Short Communication

Study the Effect of Urokinase-Type Plasminogen Activator (UPA) and Some Biochemical Parameters in Iraqi Hemodialysis Patients with Type 2 Diabetes

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Abstract

The most common cause of end-stage renal disease (ESRD) and leading ultimately to hemodialysis (HD) is type 2 diabetes mellitus (T2DM). The current study aims to assess the role of serum urokinase plasminogen activator (UPA) levels among Iraqi hemodialysis patients with ESRD with type 2 diabetes. The study encompassed 50 patients aged 40–74 years (35 males and 15 females), admitted to the Iraqi dialysis center at Baghdad Teaching Hospital, Al-Hayat Center at Al-Karama Teaching Hospital, and Hamida Al-Misfah Dialysis Center in Imam Al-Kadhimin Medical City for the period from October 2022 to February 2023. Were diagnosed based on previous medical reports, and laboratory tests by a consultant nephrologist. UPA, Blood. Urea, Creatinine, fasting serum glucose (FSG), HbA1c, Insulin, HOMA-IR, and lipid profile levels were determined. The present study showed a significant increase in serum UPA levels in HD patients in ESRD with T2DM compared to control. In addition, there was an important negative correlation between UPA and Hb1AC, FSG, and a positive correlation with VLDL-C and TG in HD patients in ESRD with T2DM patients. This study demonstrates increased UPA serum levels in HD in ESRD with T2DM patients and associated with FSG, Hb1AC, TG, and VLDL this shows that it can be considered a good marker for the development of diabetes complications, the most important of which is diabetic kidney disease (DKD).

Keywords: Creatinine, diabetes mellitus, kidney failure, lipid profile, urea, urokinase-type plasminogen activator

Introduction

End-stage renal disease (ESRD) or kidney failure is a medical condition characterized by impaired kidney function, resulting in the inadequate removal of metabolic waste products from the bloodstream and the compromised regulation of extracellular fluid volume, oxidation, and pH. Kidney failure is characterized by the kidneys' inability to effectively eliminate the body's metabolic waste products or perform their regulatory functions.[1] When the kidneys are unable to filter blood normally, a process called hemodialysis (HD) may be used to eliminate waste products from the body.[2] Diffusion and convection remove substances from circulation.[3] The etiology of renal function decline and the underlying pathophysiological processes are intricate, multifaceted, and not yet fully elucidated.[4] The most common cause of ESRD and leading ultimately to HD is type 2 diabetes mellitus (T2DM).[5] Called non-insulin depended on diabetes mellitus accounts for 90% of the population with diabetes of this type. A complication of diabetes occurs after many years of uncontrolled hyperglycemia.[6] It is Numerous micro- and macrovascular problems are linked to it, all of which reduce the patient's overall stamina.[7] Diabetic kidney disease (DKD) is a condition that impacts approximately 40% of individuals with T2DM.[8] This leads to ESRD and is marked by elevated blood pressure, reduced eGFR, and increased albumin excretion.[9]

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Urokinase-type plasminogen activator (UPA) or just "urokinase" Although UPA is not a phosphorylating "kinase," the historical name is still in common use. Kidney tubular cells release this protein to keep tubules clear of clots and other protein-based obstructions. Urine contains this protein even though it is not a waste product.[10] The urokinase plasminogen activator system (UPAs) includes the UPA as one of its constituents, which may attach to its receptor and start a proteolytic cascade, which ultimately results in the conversion of plasminogen to plasmin. UPAs are important in fibrinolysis, inflammation, atherosclerotic plaque development, matrix remodeling during wound healing, tumor invasion, angiogenesis, and metastasis.[11]

Study aim

Assess the role of serum UPA levels among Iraqi HD patients with ESRD with T2DM.

Materials and Methods

This study was applied to 50 patients (35 males and 15 females), between the ages of 40–74 years. Participants were drawn from the patients who come to the Iraqi dialysis center at Baghdad Teaching Hospital, Al-Hayat Center at Al-Karama Teaching Hospital, and Hamida Al-Misfah Dialysis Center in Imam Al-Kadhimin Medical City for the period from October 2022 to February 2023. A comprehensive investigation of the patient's medical history, test data, and clinical evaluations by a nephrology expert led to the diagnosis. Moreover, 50 healthy, the age range of 40–61 years individuals selected as the control group. Informed consent was taken from all cases before their enrollment in this study.

Patient selection: This study includes Iraqi hemodialysis patients in the ESRD, as all patients suffer from Hypertension and T2DM without any other medical history. Only two of the patients had a history of renal cysts and kidney stones.

Exclusion Criteria: Patients with type 1 diabetes, heart disease, malignant tumors, liver, lupus erythematosus, and thyroid disorders were excluded. In addition, patients who had previously undergone kidney transplantation and patients with congenital kidney atrophy were not included in the study.

Before beginning HD and getting their heparin dose, each patient had 10 mL of venous blood collected. Patients were given fistula blood samples (site of needle puncture in the vein) the 3 mL was transferred into a tube containing ethylenediaminetetraacetic acid (EDTA) for HbA1C quantification. A volume of 7 mL was transferred into a Gel tube to obtain separated serum through centrifugation at a speed of 3000 rpm for a duration of 15 min. To analyze fasting glucose, urea, and creatinine the remains were transferred to an Eppendorf tube and stored in a deep freezer (−20 °C) for longer use Investigation (UPA, lipid profile, and insulin). Serum was centrifuged from venous blood samples collected from the control group using a disposable syringe.

Weight (kg) divided by height (in m^2) was used as the formula used to determine body mass index (BMI).[12] Sandwich enzyme-linked immunosorbent assay (ELISA) kit was a method for measuring UPA in the serum. Bought from My BioSource Cat. No.: MBS3801100. The sensitivity was determined to be 1 pg/mL An automated analyzer Neochem 100 was used to measure fasting serum glucose (FSG), blood urea, and creatinine. The SD Biosensor F200 was used to measure HbA1c. Insulin, TC, TG, and HDL-C, were measured using an automated analyzer (Huma Reader HS). VLDL-C is determined by dividing the triglyceride levels (in mg/dL) by 5 and the Friedewald formula (TC – [HDL-C * VLDL-C]) is used to determine LDL-C.[13] HOMA-IR can be calculated using the formula (FSG [mg/dL] * fasting insulin [μU/mL]/405).[14]

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 using Pearson correlation. We deemed a *P* value of 0.05 to be statistically significant. The cutoff value, sensitivity, and specificity were calculated using a Receiver Operating Characteristics (ROC) curve analysis performed in SPSS version 28.

Ethical approval

The University of Baghdad, College of Education and Pure Sciences Ibn Al-Haytham, Department of Chemistry approved this work. Research approval number 4737 is dated September 13, 2022.

Results

BMI, age, and biochemical characteristics of HD in the ESRD with T2DM patients, and control are presented in Tables 1 and 2, respectively.

There is no significant ($P > 0.05$) change in BMI and insulin between the patients and the control group. There was considerable elevation ($P \leq 0.01$) in UPA, B. Urea, Creatinine, FSG, HbA1c, Home-IR, TC, TG, LDL-C, and VLDL, whereas a considerable decrease ($P \leq 0.01$) was detected in serum HDL-C level in HD in the ESRD with T2DM patients as paralleled to the controls.

Correlations regarding UPA and some biochemical parameter levels among HD in the ESRD with T2DM patients are in Table 3.

Considerable significant negative correlation ($P \leq 0.05$) was found between serum UPA and Hb1AC, FSG, there

Table 1: The BMI, age of HD in ESRD patients with T2DM, and control group

Parameter	Control, $n = 50$	Patients, $n = 50$	*P*-value
BMI (kg/m^2)	26.521 ± 3.248	27.864 ± 4.695	0.10
Age (years)	47.840 ± 5.730	59.420 ± 8.562	≤0.001

BMI: body mass index

Data are expressed as mean ± SD. $P \leq 0.01$: high significant, $P > 0.05$: nonsignificant

Table 2: Biochemical characteristics of HD in the ESRD with T2DM patients and control

Parameter	Control, $n = 50$	Patients, $n = 50$	*P*-value
UPA (pg/mL)	171.218 ± 37.255	362.200 ± 63.549	≤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
FBG (mg/dL)	87.660 ± 8.153	158.019 ± 51.461	≤0.001
HbA1c (%)	5.174 ± 0.532	8.340 ± 1.274	≤0.001
Insulin (µIU/mL)	13.404 ± 1.931	14.546 ± 4.586	0.110
HOMA-IR	2.915 ± 0.576	5.625 ± 2.368	<0.001
TC (mg/dL)	161.490 ± 22.463	230.343 ± 48.166	≤0.001
LDL (mg/dL)	81.191 ± 23.674	147.031 ± 48.820	≤0.001
TG (mg/dL)	131.252 ± 49.295	216.372 ± 55.016	≤0.001
VLDL (mg/dL)	26.250 ± 9.859	43.274 ± 11.003	≤0.001
HDL (mg/dL)	54.049 ± 4.297	40.038 ± 8.957	≤0.001

UPA: urokinase-type plasminogen activator, B. Urea: blood urea, FSG: fasting serum glucose, HbA1c: glycosylated hemoglobin, Home-IR: homeostatic model assessment-insulin resistance, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triacylglycerol, VLDL: very low-density lipoprotein, HDL-C: high-density lipoprotein cholesterol

Data are expressed as mean ± SD. $P \leq 0.01$: high significant, $P > 0.05$: nonsignificant

Table 3: Pearson correlations between UPA age, BMI, and biochemical parameters of HD in ESRD with T2DM patients

Parameter	Person correlation
Age (years)	−0.043
BMI (kg/m^2)	−0.025
B. Urea (mg/dL)	−0.107
Creatinine (mg/dL)	−0.066
FSG (mg/dL)	−0.278*
HbA1c (%)	−0.326*
Insulin (µIU/ml)	0.098
HOMA-IR	−0.143
TC (mg/dL)	0.160
TG (mg/dL)	0.422**
HDL (mg/dL)	−0.214
LDL (mg/dL)	0.102
VLDL (mg/dL)	0.422**

FSG: fasting serum glucose, HbA1c: glycosylated hemoglobin, Home-IR: homeostatic model assessment-insulin resistance, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triacylglycerol, VLDL: very low-density lipoprotein, HDL-C: high-density lipoprotein cholesterol

*$P \leq 0.05$: significant

**$P \leq 0.01$: high significant

was an increase in significant positive correlations ($P \leq 0.01$) between serum UPA with VLDL-C, TG. While there is no significant correlation ($P > 0.05$) between UPA and insulin, Home-IR, TC, HDL-C, and LDL-C.

To evaluate the potential of UPA as a dependable biomarker for DKD, [Table 4] presents the calculation of the area under curve, along with the determination of cutoff value, sensitivity, and specificity.

Table 4 shows to have an area under the curve of UPA 0.958. Where the cutoff point was 0.138 with 94% sensitivity and 93% specificity, these findings indicate that UPA can be utilized in a DKD diagnostic biomarker panel.

Discussion

The enlargement of the interstitial matrix may arise from the escalated synthesis of matrix proteins by stimulated fibroblasts, as well as diminished degradation by proteases present in connective tissue, such as metalloproteinases and serine proteases. Several studies have reported evidence indicating that kidney UPA mitigates interstitial

Table 4: The cutoff value, sensitivity, and specificity to HD in ESRD with T2DM patients and control

ROC of UPA	Sensitivity	Specificity	Area under the curve	Accuracy		Cutoff value
				LB	UB	
Control and patient	0.943	0.938	0.958	0.931	0.953	0.138

ROC: receiver operative characteristics, LB: lower bond, UB: upper bond

fibrosis resulting from kidney injury. The participation of UPA is believed to occur for various reasons: (1) Proximal and distal tubules in the kidneys produce UPA in large quantities. (2) The inhibitor Plasminogen activator inhibitor-1 (PAI-1) promotes interstitial fibrosis, whereas its receptor Urokinase-type plasminogen activator receptor (UPAR) reduces kidney fibrosis. (3) UPA is capable of reducing fibrosis in both the liver and the lung. (4) Hepatocyte growth factor (HGF) is a powerful anti-fibrotic growth factor that may be activated by UPA.[15]

In the current study, we noticed an increase in the level of UPA in patients compared to healthy subjects Table 2.

A recent study was conducted on patients with T2DM. Patients with T2DM who had greater UPA levels were able to secrete more insulin than those whose UPA levels were lower. Therefore, UPA may play a crucial part in insulin secretion, cell regeneration, and the development of T2DM. It is hypothesized that UPA deficiency contributes to the onset of T2DM, suggesting a novel approach to the investigation and therapy of this disease.[16] In a study conducted, UPA was found to be significantly higher in DKD patients. This study shows that UPA may be utilized as a diagnostic biomarker for DKD.[17] Which agrees with the results of our study [Table 4].

With GFR keeps going down, makes urea, creatinine, and other chemicals buildup in the blood.[18] Dialysis therapy and kidney failure can disrupt glucose homeostasis, making it more difficult to keep blood sugar levels in check. The inability to flush out excess plasma glucose in the urine causes postprandial hyperglycemia in patients with ESRD. Considering that, most of the relevant factors, including high blood urea concentrations or metabolic acidosis, result in higher HbA1c readings.[19] Diabetic people have a higher chance of having dyslipidemia, and diabetes is a recognized cause of this condition.[20]

Conclusions

This study demonstrates increased UPA serum levels in HD in ESRD with T2DM patients and associated with FSG, Hb1AC, TG, and VLDL this shows that it can be considered a good marker for the development of diabetes complications, the most important of which is DKD.

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Conflicts of interest

There are no conflicts of interest.

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