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The Role of Urokinase-Type Plasminogen Activator (UPA) Level and Some Biochemical Parameters in Iraqi Hemodialysis Patients

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Abstract

The term end-stage kidney disease (ESKD) is often used to describe people who have the last stage of chronic kidney disease (CKD) and are undergoing dialysis or a kidney transplant for treatment. Hemodialysis (HD) is the most prevalent technique that is utilized to eliminate waste and other hazardous chemicals from the body. The study aims to assess the role of serum Urokinase plasminogen activator (UPA) levels among Iraqi hemodialysis patients. The study encompassed 50 patients aged 40–74 years (21 males and 29 females) admitted to the Iraqi dialysis center at Baghdad Teaching Hospital for the period from October 2022 to February 2023. They were diagnosed based on previous medical reports and laboratory and clinical tests by a consultant nephrologist. UPA, liver enzymes, blood urea, creatinine, albumin, total protein, sodium, potassium, total Ca, and PO_4 levels were determined. This study demonstrates higher levels of UPA in HD patients with ESKD and correlates with ALP; also, UPA can be considered a good marker for the prevention of the development of kidney fibrosis.

Keywords: Urinary-type plasminogen activator, kidney failure, liver enzymes, urea, creatinine, electrolytes.

1. Introduction

Chronic kidney disease (CKD) is a form of kidney disease characterized by a gradual decline in kidney function [1]. Kidney Disease Improving Global Outcomes (KDIGO) uses markers of kidney damage, such as proteinuria and the glomerular filtration rate, to define CKD [2]. So, it is usually defined as a decrease in kidney function, an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m^2, or markers of kidney damage, such as albuminuria, hematuria, or imaging abnormalities that have been present for at least 3 months [3]. End-stage kidney disease (ESKD), now known as kidney failure [4], occurs when the kidneys are unable to remove the body's metabolic wastes or proceed with their regulatory assignments [5]. Kidney failure may also be described as a decline in renal function [6].

Dialysis is the initial method of replacing renal function [7]. Hemodialysis (HD) is the most prevalent technique that is used to eliminate waste and other hazardous chemicals from the body [8]. Toxins in uremia are flushed out of the body by transporting over a permselective barrier (the membrane) from the blood to the dialysis fluid compartment [9]. By keeping the correct fluid and electrolyte balance, this process purifies the blood, preserves the body's homeostatic environment, and controls blood pressure within normal ranges [8].

Kidney disorders cause most instances of acute urination, and this suggests a malfunction in most of the nephrons, while in other cases, the etiology of the illness is unclear [10]. Despite advances in knowledge and diagnostics, many countries have a high proportion of ESKD patients with unknown causes [11]. The cau s of CKD vary between countries, ethnicities, and ages [12]. Hyperten ion is one of the major causes of ESKD [13]. Other ca ses include CKD, Urinary tract obstruction, recurrent kidney stones, and kidney or bladder congenital disabilities [2].

The urokinase-type plasminogen activator (UPA) is a mosaic protein with a modular structure similar to other serine proteases of the coagulation and fibrinolytic systems [14]. Although UPA is not a phosphorylating "kinase," the historical name is still used daily [15]. The kind y is a rich source of UPA [16]. Despite its abundance, the primary physiological role of UPA in the kidney is unclear. There is evidence to suggest it can stop kidney stones from forming [17]. The UPA activity has been associated with several proteolytic effects that should decrease fibrosis [16].

Further studies have reported the presence of urokinase in plasma, seminal fluid, and the extracellular matrix (ECM) of many tissues [18]. UPA has been shown to have an essential role in many different physiological processes, including intravascular fibrinolysis, angiogenesis, tissue regeneration, and immunological response. Several clinical situations have been shown to causally entail a dysregulated synthesis of UPA, such as cancer development and metastasis [19]. This study aims to assess the role of serum UPA levels among Iraqi hemodialysis patients with ESKD.

2. Materials and Methods

2.1 Patients

The present study was applied to 50 patients (21 males and 29 females) in an age range of 40–72 years. Prior to their inclusion in this study, all patients provided informed consent after being duly informed of the study's nature and purpose. A selected sample of patients who attend the Iraqi dialysis center at Baghdad Teaching Hospital for the period from October 2022 to February 2023. Moreover, 50 healthy individuals in the age range of 40–61 years old were selected as a control group. A consultant nephrologist made the diagnosis based on medical reports and lab and clinical tests. Before anyone was included in this study, they all gave their consent after being told about it.

All Iraqi hemodialysis patients with ESKD in this study have blood pressure disease without other medical conditions. Seven patients had kidney cysts, two had urinary tract infections, two had bladder diseases, and one had kidney stones. Therefore, these patients were not excluded. Diabetes, heart disease, malignancies, liver, lupus, and thyroid disorders were excluded. It also excluded patients with kidney transplants and congenital kidney atrophy. Body mass index (BMI) was calculated by taking a person's weight in kilograms and dividing it by the square of their height (m^2) [20]. The BioSource- MBBS3801100. It was used to find the concentration of UPA in the serum. It turned out that UPA in humans was very sensitive in this group. It was found that the sensitivity was 1 pg/mL. Blood. Urea (B. urea), creatinine, albumin, total protein, total calcium, PO_4, and liver enzymes (AST, ALT, and ALP). They used standard biochemical techniques, such

as the Neochem 100 Automated Analyzer. The SFRI ionix also evaluated sodium ions (Na^+) and potassium ions (k^+).

2.2 Blood sample collection

Before each patient's hemodialysis session, a venous blood sample (10 ml) was taken. From the fistula, blood samples were taken from the patient (site of the needle puncture in the vein). The serum was separated by transferring the sample to a Gel tube and centrifuging it at 3000 rpm for 15 minutes. To measure blood urea, creatinine, albumin, total protein, Na^+, k^+, total Ca, PO_4, and liver enzymes (AST, ALT, and ALP), the remains were transferred to an Eppendorf tube and stored in a deep freezer (-20°C) for longer-term use (UPA). The control group also had venous blood samples taken with a disposable syringe and centrifuged to get serum.

2.3 Statistical analysis

Statistical values are presented for all parameters as means±SD. Groups in the experiment were compared using the t-test. In addition, the study calculated the correlation coefficient of the variables to see how closely they were related. This study considered a *p*-value of ≤ 0.05 to be statistically significant. Receiver operating characteristics (ROC) curve analysis was used to determine the cut-off value, sensitivity, and specificity by using the Statistical Package for Social Sciences (SPSS) version 28.

3. Results

Tables 1 and **2** present the BMI, age, and biochemical characteristics of HD patients in the ESKD and control groups, respectively.

There is no statistically significant ($p > 0.05$) difference in BMI or total protein between the patients and the control group, but there is a considerable elevation ($p \leq 0.01$) in UPA Blood. Urea (B. Urea), Creatinine, Na^+, k^+, PO_4, ALT, and ALP, whereas a statistically significant ($p > 0.05$) difference was detected in serum AST and total Ca levels in HD patients in the ESKD as compared to the controls.

Table 1. Level of BMI, age of HD patients and control group.

Parameter	Control (n= 50)	Patients (n=50)	*P*-value
BMI (kg/m^2)	26.521±3.248	26.590±4.433	0.93
Age (Years)	47.840±5.730	54.240±9.054	≤ 0.001

Data are expressed as mean±SD. p ≤ 0.01: high significant, BMI: Body mass index.

Table 2. Biochemical characteristics of HD patients and control group.

Parameter	Control (n=50)	Patients (n=50)	*P*-value
UPA (ρg/mL)	171.218±37.255	264.344±37.767	≤0.001
ALP (U/L)	63.080± 14.334	446.446± 585.708	≤0.001
AST (U/L)	24.960±2.356	13.996± 6.148	0.003
ALT (U/L)	24.480± 5.632	15.236± 20.669	≤0.001
B.Urea (mg/dL)	32.720±8.122	145.269±39.032	≤0.001
Creatinine (mg/dL)	0.730±0.154	8.063±2.705	≤0.001
Albumin (g/dL)	4.596±0.385	4.149±0.421	≤0.001
Total. Protein g/dL)	6.952±0.465	6.989±0.630	0.740
Na^+ (mmol/L)	140.320± 3.000	136.800± 4.015	≤0.001
K^+ (mmol/L)	4.330± 0.427	5.343± 0.811	≤0.001
Total Ca (mg/dL)	8.938± 0.470	8.474±1.102	0.007
PO_4 (mg/dL)	3.764± 0.774	4.939±1.436	≤0.001

Data are expressed as mean±SD. p ≤0.01: high significant, UPA: urokinase-type plasminogen activator, ALP: Alkaline phosphatase, AST aspartate aminotransferase, ALT: alanine aminotransferase, B.Urea: Blood Urea, Na^+: Sodium ion, k^+: potassium ion, Total Ca: Total Calcium, PO_4: phosphate.

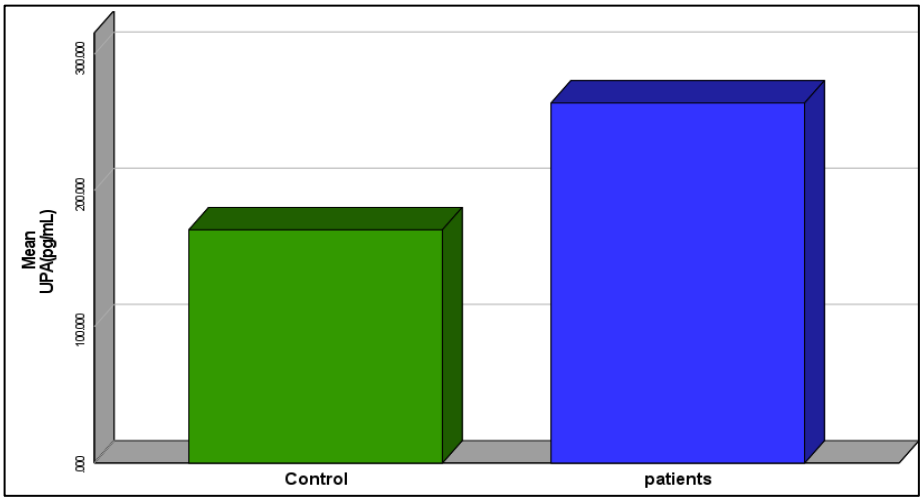

Figure 1. The comparison between Control and patients for UPA.

A considerable positive correlation ($p \leq 0.05$) was found between serum UPA and ALP (person correlation 0.285), as shown in **Figure 2.**

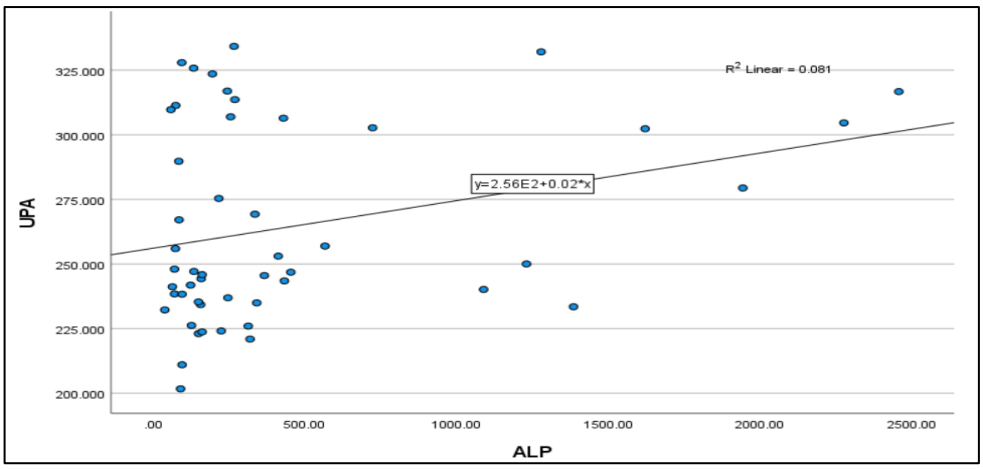

Figure 2. Correlation between UPA and ALP for patients

To assess if the UPA could be a reliable biomarker of CKD, the area under the curve (AUC) was calculated in addition to the cut-off value, sensitivity, and specificity in **Table 3**.

Table 3: The cut-off value, sensitivity, and specificity calculated by applying ROC to patients and control

ROC of UPA	Sensitivity	Specificity	AUC	Accuracy		Cut-off value
				LB	UB	
Control & Patients	0.903	0.898	0.918	0.901	0.923	0.189

LB:Lower bond, UB:Upper bond.

Figure 3 shows an AUC of UPA 0.918, where the cut-off point was 0.189 with 90% sensitivity and 89% specificity. These findings indicate that UPA can be utilized in a CKD diagnostic biomarker panel.

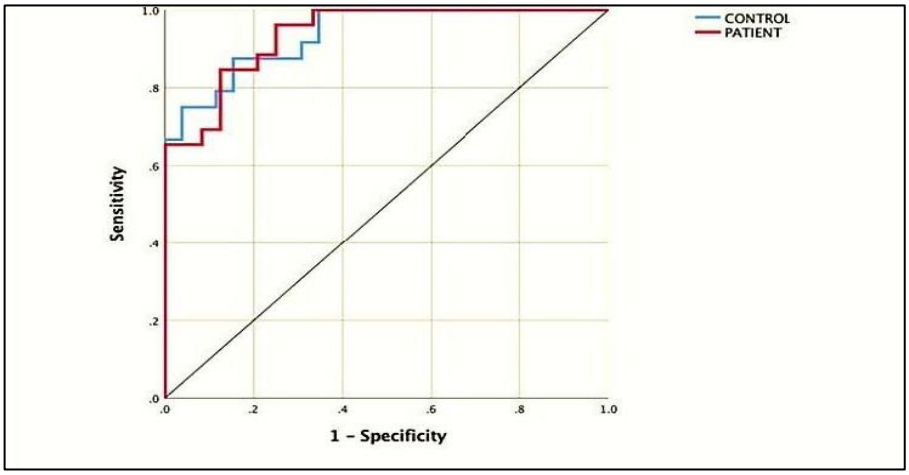

Figure 3. The ROC curve of UPA.

The ROC curves indicate the AUC (sensitivity vs 1-specificity) for UPA, in the serum of HD patients in the ESKD and control.

4. Discussion

Kidney function declines with age. In general, GFR starts to drop between the ages of 30 and 40 at a rate of around 8 ml/min per 1.73 m^2 every decade [21]. In addition, up to 10% of the global adult population has CKD [22]. Furthermore, it is a risk factor for CKD that cannot be changed [2].

CKD has been linked to elevated UPA levels. Patients with CKD may have 2- to 4-fold higher endogenous plasma UPA levels than healthy individuals due to increased UPA release from damaged kidneys [24]. In a study conducted, it was observed that it increased significantly in hemodialysis patients who suffer from heart disease compared to patients who do not have heart disease [25]. This is consistent with the results of the current study, where UPA is significantly elevated compared to control, as shown in **Figure 1** and **Table 2**.

Experimental evidence suggests UPA may have protective effects, but the role of UPA in kidney diseases is not well understood [26]. Actually, fibrosis CKD is a typical end pathway for numerous progressive chronic kidney disease causes [27].

There is a possibility that UPA may interact with many cellular receptors, some of which promote and some of which prevent kidney fibrosis. Hence, the total impact on fibrosis may change based on the types of receptors that are accessible. There is mounting evidence that UPA may have organ-specific effects during fibrotic reactions. This is due to the fact that a variety of experimental approaches to altering UPA activity have shown lower fibrosis in the lung and liver and increased fibrosis in the heart in mice with much greater UPA levels [28].

Both proximal and distal tubules abundantly produce UPA, which is also a source of endogenous kidney antifibrotic action. Activation of plasminogen, destruction of the provisional matrix protein fibrin, activation of the antifibrotic growth factor hepatocyte growth factor (HGF), and a minor ability to destroy specific extracellular matrix proteins, including fibronectin, are some of the documented antifibrotic effects of UPA [29].

It has been demonstrated that the plasminogen system promotes some kidney disease processes. The plasminogen system is a potential target for slowing the course of kidney illness, as current research shows that it exacerbates kidney disease through both direct and indirect hypertensive effects [30].

Serum ALP levels are known to rise in patients with CKD [31], and an inverse relationship has been demonstrated between ALP values and e-GFR [32].ALP plays an important role in inflammation, and elevated ALP in chronic diseases is almost always associated with negative outcomes [33].

Possible explanations for the relationship between ALP and kidney damage include low-grade inflammation, which is a feature of many chronic clinical disorders, including essential hypertension. It is possible that the connection between ALP and kidney damage can be explained by endothelial dysfunction, which is a powerful and independent predictor of cardiovascular events in a variety of clinical situations, including essential hypertension. Endothelial dysfunction can be caused by inflammation and vascular calcification, which can lead to damage to the kidneys [32].

Several studies found lower AST and ALT in CKD patients than in the average population [34]. The pathophysiological mechanism for this drop in serum aminotransferase levels in people with CKD is still not precise [35].

It was speculated that factors like aminotransferase withdrawal during the HD session, high lactate serum levels that rapidly consume Nicotinamide Adenine Dinucleotide Phosphate (NADPH) during biochemical dosages, and the presence of uremic substances would prevent these enzymes from working. These factors could all contribute to this decrease [36]. Research suggests that low alanine aminotransferase levels in patients with chronic kidney failure prior to hemodialysis may be due in part to hemodilution [37].

Everyday metabolic waste products excreted by the kidneys include urea and creatinine [38]. With chronic kidney failure, kidney clearance, or glomerular filtration rate (GFR), keeps going down, which makes urea, creatinine, and other chemicals build up in the blood [39]. The amount of protein in the serum is determined by the equilibrium between its rate of synthesis and catabolism or loss [40]. ESKD patients often have hypoalbuminemia due to decreased albumin synthesis or breakdown [41]. An injured kidney lets some albumin pass into the urine. Albumin in the urine is a sign of kidney damage [42].

Patients on hemodialysis often experience hyponatremia [43]. As the glomerular filtration rate goes down, the kidneys' ability to get rid of water loads becomes more limited. As a result, the range of water intake that allows normal Na levels to stay stable gets narrower [44]. Potassium migration into cells happens concurrently with sodium outflow in a ratio of 2:3, and both processes are powered by the Na-K-ATPase pump [45]. The more urine that is passed, the less sodium is sent to the distal tubules, which results in less potassium being excreted [45]. This explains why hyperkalemia is more prevalent in advanced kidney failure when the GFR (and, consequently, tubular flow) decreases [46].

Those with ESKD always have high phosphate levels [47]. The kidneys rid the body of 14 milligrams per kilogram every day. Therefore, it should come as no surprise that kidney failure reduces phosphate elimination [48].

Hypocalcemia is common in ESKD [49]. Actually, a typical end pathway for numerous progressive CKD is that the production of 1,25-dihydroxyvitam in $1,25(OH)_2D$ will decline as GFR declines because of phosphate retention, which will increase the synthesis of fibroblast growth factor-23(FGF-23). Increased levels of FGF-23 reduce the function of the enzyme 1-α hydroxylase. Reduced levels of $1,25(OH)_2D$ lead to decreased calcium resorption from bones, increased Ca excretion, and reduced Ca absorption in the intestine, which lowers blood calcium levels [50].

5. Conclusion

This study demonstrates increased levels of UPA in HD patients with ESKD and correlates with ALP; also, UPA can be considered a good marker for the prevention of the development of kidney fibrosis.

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Conflict of Interest

The authors declare that they have no conflicts of interes.

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Ethical Clearance

The samples were gained according to Local Research Ethics Committee approval in the Iraqi Ministry of Health No.37751 on 11/9/2022.

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