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Diagnostic Value of Serum Paraoxonase-1 Activity and Ceruloplasmin Levels in Patients with Renal Failure

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ABSTRACT
Renal failure is characterized by systemic metabolic, hematological, and biochemical alterations that contribute to accelerated oxidative stress and chronic systemic inflammation. Paraoxonase-1 (PON1) acts as an essential antioxidant enzyme bound to high-density lipoproteins, whereas ceruloplasmin serves as an acute-phase reactant with pro-oxidant potential under pathological conditions. However, the diagnostic utility of their simultaneous alterations in renal impairment remains to be fully elucidated. This study evaluated the diagnostic potential of serum paraoxonase-1 (PON1) activity and ceruloplasmin concentration in patients with renal failure. A case-control study was conducted comprising 60 renal failure patients and 30 age- and gender-matched healthy controls. Fasting blood samples were collected to analyze standard hematological, metabolic, renal, and hepatic parameters, along with serum PON1 activity (spectrophotometrically) and ceruloplasmin levels (nephelometrically). Renal failure patients demonstrated significant hematological impairments (decreased RBC, Hb, hematocrit, WBC, and platelets; ($P<0.05$) and metabolic dysregulation, including elevated serum glucose, triglycerides, and cholesterol alongside reduced total protein and albumin ($P<0.05$). Serum urea, creatinine, uric acid, potassium, and phosphorus were significantly elevated, whereas sodium was decreased ($P<0.05$). Serum PON1 activity was significantly reduced in renal failure patients compared to healthy controls (226.1 ± 135.4 vs. 758.5 ± 353.9 nmol/ml/min, $P<0.001$), whereas serum ceruloplasmin concentration was significantly higher (262.6 ± 40.9 vs. 233.3 ± 37.8 mg/L, $P<0.001$). In conclusion, the reciprocal shift in serum PON1 activity and ceruloplasmin concentration reflects impaired antioxidant defense and a heightened inflammatory state in renal failure, serving as useful non-invasive biomarkers associated with renal impairment.

CITATION
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INTRODUCTION

Renal Failure (DN), a frequently occurring micro vascular complication of diabetes mellitus, is referred to as kidney disease (DKD) and constitutes about 30% to 40% of all patients suffering from diabetes, being the principal cause of end-stage renal disease (ESRD) worldwide (Zhuang et al., 2014; Samsu, 2021). The current conventional clinical assessment of kidney disease is primarily based on non-specific biomarkers, such as urinary albumin excretion tracking the natural history from norm albuminuria to micro and macro albuminuria, and progressive decline in estimated glomerular filtration rate (eGFR) (Samsu, 2021;

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Perez-Gomez et al., 2019). Nevertheless, mounting clinical and histopathological evidence demonstrates that significant structural damage such as glomerular basement membrane thickening, podocyte loss, and mesangial matrix expansion often occurs long before clinically identifiable albuminuria or eGFR changes (Samsu, 2021; García-Carro et al., 2021). As such, reliance on traditional clinical measures results in a diagnostic lag that highlights the urgent need for novel, highly-sensitive non-invasive biochemical biomarkers to detect potentially reversible early renal subclinical injury with high prognostic resolution for risk stratification (Zhuang et al., 2014; García-Carro et al., 2021).

Renal Failure is the simplest form, broadly defined as one of a various multi-factorial cascades ignited by chronic intracellular and extracellular hyperglycemia (Jha et al., 2016). In the presence of chronic hyperglycemia, inappropriate metabolic pathways lead to activation of superfluous ROS generating processes including the polyol pathway, advanced glycated end-product (AGE) accumulation and protein kinase C (PKC) signaling (Jha et al., 2016), (Rayego-Mateos et al., 2020). This chronic oxidative stress disturbs the subtle redox balance of renal tissue and initiates a state of persistent subclinical inflammation with endothelial dysfunction, high vascular permeability, and extracellular matrix deposition (Rayego-Mateos et al., 2020; Forbes & Cooper, 2013).

Endogenous enzymatic antioxidant defenses become depleted both qualitatively and quantitatively in this pathogenic context (Forbes & Cooper, 2013). Paraoxonase-1 (PON1), a calcium-dependent esterase with strict hepatic synthesis and physical-chemical binding to high-density lipoprotein (HDL) particles, is the foundation of the vascular antioxidant system (Litvinov et al., 2022). PON1 hydrolyzes lipid peroxides and protects HDL and LDL from oxidative modification (Litvinov et al., 2022; Kovacs et al., 2020) , resulting in protection of vascular endothelial cells. In recent years, clinical investigations have shown that the serum paraoxonase (PO) and arylesterase catalytic functions of PON1 are markedly reduced in patients with type 2 diabetes mellitus (Kovacs et al., 2020), (Bordas et al., 2021). The reduced serum PON1 activity leads to impaired HDL function and an increased rate of lipid peroxidation in the glomerular capillaries (Litvinov et al., 2022; Bordas et al., 2021).

Conversely, chronic systemic inflammation is associated with the increase of positive acute-phase reactants, one of which is ceruloplasmin exerting an important double-edged role (Linder, 2020). Ceruloplasmin is a multicopper oxidase produced in the liver, accounting for 95% of circulating copper and exhibiting ferroxidase activity required for iron balance (Linder, 2020), (Chapman & Moles, 2021). Nevertheless, during a state of chronic inflammation and hyperglycemia, an increasingly higher circulating ceruloplasmin levels become ineffective as protective antioxidant entity and turns into pro-oxidant effects (Chapman & Moles, 2021), (Venkataraman & Subramanian, 2019). High concentrations of ceruloplasmin could aggravate lipid peroxidation, leading to podocyte dam-age and tubulointerstitial fibrosis through the catalysis of hydroxyl radical generation via Fenton-type reactions (Chapman & Moles, 2021; El-Bahr et al., 2022). Biochemical studies have also shown that serum ceruloplasmin concentrations are upregulated in patients who develop renal impairment, and this is positively correlated with the amount of urinary albumin excretion (Venkataraman & Subramanian, 2019), (El-Bahr et al., 2022).

Since these enzymes exhibit a biological ambivalence (PON1 protects against oxidative stress while ceruloplasmin facilitates inflammation), the simultaneous activity of both allows for a unique diagnostic insight into renal injury (Bordas et al., 2021; El-Bahr et al., 2022). The reciprocal shift, expressed as a large decrease in protective PON1 activity concurrently with an abnormally elevated concentration of ceruloplasmin (a classic acute phase protein), is much more closely correlated with systemic redox-inflammatory state than either parameter measured alone (Kovacs et al., 2020), (Venkataraman & Subramanian, 2019). Therefore, this study aims to evaluate the changes in serum PON1 enzymatic activity and ceruloplasmin concentration in patients with renal failure compared to healthy controls, and to assess their association with clinical hematological, metabolic, and renal parameters.

MATERIALS AND METHOD

This study was performed in a group of renal failure patients at General Baquba Hospital for the period from 1/1/2026 to 1/6/2026. The study subjects consisted of 60 cases (30 men, 30 women) with renal failure aged between 20-55 years and a control group of age-and gender-matched 30 healthy controls (15 men, 15 women) who did not have any diseases.

Blood Sampling Method

Venous blood (5 mL) was collected from each of the study participants in the fasted state during the morning before breakfast. Blood Samples for Hematological Parameters: Blood samples were drawn into separate test tubes containing EDTA as an anticoagulant to assess hematological parameters. A second set of 5 mL venous blood samples were obtained from the same subjects without anticoagulation to conduct biochemistry tests. At the time of blood coagulation, serum was isolated by centrifugation for 20 min at 3,000 rpm. Serum samples were obtained, and stored at −20°C until performing the analyses.

Determination of Hematological Parameters

Red blood cell (RBC) count, white blood cell (WBC) count, and platelet count were determined in the hospital's hematology laboratory using a hemocytometer. Hemoglobin concentration was measured according to Wong's method (Wong, 1928), and the hematocrit percentage was determined using heparinized capillary tubes.

Determination of Biochemical Parameters in Blood Serum

In the hospital's biochemistry laboratory, biochemical parameters in serum were determined for the participants of this study. We calculated the blood glucose concentration by Blood glucose with Bicon company reagents via the Trinder method (Trinder, 1969), based on GOD-PAP. Concentration of total protein in serum was determined based on the Biuret method (Weichselbaum, 1946) using reagents by Bicon company with subsequent measurement of absorbance by a spectrophotometer. The sample for serum (albumin concentration) was obtained from sensitive chromatic determination of the Albumin concentration using reagents Bicon company according to the Bromocresol green (Doumas et al., 1971; Webster, 1974).

Serum globulin level was calculated as total serum protein concentration minus serum albumin concentration. Serum triglycerides concentration was measured by the GPO-PAP method based on Young and Pestaner (Young et al., 1975) and Fossati and Principe (Fossati & Prencipe, 1982). The CHOD-PAP method (Richmond, 1973) was used to assess serum cholesterol concentration, and the method of Burstein et al. was used to measure high-density lipoprotein (HDL) concentration (Burstein et al., 1970) and low-density lipoprotein (LDL) level was calculated according to the Friedewald equation (Friedewald et al., 1972).

The concentration of urea was measured with the urease enzyme (Fawcett & Scott, 1960), and that of uric acid following the method described by Fossatti (Fossati et al., 1980). Determination of creatinine also without protein precipitation (Bartels et al., 1972). Serum sodium and potassium were measured using the methods of Maruna & Trinder (Maruna & Trinder, 1958), calcium concentration was determined with the Arsenazo III method and phosphorus concentration was assessed according to Fiske and Subbarow (Fiske & Subbarow, 1925). Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were measured by the method of Reitman S and Frankel (Reitman & Frankel, 1957). Activity of serum alkaline phosphatase (ALP) was assayed based on the method established by Kind et al (Kind & King, 1954).

The enzymatic assay of paraoxonase activity was assessed based on the method described by Sampson et al (Sampson et al., 2005). Following advice from Abbott et al. (Abbott et al., 1995). Before the analysis of PON-1 activity, serum from controls and s was preincubated with 5 µmol/l serine for 10 min at room temperature in order to inhibit serum butyrylcholinesterease activity elevated in diabetes which would interfere with determination of PON-1 activity in the serum from subjects with diabetes (Lee et al., 2015). The substrate used was paraoxon (O, O-diethyl P-nitrophenyl phosphate; 1.0 mmol/l; Sigma chemical Co., St Louis, Missouri, USA), and enzyme activity was determined at 37°C in a solution of 50 mmol/l Tris/HCL buffer (pH 6.8) containing 1.0 mmol/l CaCl2. The P-nitrophenol generation rate was measured in a spectrophotometer RA50 (Bayer, Pittsburgh, Pennsylvania, USA) measuring the increase of A405 at 37°C.

According to the most current information, a meta-analysis demonstrated that Ceruloplasmin why not try here was assessed rigorous in sort 2 diabetes individuals. Serum ceruloplasmin level was assessed based on a nephelometric method (BN II System; Siemens, Marburg, Germany) (Suresh et al., 2012).

Statistical Analysis

Data were analyzed using SPSS. Quantitative variables were expressed as (Mean ± SD). Student's t-test was applied for comparing two groups (renal failure vs. healthy controls). One-way ANOVA was utilized where appropriate. A P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

After statistical analysis of hematological and biochemical parameters in renal failure patients, the following was revealed:

First Hematological Parameters

We found a statistically significant decrease in red blood cell (RBC) count, hemoglobin concentration and hematocrit value, as well as white blood cells (WBC) count and platelet count on renal failure patients when compared to healthy individuals non affected by renal failure (see Table 1).

Table 1: Hematological changes associated with renal failure disease

Group / Parameters	Red Blood Cell Count (×106 cells/mm3)	Hemoglobin Concentration (g/100 mL)	Hematocrit (%)	White Blood Cell Count (×103 cells/mm3)	Platelet Count (×103 cells/mm3)
Healthy Group (Mean /pm SD)	4.72 /pm 0.35	13.36 /pm 1.01	41.10 /pm 4.07	7.9 /pm 0.5	307.4 /pm 30.9

Renal Failure Group (Mean /pm SD)	3.76 /pm 0.33*	10.43 /pm 1.04*	32.50 /pm 3.00*	6.2 /pm 0.4*	197.2 /pm 20.3*
Percentage Change (/%)	-20.34	-21.93	-20.92	-21.52	-35.86

Second-Biochemical Parameters

A. Metabolic Parameters:

Significant changes were observed as follows:

1. Increase in blood serum concentration of glucose, triglycerides, and cholesterol in renal failure patients compared to the healthy group (see Table 2).
2. Decrease in total proteins and albumin concentration in the blood serum of renal failure patients compared to healthy controls as shown in Table 2.
3. No significant change occurred in serum globulin of patients compared to healthy controls.

Table 2: Metabolic changes associated with renal failure disease

Group / Parameters	Serum Glucose Concentration (mg/dL)	Serum Triglycerides Concentration (mg/dL)	Serum Cholesterol Concentration (mg/dL)	Serum Total Proteins Concentration (g/dL)	Serum Albumin Concentration (g/dL)	Serum Globulin Concentration (g/dL)
Healthy Group (Mean ± SD)	101.5±8.3	138.7±6.61	145±9.5	7.36±0.31	4.35±0.38	3.01±0.28
Renal Failure Group (Mean ± SD)	147±10.7∗	168±7.3∗	179±8.3∗	6.4±0.29∗	3.3±0.31∗	3.1±0.21
Percentage Change (%)	+44.87	+21.16	+23.44	−13.04	−24.14	+2.99

B. Renal Functions:

1. The patients had significantly higher serum urea, uric acid, and creatinine concentrations and also serum potassium and phosphorus ion concentrations than the healthy control subjects (Table 3).
2. Serum sodium ion concentration decreased significantly in the renal failure patients compared to the healthy controls, as shown in Table 3.
3. In renal failure patients, the serum calcium ion concentration was not statistically significantly lower than in healthy controls (Table 3).

Table 3: Renal function changes associated with renal failure disease

Group / Parameters	Serum Urea Concentration (mg/dL)	Serum Uric Acid Concentration (mg/dL)	Serum Creatinine Concentration (mg/dL)	Serum Sodium Ions Concentration (mEq/L)	Serum Potassium Ions Concentration (mEq/L)	Serum Calcium Ions Concentration (mg/dL)	Serum Phosphorus Ions Concentration (mg/dL)
Healthy Group (Mean ± SD)	18.3±1.7	4.2±1.41	0.95±0.53	140.8±2.1	4.10±0.34	9.5±0.3	3.99±0.41
Renal Failure Group (Mean ± SD)	65.4±10.1∗	10.9±3.3∗	13.9±4.1∗	133.9±3.3∗	8.7±0.8∗	8.5±0.5∗	7.3±0.7∗
Percentage Change (%)	+257.32	+159.62	+1365.26	−4.90	+101.70	−10.62	+82.25

Values expressed as {Mean ± SD} . Statistical significance set at $P < 0.05$ compared to the Healthy Group

C. Liver Functions:

The results showed significant increases in the activities of aminotransferase enzymes (alanine aminotransferase, ALT; aspartate aminotransferase, AST), alkaline phosphatase (ALP), as well as total bilirubin concentration in the blood serum of renal failure patients compared to healthy controls (Table 4).

Table 4: Liver function changes associated with renal failure disease

Group / Parameters	Serum Alanine Aminotransferase (ALT) Activity (U/L)	Serum Aspartate Aminotransferase (AST) Activity (U/L)	Serum Alkaline Phosphatase (ALP) Activity (U/L)	Serum Total Bilirubin Concentration (mg/dL)
Healthy Group (Mean ± SD)	21.7±2.16	24.9±2.26	85.7±3.25	1.05±0.55
Renal Failure Group (Mean ± SD)	38.23±4.12*	34.51±3.19*	397±45.2*	4.65±0.39*
Percentage Change (%)	+67.18	+38.59	+363.24	+342.86

Values expressed as {Mean ± SD}. Statistical significance set at P < 0.05 compared to the Healthy Group.

Laboratory results for the studied groups are shown in table 5. Analysis of variance test showed a significantly lower PON1 activity in the patient groups compared with control groups (P < 0.001) (Table 5). Paroxonase activity levels were not significantly different between patients with Renal Failure and those without.

So, this analysis indicated a significantly greater rate of progression of Renal Failure by baseline ceruloplasmin (P<0.001) (Table 5). Basal levels of ceruloplasmin were significantly greater in the Renal Failure Group compared with Control Group (262.6±40.9 mg/L vs 233.3±37.8 mg/L, P<0•001).

Table 5: The levels of Paraoxonase activity and Ceruloplasmin associated with renal failure disease

Group / Parameters	Healthy Group (Mean ± SD)	Renal Failure Group (Mean ± SD)	P value
Paraoxonase activity (nmol/ml/min)	758.5 ± 353.9	226.1 ± 135.4	<0.001
Ceruloplasmin, mg/L	233.3±37.8	262.6±40.9	<0.001

Discussion

This study clearly shows that renal failure patient attending General Baquba Hospital for Nephrology and Urology are with reduced red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin concentration, and hematocrit. This pattern of changes matches previous observations demonstrating that renal failure is associated with broad-spectrum hematological disorders, such as anemia and dysfunction of leukocytes. Anemia and decreased WBC count in renal failure patients are frequently accompanied by inadequate erythropoietin production (hormone produced by juxtaglomerular apparatus in kidney), other aspects into play include deficiencies of iron and folic acid, an increased rate of destruction of RBCs, together with blood loss in urine (Al-Abachi et al., 2012), sodium retention and programmed cell death or apoptosis (alongside the accumulation of nitrogenous wastes in the body) nitrogenous wastes and toxic substances that cannot be excreted during renal failure which correlates with impaired bone marrow erythropoiesis and shortened RBC life span (Gouva et al., 2006).

In patients with renal failure, platelet count also decreased significantly. This reduction is observed in parallel with lower erythropoietin levels, showing a concomitant decrease in platelet numbers; given the structural similarities between erythropoietin and thrombopoietin, it has been proposed that levels of erythropoietin regulate platelets given that erythropoietin levels are closely linked to platelet dynamics (Al-Abachi et al., 2012; Rajagopalan et al., 2013).

This study showed the lowest levels of serum total protein, albumin and renal failure patients versus healthy patients at General Baquba Hospital during 2026. These observations are consistent with data from a study conducted in South India in patients with renal failure (Rajagopalan et al., 2013; Viswanathan et al., 2004). In another study, renal failure patients identified a prominent increase in triglycerides and cholesterol levels (Fawcett & Scott, 1960). The observed results are similar to data published in the period (Rajagopalan et al., 2013), (Amin et al., 2006), (Singh et al., 2006), on renal failure patients within the Indian population between 2006-2013.

However, systemic diseases at advanced stages are often associated with altered kidney function their marker being serum urea, creatinine and uric acid concentrations. Blood serum levels of urea, creatinine and uric acid were significantly elevated in renal failure patients which is compatible with a number of studies (Rajagopalan et al.,

2013), (Singh et al., 2006). Serum urea and serum creatinine concentrations were significantly increased in the blood samples of patients with mild to severe renal insufficiency, the higher serum urea and creatinine concentrations thus indicating greater impairment of renal function, blood parameter values showed an inverse association with the serum creatinine concentration (Rodwell, 2003).

As the kidneys are important for the regulation of sodium and potassium ion levels in blood, abnormalities of the blood level means that the kidneys are concerned. In our study results show decreased serum sodium ion levels charged with an increase in the serum potassium ion level. These observations are in agreement with records carried out between the chronic renal failure patients in Iraq during 2012 (Al-Abachi et al., 2012). Electrolyte shifts observed in the setting of renal failure that has been proposed for the decreased serum sodium concentration detected in these patients is loss or reduction of electrolyte retention by aldosterone hormone, which consequently leads to increased urinary sodium excretion (Al-Abachi et al., 2012).

Overall, the mean PON-1 activity was significantly lower in our patients with nephropathy, compared to controls. ROC curve analysis revealed a cutoff point of PON-1 activity to separate individuals with diabetes from the control group was found using 500 nmol/ml/min. These results were in agreement with other studies reporting reduced PON-1 activity in individuals with type 2 diabetes (Abbott et al., 1995), (Karabina et al., 2005). In contrast to them, Valabhji et al. Type 2 Diabetes and PON-1 Finally, (Kopprasch et al., 2003), found no association between type 2 diabetes status and PON-1 activity. This divergence may reflect methodological differences in study execution, using substrates such as phenyl acetate which may not be optimal in detecting PON-1 activity. Additionally, Kopporasch et al. Likewise, the study of ' et al. Suggested that PON-1 activity might decline later in diabetes mellitus since they did not observe significant differences between control and impaired glucose tolerant patients and early diabetes with respect to PON-1 activity.

The possible mechanisms by which PON-1 activity is reduced in type 2 diabetes are numerous. This reduction is linked to enzyme structural modifications associated with lipoxidation or glucoxidation (Baynes & Thorpe, 2000). Ferretti et al. Glycated HDL is characterized by modified physicochemical properties, and Incubation of HDL in vitro with glucose decreased the activity of HDL associated paraoxanase, according to (Ferretti et al., 2001). Furthermore, in vitro glycation of pure paraoxonase protein **is** associated with up to 40% lower enzymatic activity of paraoxonase (Hedrick et al., 1997), (Hedrick et al., 2000) and Deakin et al. As reported by (Deakin et al., 2002), smaller HDL particle size is associated with impaired cellular PON1 release to deliver PON-1 from cells: Moreover, unesterified cholesterol levels are inversely associated with HDL stability during conditions. Those lowers in action of PON-1 are pretend that reflects reduced HDL antioxidant capacity, which aligns with increased susceptibility to atherogenesis, in addition to diverse complications (Mackness et al., 2001).

In this study, baseline ceruloplasmin values were positively associated with the incidence of nephropathy. Ceruloplasmin levels showed an independent positive correlation with disease stage to Renal Failure after adjusting for conventional risk factors. These results indicate that higher ceruloplasmin levels are positively associated with renal impairment markers for developing nephropathy.

Ceruloplasmin levels have been shown to positively correlate with the progression of nephropathy, but it is not completely known how the two are correlated (Friedewald et al., 1972). In conditions of higher oxidative stress, such as type 2 diabetes mellitus (Memisogullari & Bakan, 2004), ceruloplasmin can behave as a pro-oxidant. Cu^{1+} is involved in pathways related to reactive oxygen species generation (ROS) in ceruloplasmin by oxidizing Fe^{2+}, and partly via increased availability of copper for intracellular ROS (Harris, 2003). Oxidative stress and oxidized LDL are associated with progressive kidney disease (Ujihara et al., 2002), thus, elevated ceruloplasmin levels reflect the redox-inflammatory status observed in renal dysfunction of diabetes nephropathy.

CONCLUSION

In conclusion, patients with renal failure exhibit significant systemic biochemical impairments, marked by severe oxidative and inflammatory imbalance. The significant reduction in serum PON1 enzymatic activity, combined with the elevation in ceruloplasmin concentration, highlights an altered redox-inflammatory status in renal failure. These observed changes suggest that PON1 activity and ceruloplasmin levels may serve as potential non-invasive complementary markers for assessing renal impairment. However, prospective longitudinal studies are required to establish their prognostic value in predicting disease progression.

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