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Assessment of Urokinase Plasminogen Activator Receptor (uPAR) in Nephropathy Type 2 Diabetic Patients with Microalbuminuria

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Abstract

The glycosylphosphatidylinositol (GPI)-anchored receptor, known as the urokinase plasminogen activator receptor (uPAR), may serve as a valuable marker for the diagnosis and prognosis of sepsis, critical illnesses, and a range of inflammatory diseases. This study examines the impact of uPAR on clinical parameters in patients with type 2 diabetes and microalbuminuria. A total of 90 participants were enrolled in a case-control design, comprising 50% diabetic individuals with microalbuminuria and the remainder being healthy individuals aged range (35-63) years. Clinical parameters, along with demographic data, were collected from participants between November 2023 to January 2024. These parameters included age, body mass index, fasting blood sugar, haemoglobin A1C (HbA1C), lipid profile, urea, creatinine, and most importantly uPAR. Using an independent samples test with a significant level of 0.05, our experiment revealed that there was a significant difference between diabetic patients and healthy individuals when it comes to clinical parameters, p-value < 0.001. All clinical parameters were shown to be higher in diabetic patients with microalbuminuria compared to healthy individuals, except for high-density lipoprotein. An increased level of uPAR in patients with type 2 diabetic and microalbuminuria may be considered an effective biomarker for the early diagnosis of diabetic nephropathy, which is associated with a higher risk of complications of the disease, especially to cardiovascular diseases

Keywords: Urokinase plasminogen activator receptor; Type 2 diabetes; Lipid profile; HbA1C; Creatinine.

1. Introduction

The glycosyl-phosphatidyl-inositol-anchored urokinase plasminogen activator receptor (uPAR) consists of three homologous domains denoted D1 (residues 1–92), D2 (residues 93–191) and D3 (residues 192–283). The receptor is present in various cell types, including cancer cells, endothelial and macrophage cells, neutrophils, and smooth muscle cells. Numerous proteases release soluble uPAR, a bioactive protein from cell surfaces,

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enabling its detection in body fluids such blood and urine. Serum uPAR has the potential to serve as a biomarker in clinical settings for the diagnosis and prognosis of sepsis and critical illnesses, along with other inflammatory disorders. uPAR has also been linked to a variety of malignancies and metastases as well as atherosclerosis, diabetes mellitus, cardiovascular disease, and other diseases [1-4].

It is important to note that healthy kidneys typically do not express the urokinase-plasminogen activator receptor (uPAR) when considering kidney disease. Research has demonstrated that uPAR is expressed de novo in the interstitial and tubular cells of kidneys, as well as in diabetic nephropathy patients[5-7]. Diabetic nephropathy affects about 30% of people with diabetes (DM) and is a leading cause of kidney failure in in this population. DM has several associated risk factors including hyperglycaemia and hypertension. It is also linked to genetic predisposition, dyslipidaemia, diabetes, insulin resistance, and hypertension. Among these, hyperglycaemia is the most important risk factor in DN development and progression [8, 9]. The prevalence of diabetes has reached epidemic levels globally, with projections indicating that over 550 million people may develop diabetes by 2035—an 8% increase from earlier estimates of 350 million affected individuals [10, 11]. Additionally, more than 40% of people with diabetes will develop chronic kidney disease. A significant portion may progress to ESKD, requiring renal replacement therapies such as transplantation or dialysis. Consequently, this study is designed to investigates the effect of uPAR on clinical parameters in nephropathy type 2 diabetic patients with microalbuminuria.

2. Materials and methods

Forty-five patients of nephropathy in type 2 diabetic and microalbuminuria (20 males and 25 females), aged between 35 and 63 years were enrolled. Additionally, 45 healthy samples (29 males and 16 females) were collected from the National Diabetes Centre between November 2023 and January 2024. The duration of diseases among the participants ranged from 5-10 years. Several demographic and clinical parameters were collected, including age, gender, blood pressure, and body mass index (BMI) which is computed as kilograms of body weight divided by the square of the height in meters (kg/m^2). The microalbumin kit, which includes reagent strips for determining albumin and creatinine in urine, was utilized to identify the patients with microalbuminuria (30-300 mg/g). The strips are read instrumentally, using the compelizer/Human system. Additionally, fasting blood samples of 5 ml were collected, 2 ml of blood in EDTA tube used to determine the glycated haemoglobin (HbA1c), while 3 ml in a gel tube to obtained serum which centrifuged at 1500 xg and used to investigate all parameters including glucose, total cholesterol, triglycerides , and high-density lipoprotein cholesterol, blood urea and serum creatinine was determined by(cobas c111/Germany). The quantification of urokinase plasminogen activator receptor (uPAR), was performed using ELISA kits produced by a Chinese Company called Fine Kit.
An independent sample t-test was employed to evaluate the significance of differences in mean values among the clinical parameters of diabetic patients with microalbuminuria and healthy individuals. A significant level of 95% was established, indicating that a *p*-value of less than 0.05 denotes a statistically significant difference. Additionally, correlation analysis of the clinical parameters was determined using the correlation coefficient (r), which in turn facilitates the visualization of parameter association providing insights into what extent they are moving together.

3. Results

Table 1 presents the demographic data of the participants, indicating that BMI, diastolic, and systolic blood pressure (DBP) were higher in diabetic patients with microalbuminuria. While some demographics such as age was almost similar in both groups, the difference in

clinical parameters between diabetic patients with microalbuminuria and healthy individuals was significant. As shown in Table 2, all clinical parameters, including fasting blood glucose (FBS), randomly measured blood sugars (RBS), glycated haemoglobin (HbA1c), triglycerides, total cholesterol, blood urea and urokinase plasminogen activator receptor (uPAR)were substantially higher in diabetic patients with microalbuminuria when compare to healthy people, with exception of high-density cholesterol (HDL) that was significant lower in diabetic patients with microalbuminuria.

Table 1: Participants' demographic parameters at baseline.

Parameters	Healthy (n=45) (Mean ± SD)	Patient (n=45) (Mean ± SD)	p-value
Age (year)	48.24±5.81	51.33±5.43	0.101
Weigh (kg)	75.04±10.38	80.4±11.83	0.05
Height (cm)	169.33±5.33	165.04±8.146	0.007
BMI (kg/m2)	26.16±3.38	29.04±2.91	0.0001
SBP (mmHg)	124.50±6.10	137.11±6.16	0.0001
DBP (mmHg)	80.86±2.11	86.11 ±5.52	0.0001

Table 2: Participants'clinical parameters.

Parameters	Healthy (n=45) (Mean ± SD)	Patients (n=45) (Mean ± SD)	p-value
FBS (mg/dl)	84.24±5.39	183.08±40.05	0.0001
RBS (mg/dl)	126.2±7.04	231.37±51.5	0.0001
HbA1c (%)	4.85±0.31	8.39±1.35	0.0001
TC (mg/dl)	157.04±29.75	210.7±39.9	0.0001
TG (mg/dl)	93±9.20	180.2±33.27	0.0001
HDL (mg/dl)	52.5±5.50	44±2.8	0.0001
Urea (mg/dl)	28.42±6.80	35.40±7.38	0.0001
Creatinine (mg/dl)	0.7±0.1	1.45±2.08	0.019
uPAR (mg/d)	2.29±1.43	4.08±0.33	0.0001

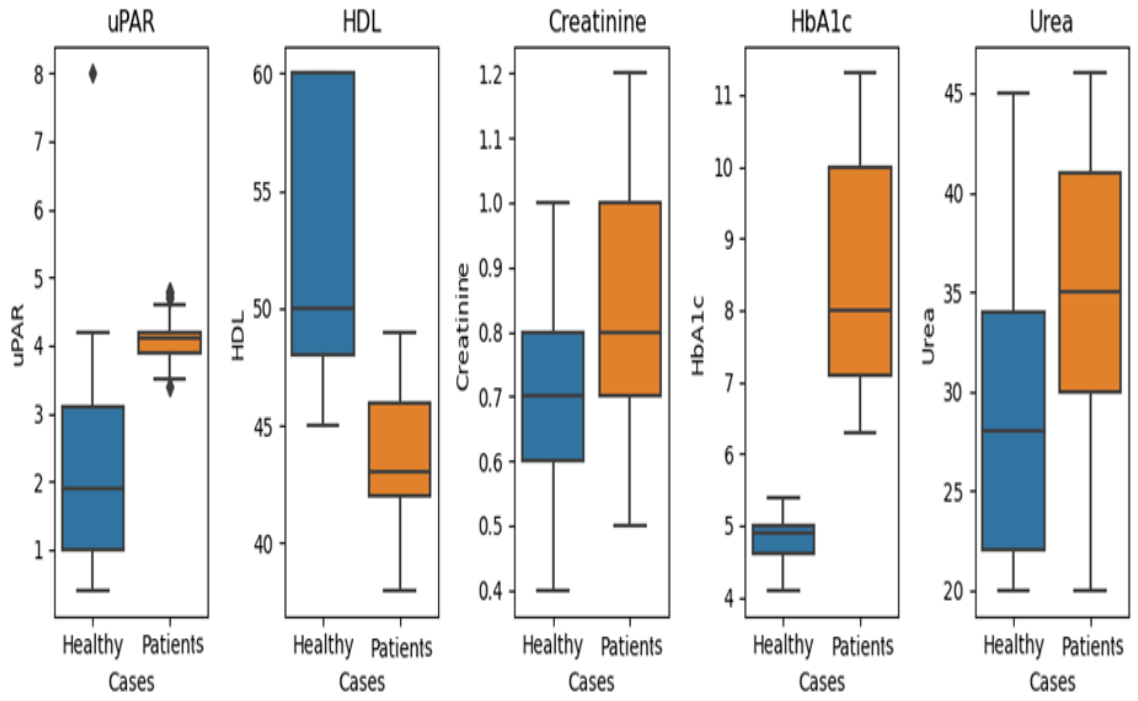

Figure 1: Box plot presenting the distribution of several clinical variables in diabetic patients with microalbuminuria and healthy individuals.

Figure 1 clearly illustrates the significant differences in key clinical parameters in both groups. The uPAR level was notably higher among diabetic patients with microalbuminuria than healthy individuals, *p*-value <0.001.
Similarly, urea level was significantly higher among diabetic patient with microalbuminuria than in healthy individuals, *p*-value <0.001. Creatinine levels were significantly higher in patients compared to healthy individuals, *p*-value=0.019. Creatinine is a waste product produced. muscles metabolism that is excreted through the kidney. Increased levels of creatinine and/or urea may suggest kidney dysfunction or impaired renal clearance, or even dehydration at the best-case scenario.

As shown in Figure 1, HDL was the only clinical parameter that was significantly lower in diabetic patients with microalbuminuria compared to healthy individuals, *p*-value<0.001. HDL recognized as "good" cholesterol, playing a crucial role in transporting cholesterol away from tissues to the liver for excretion. The lower HDL levels observed in patients may indicate an increased risk of cardiovascular diseases and metabolic disorders.
Furthermore, Table 3 illustrates a positive correlation between uPAR level and various clinical parameters (weight, BMI, RBS, HbA1c, and HDL). While the table presents a correlation analysis of uPAR level when it comes to patients and healthy individuals, however, it is imperative to analyse each group alone to reveal any hidden correlation or changes that may result from clinical parameters at different ranges.

Table 3: Correlation coefficient of uPAR to other clinical parameters in the patients' group.

Parameters	uPAR (r) Correlation Coefficient	p-value
Age	0.137	0.370
High	0.271	0.071
Weight	0.391**	0.008
BMI	0.336*	0.024
FBS	0.378	0.243
RBS	0.312	0.037
HbA1c	0.330	0.043
TC	-0.206	0.175
TG	0.350	0.745
HDL	-0.391	0.001
Urea	0.557	0.303
SBP	0.343	0.348
DBP	0.339	0.363

4. Discussion

The serum levels of soluble urokinase-plasminogen activator receptors (suPARs) exhibit an independent relationship in nephropathy type 2 diabetic patients with microalbuminuria [12]. Microalbuminuria is a strong indicator of renal involvement with diabetes mellitus. It is an early indication of diabetic kidney disease. Microalbuminuria is an independent factor that can contribute to a decline in renal function, making the reduction of urinary albumin is a key goal in managing diabetic nephropathy. The risk factors for this condition are believed to be a continuum that begins with urinary excretion of albumin within normal limits [2,13]. Therefore, early identification of diabetic kidney disease is essential, and uPAR is proposed as a biomarker that could be used for this. Understanding the interaction between

albuminuria, renal dysfunction loss, and uPAR is crucial to understanding the underlying mechanisms and determining whether uPAR functions solely as a biomarker of renal involvement. Current evidence suggests that uPAR can indeed serve as a marker of renal disease. Further research is needed to explore whether albuminuria or podocyte damage induced because of suPARs can be linked to chronic kidney diseases.

This study found a significant increase in serum uPAR levels among diabetic patient with nephropathy compared to healthy individuals, *p*-value <0.001. This finding aligns with the observations of Wang T, Zhang Q, *et al*. [14]and Darenskaya, M., *et al*. [15]. Additionally, uPAR levels were positively correlated with clinical parameters, especially HbA1c in diabetic patients with microalbuminuria, confirming similar clinical observations by Gabriela Lupușoruhis *et al*.[16]. HbA1c, and lipid profile (LDL, HDL, and TC) were significant increase in diabetic patients with microalbuminuria when relative to healthy individual (*p*-value <0.001). These observations are consistent with the studies by Ozder A.[17], and Sama Al-Shaheeb,*et al*. [18], which suggest that these factors may serve as risk indicators for type 2 diabetes that can be employed to predict chronic kidney diseases [19]. Patients with type 2 diabetes often experience lipid abnormalities, which have been linked to insulin resistance and increased fatty acid release. This in turn, can decrease insulin dependent muscle free fatty acid absorption and increase hepatic fatty acid synthesis in the liver [20]. In this study, there was no significant difference in mean age between participants groups. The ideal blood pressure targets in diabetic patients still vary between guidelines [21], and in our study, SBP and DBP were significantly higher in type 2 diabetic patients with nephropathy compared to healthy individuals (*p*-value<0.001). This is more likely agreed with Tunca, *et al*. [22]. Moreover, systolic BPs, diastolic BPs, Urea, and BMIwere significant higher in type 2 diabetespatientscompared to healthy individuals (*p*-value <0.001).

In conclusion, elevated uPAR levels in patients with type 2 diabetic nephropathy and microalbuminuria may serve as a valuable biomarker to begin screening for early detection of diabetic nephropathy, which raises the risk of complications from the disease, particularly cardiovascular diseases.

Conclusion

In conclusion, this study highlights the significant role of soluble urokinase-plasminogen activator receptors (suPARs) as a potential biomarker for early detection of diabetic nephropathy in type 2 diabetic patients, particularly those with microalbuminuria. Microalbuminuria, a strong indicator of renal involvement in diabetes, underscores the importance of early identification and management to prevent the progression of diabetic kidney disease. Elevated suPAR levels were observed in diabetic patients with nephropathy, aligning with prior studies, and showed a positive correlation with clinical parameters such as HbA1c and lipid profiles, which are risk indicators for chronic kidney disease. Additionally, the study confirms that patients with type 2 diabetes exhibit higher systolic and diastolic blood pressures, urea levels, and BMI compared to healthy individuals. These findings emphasize the interconnectedness of metabolic and cardiovascular complications in diabetic nephropathy. By focusing on suPAR as a biomarker, clinicians may enhance screening strategies, offering a proactive approach to managing and mitigating the risks associated with diabetic nephropathy and its broader implications, particularly cardiovascular health. Further research is essential to deepen our understanding of suPAR's role in disease progression and its potential therapeutic implications.

- **Limitations**

The main limitation that can be reported is rather small sample size of 90 participants. Future research is planned to expand the sample size to 150 to 200 cases, which will enhance the robustness of the findings and provide more comprehensive insights. Additionally, while a follow-up study could offer valuable insights into how uPAR levels may change as diabetic nephropathy progresses, this study was unable to conduct longitudinal follow-up due to resource.

- **Ethical responsibilities of authors**

The authors declared that this manuscript is their own and written by them in complete. The Data is original and collected by a specialized team supervised by the authors and all employed materials or kits are properly attributed. The authors also declared that they have not received any funding to conduct this study.In addition, all patients and healthy individuals have been informed about this study and thus they have agreed to sign a consent form.

- **Disclosure and conflict of interest**

The authors declare that they have no conflicts of interest.

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