic tools for evaluating disease severity and guiding therapeutic interventions, stressing in the importance to but a strategy that include nutritional support and oxidative stress mitigation to advance clinical outcomes in CKD patients.

DOI : <https://doi.org/10.63964/atmj.2025.1.2.3>

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1. INTRODUCTION

The kidneys filter the blood and remove waste products produced physiologically by the body, such as urea and creatinine, all of these products are toxic in blood, and the kidneys eliminate these toxins through urine production. This occurs within the nephrons, which number one million per kidney [1]. Kidney failure is a fault in the normal functions of kidneys which filtering the blood from impurities and body by-products, including regulating fluids and electrolytes, which leads to fluid accumulation in the body and the

accumulation of waste, resulting in a general imbalance in the human body [2]. Individuals of various ages are impacted by kidney disease, and issues can arise at the social, psychological, and physiological levels. Kidney transplants can also be costly [3]. According to recent research, renal failure clearly alters the blood's protein components, particularly albumin, as a decline in this protein is one of the typical vital signs in kidney failure patients, infections, and malnutrition are strongly associated with kidney failure. A study published in 2025 showed that an elevated urea-to-

albumin ratio is an important determinant of the disease [4]. These changes are not limited to albumin levels, but also include total protein and globulin levels.

Protein loss through urine and impaired hepatic synthesis due to chronic inflammation lead to a decrease in total protein levels. Certain globulin types also rise as a result of inflammation's ongoing immune system stimulation [5]. In addition to these alterations in blood proteins, kidney failure also affects oxidative stress and its antioxidants because it causes the oxidation of several large biomolecules, including proteins, lipids, and nucleic acids, which increases oxidative stress [6]. Increased stress is associated with decreased antioxidant levels and increased free radical levels. In kidney failure, ROS attack cell membranes thereby reducing the effectiveness of antioxidant enzymes [7]. These radicals, such as superoxide radicals, hydroxyl radicals, and hydrogen peroxidase, which are naturally formed from oxygen metabolism, activate macrophages and neurophiles, leading to inflammatory processes [8].

2.MATERIAL AND METHODS

study design

This study was conducted on a number of patients with kidney failure and a number of healthy individuals who were randomly selected in Al-Ishaqi District and Samarra District-Salah al-Din for the period (1/3/2025 to 1/5/2025). The studied samples were divided into two groups: first group included (25) blood samples from healthy individuals, and the second group included (25) blood samples from patients with kidney failure. Blood samples were drawn using 5 ml medical syringes. Blood was then placed in glass tubes containing gelatin (Gel tubes). The samples were then centrifuged at 3000 rpm for fifteen min to obtain blood serum, then it was frozen at -20°C until biochemical tests were conducted.

Methods

After taking blood sample collection, kidney function tests were performed, which included estimating urea and creatinine levels, as well as serum proteins, including total protein, albumin, and globulins. Pre-manufactured kits were

used for all tests. As for oxidative stress and antioxidant tests, which included total oxidant status (TOS), catalase, and ceruloplasmin ferroxidase, the following methods were used:

Determination of Total Oxidant Status (TOS)

Erel's colorimetric method [9] used the basic idea of this method is that the oxidizing cause the ferrous ion-o-dianisidine complex to oxidize to the ferric ion. The oxidation process was aided by glycerol molecules. In an acidic media, iron (III) and xylenol orange combine to form a colorful complex, and the intensity of the resulting color is evaluated using spectrophotometry. The results are expressed as micromoles of hydrogen peroxide equivalents per liter ($\mu\text{mol H}_2\text{O}_2$ Equiv./L) were obtained by calibrating the test with hydrogen peroxide. The following reagents were used:

Reagent-1

Prepared by dissolving 114 mg of xylenol orange and 8.18 g of NaCl in 900 ml of 25 mM H₂SO₄ solution. 100 ml of glycerol was added to the solution to produce a final reagent solution consisting of 150 μM xylenol orange, 140 mM NaCl, and 1.35 M glycerol. The pH value of the reagent is 1.75, and this reagent is stable for at least 6 months at 4°C.

Reagent -2:

Prepared by dissolving 1.96 g of ferrous ammonium sulfate and 3.17 g of o-dianisidine dihydrochloride in 1000 ml of 25 mM H₂SO₄ solution. The final reagent consisted of 5 mM ferrous ammonium sulfate and 10 mM o-dianisidine dihydrochloride. This reagent is stable for at least 6 months at 4°C.

Measurement:

11 μL of the second reagent, 35 μL of the sample (blood or other fluids, whether pure or containing complex oxidants), and 225 μL of the first reagent were taken. The wavelengths used for the measurements were 800 nm for the secondary wavelength and 560 nm for the primary wavelength. As a baseline for the sample, the initial absorbance measurement was obtained prior to combining reagents R1 and R2. About three to four minutes after mixing, the reaction achieved a steady state, or when the reaction line became horizontal, at which point the final reading was taken. The concentrations were computed using the standard curve shown in Figure 1.

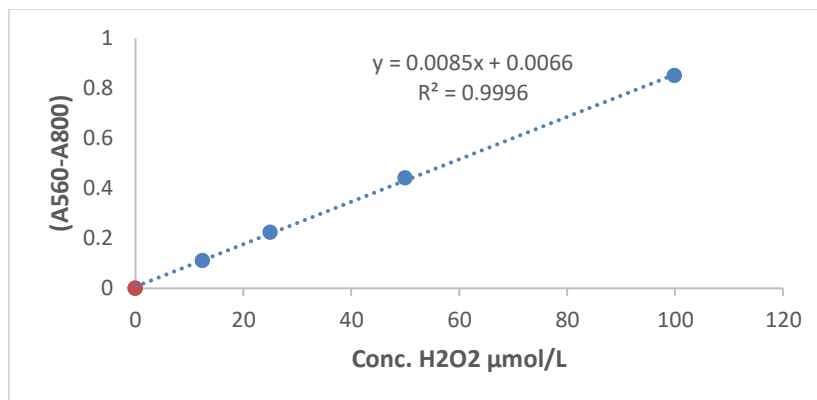


Figure (1) Standard calibration curve for TOS

The Hadwan colorimetric method [10] was used. The method principle based on the ammonium metavanadate reaction with hydrogen peroxide at acidic pH, reducing vanadium (V) to (III). Hydrogen peroxide causing the formation of an orange-red peroxovanadium complex, which absorbs at 452 nm. As in the following equation:
 $H_2O_2 + NH_4VO_3 + H_2SO_4 \rightarrow NH_4[VO(O_2)SO_4] + 2H_2O$
 solution.

The following solutions were used for this purpose:
 First solution: Vanadium reagent: Prepare a 0.01 M solution of sodium metavanadate in 0.5 M sulfuric acid.
 Second solution: Phosphate buffer solution: Prepared at a concentration of 50 mM and pH = 7.
 The third solution was: Hydrogen peroxide: Prepared at a concentration of 10 mM using phosphate buffer

Solutions used:, ,	sample	standard	cuvette
serum			
water	25 microliters	2025 microliters
hydrogen peroxide	2000µl	2000µl
Mix with a mixer and incubate at 37°C using a water bath.			
Vanadate solution	2000 microliters	2000 microliters	2000 microliters
Once the saturating solution has been zeroed in, let the tubes sit at room temperature for ten min before reading the absorbance at 452 nm.			

Catalase Activity of test kU = 2.303/t * log S°/S

Determination of Ceruloplasmin Ferroxidase

A new spectrophotometric method was used to measure the activity of ceruloplasmin ferroxidase by Hadwan et al. [11] using a microplate protocol. A mixture of 25 µL of serum diluted fivefold with 0.15 M sodium chloride solution and 100 µL s of 0.45 M acetate buffer (pH 5.8) was prepared and incubated at 37°C for 5 min in a 96-well plate.then 25 µL of 5 mM ferrous ammonium sulfate solution, the second reagent, was then added and mixed well. Then, 100 µL of reagents 3 and 4 were added to each well, and the plate was incubated for an additional 5 minutes at

37°C. The absorbance was then measured at a wavelength of 490 nm using reagent 3 and 450 nm when using reagent 4. Distilled water was used in a blank well.

Calculations: activity was calculated using to the following equation:

Ferric ion in tube =(ATest/ ASTD)x Conc. of STD Ferroxidase (UL)=(Conc.of ferric ion in test tube / time(5min))x(Total volume(ml)/ Volume of the sample (ml))

The Concentrations were calculated according to the standard curve shown in Figure 2.

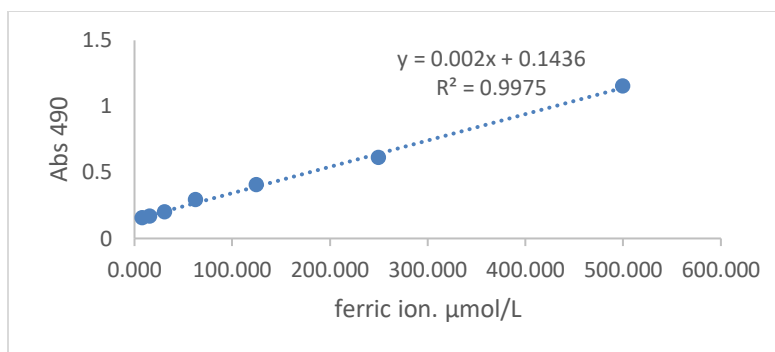


Figure (2) Standard calibration curves for ceruloplasmin ferroxidase.

3.RESULTS AND DISCUSSION

Kidney Function Test

Kidney function tests, including urea and creatinine levels, were performed for the study groups to compare samples from the patient group with those from the healthy group. The results are shown in Table (1).

Table 1: The mean +standard deviation of urea and creatinine og groups under investigation

Groups	Urea mg\dl	Creatinine mg\dl
Control	36.14 ±6.33 b	0.87± 0.176 b
Patients	207.62±65.491 a	10.15±2.42 a

The mean ± standard deviation (mean ± SD) of urea level in patients was 207.62 ± 65.49 mg/cm³ and in healthy controls was 36.142 ± 6.33 mg/cm³, as shown in Table (1) and Figure (3).

The urea levels in the kidney failure in patients were significantly higher than those in the healthy group, according to the above data, at the probability level of P≤0.05. The reduced excretion of urea, which comprises nitrogen from the metabolism and synthesis of proteins produced in the liver and eliminated by the kidneys, is the cause of the elevated urea level in patients with renal failure [12]. Because they are sensitive to all changes, urea levels are regarded as a crucial signal in assessing the effectiveness and function of the kidneys [13]. Its rise indicates that the blood of renal contains more urea, and elevated levels of it cause more damage. Increased oxidative stress, cell death, insulin resistance, and inflammatory variables are all part of this rise, [14].

The mean±standard deviation (mean±S.D) of creatinine level in patients was 10.15±2.42 mg/cm³ and in healthy controls was 0.87±0.17 mg/cm³, as shown in Table (1) and Figure (4). Total protein levels in the patient group were significantly lower than those in the healthy group (p≤0.05), according to the results. The glomerular filtration rate is weakened as a result of renal tubule injury, which causes this decline. Because of their huge molecular size, protein molecules cannot pass through the kidneys; yet, in circumstances of glomerular injury

and kidney failure, they can [15]. The mean ± standard deviation (mean ± SD) of total protein level in patients was 5.703 ± 1.14 mg/cm³ and in healthy controls was 7.081 ± 0.378 mg/cm³, as shown in Table 2 and Figure (5).

There are also other indirect factors, such as malnutrition, which is the most common adverse effects of kidney failure. The body's need for proteins to repair damaged tissue and defend the immune system increases the need for proteins, thus lowering their levels in patients. Therefore, it is an indicator of kidney disease [16]. The mean±standard deviation (mean±S.D) of albumin level in patients was 3.68±0.62 mg/cm³ and in healthy controls was 5.017±0.33 mg/cm³, as shown in Table (2) and Figure (6). The results showed a significant decrease in albumin levels at p≤0.05 in the patient group compared to the healthy group. This is because renal failure patients have elevated oxidative stress as a result of the illness. Because albumin is an endogenous antioxidant that inhibits the oxidation-reduction chain and cooperates with uric acid, glutathione, and vitamin C, the body needs to consume antioxidants, including albumin [17]. Albuminuria is the loss of albumin from the blood through the urine as a result of renal disease-induced damage to the glomeruli [18]. Reduced albumin levels and increased protein loss in the urine are caused by high levels of inflammation linked to increasing renal failure. Substances released by inflammatory cells alter protein

metabolism and accelerate albumin degradation. In addition, a decrease in albumin levels in the blood due to reduced kidney function causes a build-up of toxins [19].The mean±standard deviation

(mean±S.D) of globulin level in patients was $2.63\pm0.63/cm^3$ and in healthy controls was $1.96\pm0.41 mg/cm^3$, as shown in Table (2) and Figure (7).

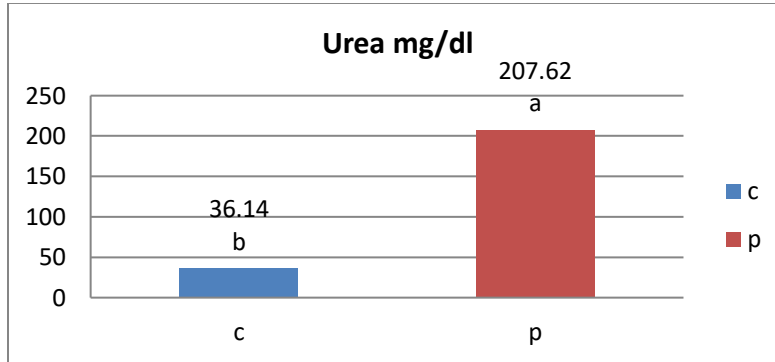


Figure (3) urea levels in serum

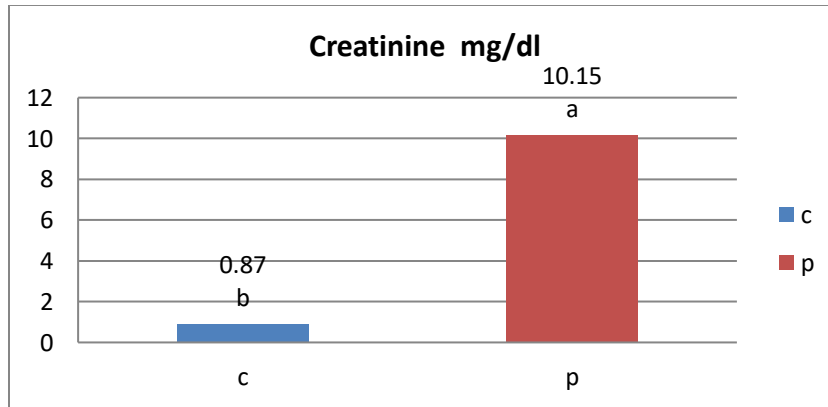


Figure (4) Creatinine level in serum

Tabel2: The mean +standard deviation of Total protien,Albumin and Globulin of groups under investigation

Groups	Total protein mg\dl	Albumin mg\dl	Globulin g\dl
Control	$7.08\pm0.37a$	$5.01\pm0.33a$	$1.96\pm0.41 b$
Patients	$5.70\pm1.14 b$	$3.68\pm0.62 b$	$2.63\pm0.63 a$

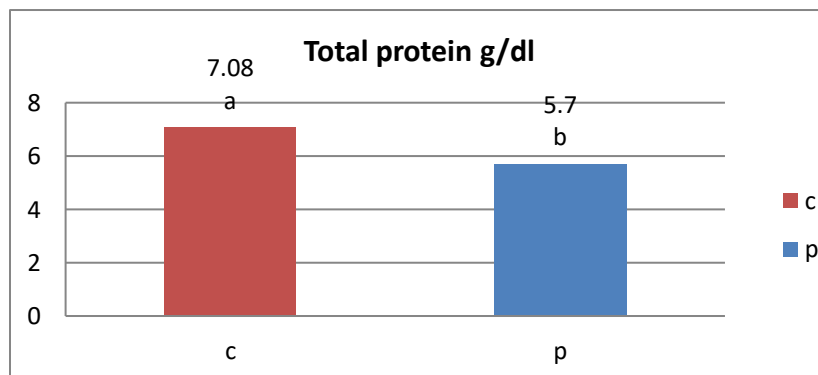


Table (5) Total protein level in serum

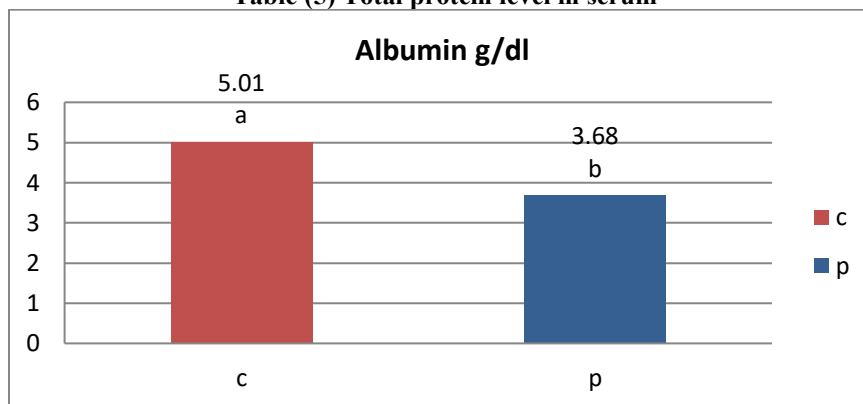


Figure (6) albumin level in serum

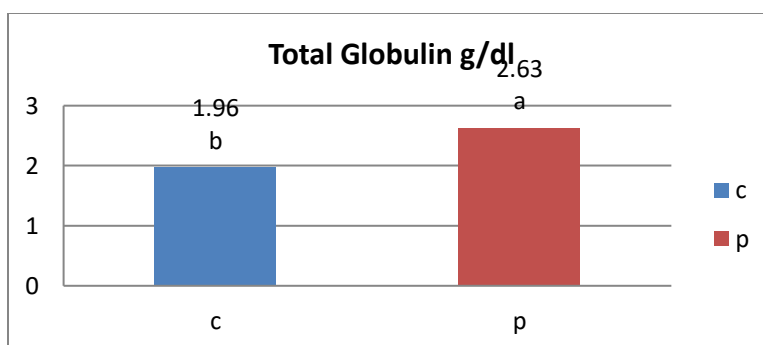


Figure (7). globulin level in serum

At a significance threshold of $P \leq 0.05$, the study found that patients' serum globulin levels were higher than those of healthy people. These findings are in line with a study performed in 2023 by Clingan et al. [20], which showed that patients with renal failure had higher amounts of globulin, a significant component of total protein. An inflammatory condition or immunological response is indicated by an increase in globulin, the main component of non-albuminuric total protein, which is made up of several inflammatory proteins [21]. Serum globulin levels are related with conditions such as infection, inflammation, and liver disease, or they may decrease when there are problems that cause decreased globulin synthesis or increased globulin loss [22]. The inflammation is common in patients with kidney failure, caused by urinary toxins, oxidative stress, and dialysis-related factors [23]. Patients with kidney failure are at increased risk of death if they have high globulin levels and coexist with several conditions such as coronary artery disease or chronic obstructive pulmonary disease (COPD). Furthermore, those with elevated ferritin and globulin levels above 3.2 g/cm³ are at higher risk of death [24].

Globulin is biggest component of total serum protein and is calculated as the difference between total protein and albumin. [22]. Low total protein and albumin combined with high globulin levels lead to a condition called protein-energy wasting (PEW), which define as the decrease in the body's protein and energy stores due to malnutrition and inflammation and is associated with negative health outcomes for kidney failure patients [25]. From these results, it is clear that low total protein levels are a common feature of CKD patients, which contributes significantly and directly to the body's ability to confront oxidative stress, especially with low albumin, which is an important antioxidant and reduces free radicals. Therefore, low total protein is an indicator of deterioration in the patient's nutritional and defensive status and increases the aggravation of oxidative stress damage associated with kidney failure [26]. Total oxidant status, catalase, and ceruloplasmin ferroxidase were examined for the study groups to confirm the similarity of the patient and healthy group samples. The results were as shown in Table (3). The mean±standard deviation (mean±S.D) of TOS levels in patients was $60.87 \pm 13.14 \mu\text{mol/L}$ and

in healthy controls was $31.56 \pm 9.42 \mu\text{mol/L}$, as shown in Table (3) and Figure (8).

The findings demonstrated that, at a probability level of ($P \leq 0.005$), the patient groups catalase activity level was lower than of the healthy group. By breaking down hydrogen peroxide (H_2O_2) and turning it into oxygen and water, the vital antioxidant enzyme catalase lessens the effects of oxidative stress. Numerous illnesses, including diabetes, anemia, and high blood pressure, are linked to any decline in catalase function. As a result, some research facilities seek to develop it as a remedy for certain illnesses [27]. The reason for the decrease in catalase levels in CKD patients is due to ischemia, which is one of the stimulants of oxidative stress. And the main source of reactive oxygen species is the Mitochondria [28]. During ischemic injury, reactive oxygen species (ROS) such as peroxynitrite and hydroxyl radicals are generated. At the same time, antioxidant enzymes

such as catalase and glutathione peroxidase, which are produced in kidney tissue after increased nephrotoxicity, are depleted [29]. According to a study's findings [30], patients with CKD had considerably lower catalase activity. High concentrations of catalase, which lowers ROS and prevents lipid peroxidation, are found in the aerobic cells of the kidneys, additionally, a lack of catalase results in the buildup of ROS within mitochondria, breaking down their structure and function and causing mitochondrial malfunction [31]. CKD pathology leads to increased in oxidative stress, and that causes varying levels of catalase in patients with the disease, indicating a connection between worsening kidney damage and reduced antioxidant capacity [32]. The mean \pm standard deviation (mean \pm SD) of ceruloplasmin ferroxidase activity level in patients was $167.01 \pm 43.63 \mu\text{mol/L}$ and in healthy controls was $285.7 \pm 41.59 \mu\text{mol/L}$, as shown in Table (3) and Figure (10).

Tabel3: The mean +standard deviation of TOS, Catalase and Cp-FeOx of groups under investigation

Groups	TOS	Catalase	CP- FeOx
Control	31.56 ± 9.42 b	44.68 ± 10.29 a	285.7 ± 41.59 a
Patients	60.87 ± 13.14 a	26.16 ± 4.81 b	167.01 ± 43.63 b

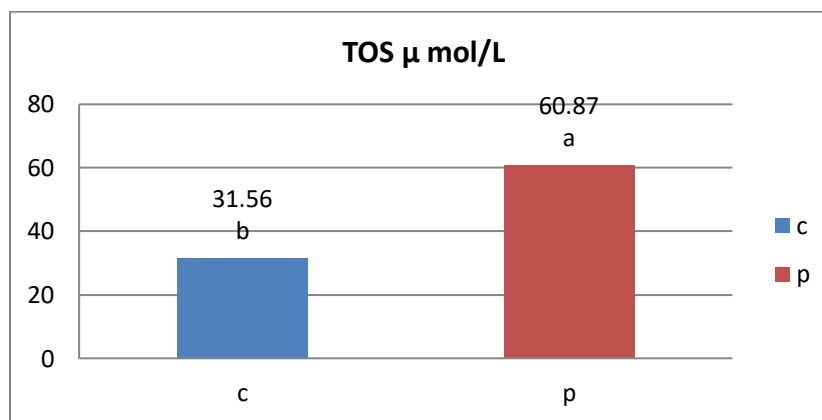


Figure (8) TOS level in serum

The results showed an increase in the overall stress level in the infected group compared to the control group (healthy individuals), at a probability level of $p \leq 0.005$. The study results are in agreement with the findings of Abod et al. [33], which confirmed elevated TOS levels in patients with renal failure and the resulting impaired kidney function. Stress was observed to develop and antioxidant capacity decreased due to several factors, including lipid peroxidation and the resulting elevated levels of malondialdehyde (MDA) [34]. Additionally, NADPH-ox is

overexpressed in the kidney and immune cells of CKD patients, which results in higher superoxide generation and less free radical scavenging [35]. In CKD, there is a decrease in antioxidant enzymes such glutathione peroxidase, catalase, and vitamins C and E. ROS builds up as a result of this shortage, which raises TOS [36]. Chronic kidney disease (CKD) is characterized by a high immunological response and elevated CRP, TNF- α , and IL-6. These factors, in turn, cause elevated TOS [32]. The mean \pm standard deviation (mean \pm SD) of catalase activity level in patients was 44.68 ± 10.29 U/L and

in healthy controls was 26.16 ± 4.81 U/L, as shown in Table (3) and Figure (9).

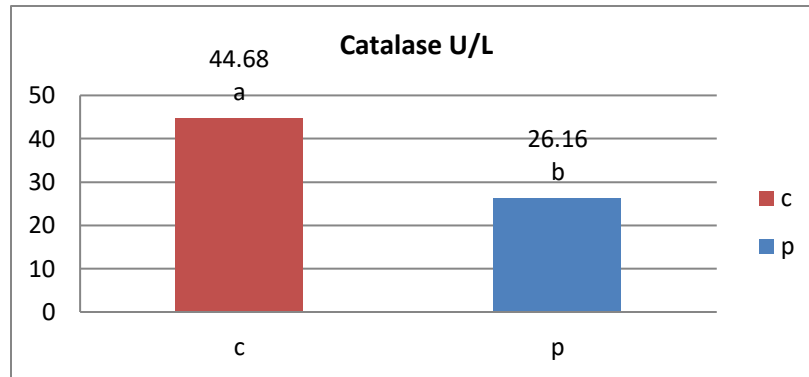


Figure (9) Catalase activity level in serum

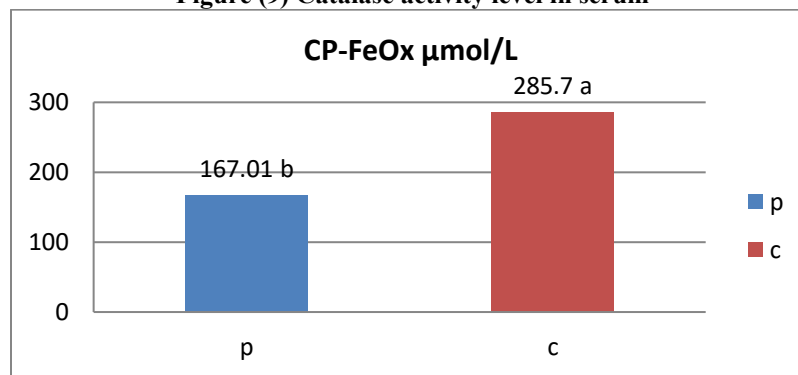


Figure (10) Ceruloplasmin ferroxidase activity level in serum

The results showed a significant decrease in the CP-FeOx activity level in the patients group compared to the healthy group at a probability level of ($P \leq 0.005$). Ceruloplasmin is a human protein found in blood serum that carries 95% of the total copper and is the largest enzymatic antioxidant which play a protection role by inhibiting iron-dependent lipid peroxidation and preventing the formation of hydroxyl radicals [OH] from hydrogen peroxide through its participation in the ferroxidase reaction. It also inhibits copper-catalyzed lipid peroxidation, in addition to consuming nitric oxide in plasma through its activity as NO oxidase, and enhances the oxidation of LDL lipoprotein [37, 38]. As a ferroxidase-active protein, ceruloplasmin contributes to iron metabolism by oxidizing iron ions (Fe^{2+}) to Fe^{3+} , which then binds to transferrin and stops the production of harmful iron products [39, 40]. Ceruloplasmin is one of the ferroxidase enzymes that are crucial for maintaining iron balance. Thus, iron buildup brought on by ferroxidase deficiency impacts immunological response and brain function [41]. Iron buildup in tissues, including iron deposited in the body and liver, is one of the most significant signs of kidney

failure. This increases oxidative stress, which in turn increases vascular disease and kidney damage overall [42].

When iron accumulates due to disease, free iron increases, which is very reactive and generates hydroxyl radicals through Fenton reactions, causing damage to plasma proteins and depleting antioxidants, including ceruloplasmin, which reduces its effectiveness [43]. In addition, CKD causes changes in copper and iron metabolism, which leads to a decrease in the effectiveness of ceruloplasmin ferroxidase [44]. With the increase of iron, it collapses, which exceeds the ability of ceruloplasmin to regulate, leading to disruption of its function and a decrease in its activity [45].

5.CONCLUSIONS

The Damage to renal tubules and protein loss, which results in lower levels of total protein and albumin, impact the nutritional and immunological condition of individuals with renal failure. Elevated globulin and acute-phase proteins are also caused by the inflammatory response linked to renal failure. Because of the buildup of free radicals, this chronic inflammatory disease and

reduced renal function undoubtedly cause an imbalance of oxidants and antioxidants. This comes on top of the body's diminished capacity to expel hydrogen peroxide as a result of ischemia-induced reductions in antioxidants, such as catalase, and mitochondrial dysfunction in kidney cells. Furthermore, decreased ceruloplasmin ferroxidase is due to impaired antioxidant capacity, impaired iron and copper metabolism, and the accumulation of free iron, which exacerbates oxidative Fenton reactions. Therefore, all of these factors are important in monitoring the deterioration of the clinical condition of these patients.

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