The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4373-4379

Serum suPAR and Urinary Nephrin as Novel Sensitive and Specific Markers for Diabetic Nephropathy in Patients with Type 2 DM

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ABSTRACT

Background: The most frequent reason of end-stage kidney disease (ESKD) is diabetic nephropathy (DN), highlighting the need of early detection, treatment, and prevention.

Objective: To assess the sensitivity and specificity of serum (soluble urokinase-type plasminogen activator receptor (suPAR) and urinary nephrin in cases with type 2 diabetes mellitus (T2DM) with and without nephropathy.

Methods: This prospective study was conducted on 70 patients of T2DM and 15 healthy control group of age and sex matched persons. All patients and control group were subjected to pelviabdominal U/S, laboratory investigations (CBC, ESR, liver and kidney function test, fasting and 2 hours post prandial blood sugar, urine analysis, (urine albumin creatinine ratio (UACR), nephrin, and serum suPAR levels). **Results:** ROC analysis was done for suPAR to predict DN. It showed a significant AUC of 0.869, with a 95% CI ranging from 0.785 – 0.953 (P < 0.001). The best cutoff was > 82.3, at which sensitivity and specificity were 97.1% and 68.6%, respectively. ROC analysis was done for urinary nephrin to predict DN. It showed a significant AUC of 0.760, with a 95% CI ranging from 0.642 – 0.877 (P < 0.001). The best cutoff was > 10.8, at which sensitivity and specificity were 80% and 68.6%, respectively.

Conclusions: In T2DM patients, serum suPAR and urinary nephrin were more specific and sensitive markers than microalbuminuria in early detection of DN.

Keywords: Serum suPAR, Urinary Nephrin, Diabetic Nephropathy, Type 2 DM.

INTRODUCTION

Type II diabetes mellitus (T2DM) is a complicated metabolic disorder brought on by the combination of hereditary and environmental variables, which change the activity of insulin to varying degrees in pancreatic cells as well as peripheral organs. Overweight and obesity, especially of the android type, are the primary diseases that encourage the development of DM2 [(1)]. It has been demonstrated that; the main single reason of ESKD is diabetic nephropathy (DN), highlighting the need of early detection, treatment, and prevention. The most prevalent early clinical sign of DN, microalbuminuria, has been identified as a predictor of the development of ESKD in the context of type 1 DM (T1DM) and T2DM [(2, 3)].

In certain circumstances, diabetic individuals have a gradual drop in renal functions prior to the onset of microalbuminuria [(4)]. When evaluated at a later period, microalbuminuria may no longer be present in some individuals, and it is a poor indicator of the development of macroalbuminuria [(5)]. Microalbuminuria can occur in diabetic individuals without present or future DN and also in non-diabetic people with progressing chronic kidney disease (CKD), hence it is not always indicative of the existence of diabetic kidney disease (DKD) [(6)].

In order to detect DKD early and forecast the development of ESKD, it is vital to find more sensitive and specific indicators than microalbuminuria.

A significant molecular composition of the glomerular filtration slit diaphragm between neighbouring podocytes is the transmembrane protein nephrin, which belongs to the immunoglobulin superfamily. Its expression is identified to be changed in human proteinuric disorders, including diabetes, and in experimental models of the illness [(7)]. According to a study by **Jim *et al.*** all T2DM cases with microalbuminuria and macroalbuminuria had nephronuria [(8)]. Moreover, 54% of T2DM individuals with normoalbuminuria had nephronuria [(9)].

The 3-domain membrane-bound receptor has a circulating variant called suPAR. It is expressed on a number of cells, comprising endothelial cells, podocytes, and immunocompetent cells [(10)].

SuPAR could act as a biomarker for renal illness, as well as inflammatory and immunological disorders, according to prior research. Evidence also suggested widespread usage in systemic lupus erythematosus, hyperglycemia, and sepsis [(11, 12)].

SuPAR may be a predictor of CKD and cardiovascular outcomes in individuals with mild to moderate CKD and ESKD, according to a number of studies [(13, 14)].

The development of DN biomarkers, which enable the early DN diagnosis and the degree of renal dysfunction among cases with DM has attracted enormous interest over the last 20 years [(15)].

In cases with T2DM who had nephropathy or not, we sought to assess the sensitivity and specificity of blood suPAR and urine nephrin.

PATIENTS AND METHODS

This prospective study was conducted on 85 cases. Seventy diabetic cases aged from 40 years to 60 years with 15 healthy volunteers serving as control group. The patients were recruited from Internal Medicine Department Benha University Hospital, in the period of July 2022 to November 2022.

Diabetic patients were categorized into 2 groups: Group 1 which comprised 35 cases with DN

Received: 15/11/2022
Accepted: 17/01/2023

and Group 2 which comprised 35 diabetic patients without nephropathy. Control subjects represented Group 3, which comprised 15 volunteers.

Inclusion criteria were patients of type 2 DM.
The diagnosis of T2DM was according to: ADA criteria for diagnosis of diabetes 2020 [16].

Exclusion criteria were nondiabetic patient, hypertensive patients, patients below 40 years old and those above 60 years old, diabetic patients with kidney diseases other than nephropathy, urinary tract infection, hepatic patients, cardiac patients, autoimmune diseases, obstructive uropathy and history of malignant diseases.

Entire patients and control group were subjected to the next:

Complete history taking: age, gender, history of smoking, history of hypertension, history of T2DM, and duration of DM. History of atherosclerotic CVD manifestations, coronary artery disease (CAD), cerebrovascular accident (CVA) or peripheral arterial disease (PVD). History of microvascular complications of diabetes (retinopathy, neuropathy and nephropathy), namely history of diminished visual acuity due to diabetic retinopathy, tingling and numbness of hands and feet, muscle wasting, autonomic neuropathy either by orthostatic hypotension, altered bowel habits (diarrhea alternating with constipation), urine retention and impotence. History of puffiness of eye lids, oliguria, polyuria and lower limb oedema. Medications used for treatment of diabetes either oral anti diabetic drugs or insulin and other medications.

Full clinical examination: Arterial blood pressure (BP), anthropometric measures (such as height, weight and body mass index (BMI)) and clinical assessment of diabetic vascular complications either macrovascular or microvascular complications. Macrovascular complications (CAD, CVA, or PVD). Microvascular complications (retinopathy, neuropathy or nephropathy) were assessed by fundus examination and tests for peripheral neuropathy.

Pelviabdominal U/S was done for all patients.

Laboratory investigations: 10 ml of blood was taken under complete aseptic condition after overnight fasting and divided into 2 parts: **1st part**:2 ml were put into EDTA tubes for CBC, HbA1C measurement. **2nd part**: 8 ml were put into serum separating tube and left for 30 minutes till clotting then separated for 10 min at 1500 rpm by centrifugation. The separated serum was used for chemical laboratory tests. 2 ml of serum were aliquoted and stored at -20^{o}C for subsequent measurement of serum suPAR. Another sample was taken after 2 hours for postprandial blood glucose.

Urine albumin-creatinine ratio (UACR) was calculated, nephrin in urine was measured by ELISA and suPAR levels in serum was measured by ELISA. Estimated GFR was calculated by CKD-EPI formula.

- **Complete urine analysis:** was done to detect the presence of urinary casts (RBCs, hyaline, WBCs, granular), hematuria (RBCs / high power field), pyuria (WBCs / high power field).
- **Serum SuPAR:** Serum SuPAR was done using kits (Human suPAR) ELISA Kit supplied by SunRed company, China, catalogue No.:201-12-5720
- **Sensitivity**: 4.368 pg/ml.
- **Assay range**: 5 pg/ml→1000 pg/ml.
- **Urinary nephrin:** Urinary nephrin was done using kits: (Human Nephrin (NPHN) ELISA Kit) supplied by SunRed Company, China, catalogue No: 201-12-1092.
- **Sensitivity**: 0.166 ng/ml.
- **Assay range**: 0.2 ng/ml→40 ng/ml.

Ethical consent:

After receiving the nod from Benha University's Institutional Ethics Committee, the participants provided signed consent after being fully briefed. Each participant was given a secret code number and was given a description of the study's goals. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

By utilizing SPSS version 28, data management were conducted (IBM, Armonk, New York). The Shapiro-Wilk test and approaches for data visualisation were utilized to detect the normal distribution of quantitative data. Quantitative data were evaluated by utilizing means and SD or medians and ranges in agreement with normality. Numbers and percentages were utilized to represent a categorical set of data. In terms of comparing quantitative data, one-way ANOVA or the Kruskal-Wallis test were utilized, depending on whether the data were distributed regularly or not. Chi^2 test or Fisher's exact test was utilized for comparison of categorical data. To predict DN, ROC analyses for blood suPAR and urine nephrin were performed. Calculations were made to determine areas under the curve with 95% confidence intervals, the ideal cutoff points, and diagnostic indices. The Pearson or Spearman correlation was utilized to perform associations. Serum suPAR and urine nephrin were subjected to multivariate logistic regression analysis in order to predict DN. Measured odds ratios were utilized, along with 95% CI. Each and every statistical test has 2 sides. In the context of all the previous tests, P value ≤0.05 was considered significant.

RESULTS

Age significantly differed among the studied groups. It was significantly higher in group I (55 ±5) than in groups II (50 ±6) and III (50 ±6). Additionally, disease duration was significantly greater in group I (12 ±4 years) in comparison with group II (8 ±3). No significant differences were reported regarding sex,

BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) **(Table 1).**

Table (1): Sociodemographic data of the studied groups

	Group I (n = 35)	**Group II (n = 35)**	**Group III (n = 15)**	**P-value**
Age (years)	55 ±5 [a]	50 ±6 [b]	50 ±6 [b]	**0.001**
Sex				
Males	14 (40)	14 (40)	8 (53.3)	0.638
Females	21 (60)	21 (60)	7 (46.7)	
BMI (kg/m2)	32.3 ±4.6 [a]	30.3 ±3.2 [ab]	28.5 ±6.1 [b]	0.051
Disease duration (years)	12 ±4	8 ±3	-	**<0.001**
SBP(mmHg)	125 ±13	123 ±12	121 ±12	0.631
DBP(mmHg)	80 ±10	79 ±10	79 ±7	0.907

Data are presented as mean±SD or number; Different small letters between any two measures denote significant difference, whereas identical letters denote a non-significant difference.

The most frequent antidiabetic in group I was premixed human insulin, followed by (dipeptidyl peptidase-4 inhibitors (DPP4 inhibitors), basal bolus, secretagogue, insulin sensitizers, sodium glucose cotransporter-2 (SGLT2), and sulfonylurea. On the other hand, the most frequent antidiabetic in group II was basal-bolus, followed by DPP4 inhibitors, premixed human insulin, secretagogue, sulfonylurea, and SGLT2. Additionally, the group I demonstrated significantly higher ACEI or ARBS use (Table 2).

Table (2): Medications in diabetic groups

	Group I (n = 35)	**Group II (n = 35)**	**P-value**
Antidiabetics			
Basal bolus	6 (17.1)	14 (40)	NA
DPP4 inhibitors	8 (22.9)	9 (25.7)	0.001
Premixed human insulin	13 (37.1)	5 (14.3)	0.029
Secretagogue	5 (14.3)	3 (8.6)	0.001
Sensitizers	1 (2.9)	0 (0)	0.001
SGLT2	1 (2.9)	1 (2.9)	0.001
Sulfonylurea	1 (2.9)	3 (8.6)	0.001
ACEI or ARBS	19 (54.3)	8 (22.9)	0.007

Data are presented as number (%); NA: Not applicable

Retinopathy in group I was significantly higher than group II **(Table 3).**

Table (3): Diabetic retinopathy in diabetic groups

	Group I (n = 35)	**Group II (n = 35)**	**P-value**
Retinopathy	31 (88.6)	13 (37.1)	**<0.001**

Data are presented as number (%)

Regarding CKD staging: The most frequent CKD stage was stage IV, followed by stages III-B, III-A, II, V, and I (**Figure 1).**

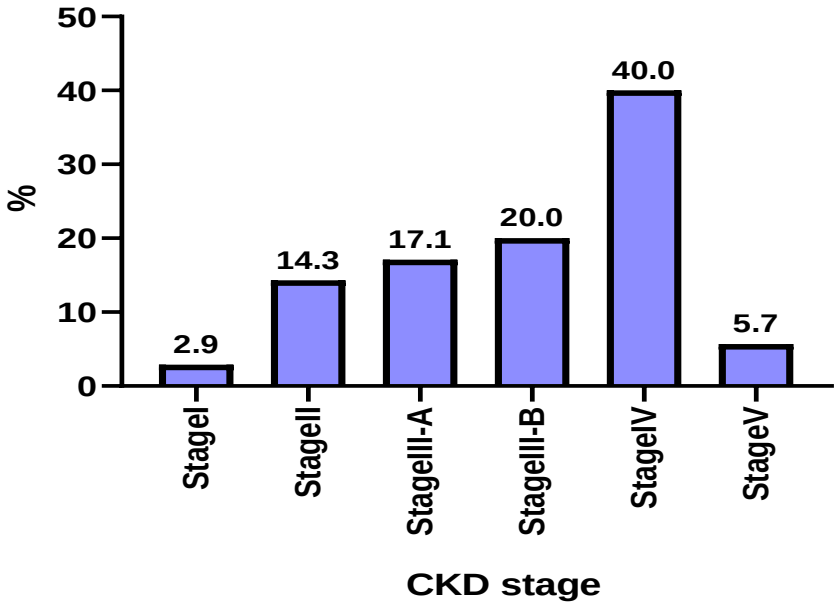


Figure (1): CKD stage in diabetic nephropathy patients

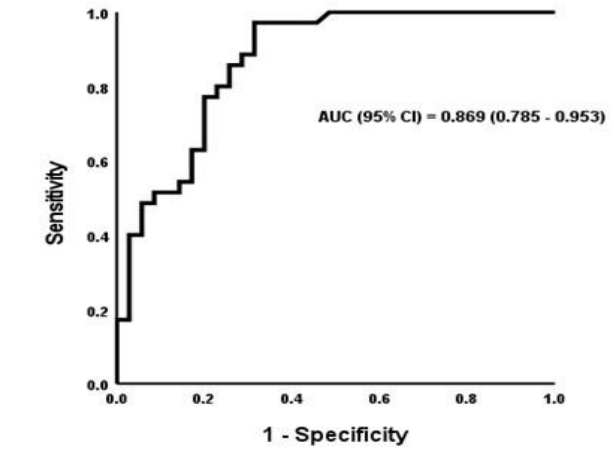
Lab investigations in the studied groups are shown in **Table 4**. Serum suPAR demonstrated a significant difference among the studied groups. It was significantly higher in group I compared to groups II. Additionally, it was significantly higher in group II than in group III. Urinary nephrin significantly differed among the studied groups. It was significantly higher in group I compared to groups II and III. Additionally, it was significantly higher in group II in comparison with group III **(Table 4).**

Table (4): Laboratory findings and serum suPAR and urinary nephrin levels in the studied groups

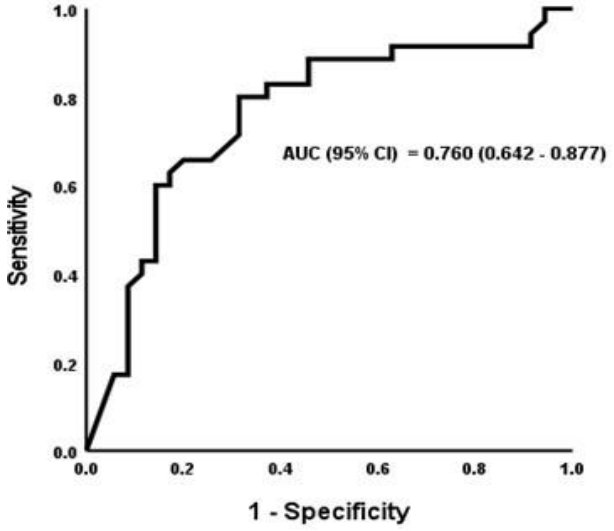
	Group I (n = 35)	**Group II (n = 35)**	**Group III (n = 15)**	**P-value**
Hemoglobin (g/dL)	10.3 ±1.4 [a]	11.2 ±1.7 [b]	13 ±0.9 [c]	**<0.001**
ALT (IU/L)	25 ±8	26 ±5	28 ±8	0.613
AST (IU/L)	30 ±10	30 ±8	27 ±7	0.476
ESR (mm/hr)	15 (5 - 42)	15 (5 - 42)	15 (5 - 25)	0.287
Creatinine (mg/dL)	2.2 ±1 [a]	0.7±0.1[b]	0.8 ±0.2 [b]	**<0.001**
eGFR(ml/min/1.73m2)	31.2 (12.6 - 112) [a]	104.2 (64.9 - 144) [b]	97 (52 - 116) [b]	**<0.001**
UACR (mg/g)	165 (65 - 500) [a]	20 (10 - 29) [b]	12.7 (10.4 - 14.5) [b]	**<0.001**
FBG (mg/dl)	129 ±21 [a]	128 ±30 [a]	83 ±9 [b]	**<0.001**
2HPP (mg/dl)	193 ±41 [a]	185 ±32 [a]	110 ±8 [b]	**<0.001**
HBA1C (%)	8.6 ±1 [a]	8.2 ±0.8 [a]	5 ±0.3 [b]	**<0.001**
Albumin in urine	21 (60.0)	7 (20.0)	0 (0.0)	**<0.001**
Serum suPAR (pg/ml)	141.3 ±5.8 [a]	85.9 ±3.5 [b]	56.2 ±5.8 [c]	**<0.001**
Urinary nephrin (ng/mL)	15.9 ±6.1 [a]	10.7 ±2.3 [b]	4.5 ±1.4 [c]	**<0.001**

Data are presented as mean±SD, median (min-max), or number (%); Different small letters between any two measures indicate a significant difference, whereas identical letters indicate a non-significant difference.

ROC analysis was done for suPAR to predict DN. It showed a significant AUC of 0.869 (P < 0.001). The best cutoff was > 82.3, at which sensitivity and specificity were 97.1% and 68.6%, correspondingly **(Figure 2 A)**. ROC analysis was done for urinary nephrin to predict DN. It showed a significant AUC of 0.760, (P < 0.001). The best cutoff was > 10.8, at which sensitivity and specificity were 80% and 68.6%, correspondingly **(Figure 2 B)**.



A)



B)

Figure (2): A) ROC analysis for suPAR to predict diabetic nephropathy and B) ROC analysis for urinary nephrin to predict diabetic nephropathy.

In group I, no significant correlations were observed between serum suPAR and other parameters, including age (P=0.609), BMI (P = 0.845), disease duration (P=0.076), SBP (P=0.808), DBP (P=0.517), hemoglobin (P = 0.933), ALT (P=0.311), AST (P=0.895), serum creatinine (P=0.170), eGFR (P=0.087), UACR (P=0.082), fasting blood glucose (FBG) (P=0.950), 2h-PP blood glucose (P=0.052), and HBA1C (P=0.706).

In group II, a significant positive correlation was observed between serum suPAR and BMI (r = 0.410, P = 0.015). No significant correlations were observed between serum suPAR and other parameters, including age (P = 0.068), disease duration (P=0.767), SBP (P=0.409), DBP (P = 0.123), hemoglobin (P=0.831), ALT (P = 0.794), AST (P=0.057), serum creatinine (P = 0.575), eGFR (P = 0.901), UACR (P=0.648), FBG (P=0.324), 2h-PP blood glucose (P=0.839), and HBA1C (P=0.254).

In group I, no significant correlations were observed between serum urinary nephrin and other parameters, including age (P = 0.338), BMI (P = 0.850), disease duration (P = 0.479), SBP (P = 0.295), DBP (P = 0.493), hemoglobin (P = 0.406), ALT (P = 0.272), AST (P = 0.752), serum creatinine (P = 0.419), eGFR (P = 0.403), UACR (P = 0.320), FBG (P = 0.739), 2h-PP blood glucose (P = 0.434), and HBA1C (P = 0.978).

In group II, no significant correlations were observed between urinary nephrin and other parameters, including age (P = 0.386), BMI (P = 0.621), disease duration (P = 0.880), SBP (P = 0.086), DBP (P = 0.083), hemoglobin (P = 0.578), ALT (P = 0.308), AST (P = 0.418), serum creatinine (P = 0.293), eGFR (P = 0.467), UACR (P = 0.772), FBG (P = 0.261), 2h-PP blood glucose (P = 0.460), and HBA1C (P = 0.444).

Serum suPAR and urinary nephrin as predictors for DN: Multivariate logistic regression analysis was done for serum suPAR and urinary nephrin to predict DN. It revealed that serum suPAR (OR=1.044, 95% CI= 1.017 – 1.071, P=0.001) and urinary nephrin (OR=1.216, 95% CI=1.077 – 1.374, P = 0.002) were significant predictors for DN, controlling for age, gender, BMI, SBP, DBP, and disease duration **(Table 5).**

Table (5): Multivariate logistic regression for suPAR and urinary nephrin to predict diabetic nephropathy

	OR (95% CI)*	**P-value**
Serum suPAR(pg/ml)	1.044 (1.017 - 1.071)	**0.001**
Urinary nephrin (ng/mL)	1.216 (1.077 - 1.374)	**0.002**

OR: Odds ratio; *Adjusted for age, gender, BMI, SBP, DBP, and disease duration

DISCUSSION

Our results corroborated **Kostovska *et al.*** [17] findings' that there were substantial differences in age across the study groups (P 0.001) in terms of the participant demographics. Patients with diagnosed DN had considerably longer illness duration than individuals without diagnosed DN (P 0.001).

Nevertheless, **Veluri and Mannangatti**[18] enlisted 40 healthy controls and 80 T2DM who were matched by age and gender. According to their findings, individuals with T2DM had a statistically significant increase in BMI in comparison with healthy controls (P=0.001). Also, age was insignificantly different among studied groups. This may be contributed to different ethnic group or geographical factors or different lifestyle.

The group I demonstrated significantly higher ACEI or ARBS use (54.3% vs. 22.9%, P = 0.007) and retinopathy (88.6% vs. 37.1%, P <0.001) than group II. **Lupuş oru *et al.*** [19] looked into

research involving 75 cases with DM and DKD, of which 28 developed DN that was confirmed by biopsy. It was noticed that 68% of patients received therapy with either ACEI or ARBs. Diabetic retinopathy occurred in 49 (65.3%) of biopsy proven DN group.

The most frequent CKD stage was stage IV (40%), followed by stages III-B (20%), III-A (17.1%), II (14.3%), V (5.7%), and I (2.9%). In line with our study, **Lupuş oru *et al.*** [19] concluded that CKD stage 4 was (36%) is the most frequent CKD stage, stage 5 was (24%), stage 3B was (18.6%), stage 2 was (8%), stage 3A was (6.7%), and stage 1 was (6.7%).

In our investigation, there were significant differences in the analysed groups' haemoglobin levels (P<0.001). Compared to groups II and III, it was much lower in group I. Moreover, compared to group III, it was much lower in group II. Our results were in the same line with those of **Wang *et al.*** [20]**,** who looked at the correlation between serum suPAR levels and the early stages of DN in people with T2DM. They discovered that suPAR was correlated with erythrocytes (r=-0.611), hemoglobin (r=-0.588), lymphocytes (r=-0.381), and the neutrophil/lymphocyte ratio (r=0.527).

Regarding serum creatinine, there was a significant difference among the groups that were being tested (P<0.001). There was no discernible difference among groups II and III, and it was much greater in group I than in groups II and III. Between the groups under study, there was a significant difference in eGFR (P<0.001). There was no discernible difference between groups II and III, although it was much lower in group I than in groups II and III. In accordance with our investigation, **Kostovska *et al.*** [17] demonstrated that diabetic cases with diagnosed nephropathy had substantially greater creatinine levels than diabetic patients without confirmed nephropathy and healthy participants (P 0.001). In comparison to diabetics without documented nephropathy, healthy individuals, and diabetic patients, diabetic patients with diagnosed nephropathy had considerably lower eGFR (P<0.001).

Moreover, **Veluri and Mannangatti**[18] showed that diabetic individuals had considerably higher creatinine levels than healthy controls (P<0.001). T2DM sufferers' eGFR values were significantly decreased compared to healthy controls (P<0.001), and there was a negative association between eGFR and serum creatinine and urine nephrin (r ¼ –0.539, respectively, p < 0.0001).

Our research found that there were significant variations between the tested groups in both fasting and 2 hours after eating blood sugar (P< 0.001 for each). In comparison with groups I and II, they were much lower in group III. HBA1C was considerably lower in group III in comparison with groups I and II (P<0.001) and significantly different amongst the examined groups overall (P< 0.001). **Motawi *et al.*** [21] found that HbA1c and FBG were substantially greater in both T2DM patients compared with controls (p< 0.01), which is consistent with our results.

A substantial difference among the studied groups was found in the serum suPAR of the current investigation (P< 0.001). Compared to groups II and III, it was much higher in group I. Moreover, compared to group III, it was much higher in group II. Amongst the groups under study, there were significant differences in urinary nephrin (P< 0.001). Compared to groups II and III, it was much higher in group I. Moreover, compared to group III, it was much higher in group II.

The current study was in the same line with those recorded by **Wang *et al.*** [20]**,** who looked into the correlation between blood levels of suPAR and the early stages of DN in T2DM patients. 13 healthy controls and a total of 106 cases with T2DM were enrolled. They noticed that subjects with T2DM had substantially greater blood levels of suPAR than did healthy controls (P< 05).

We discovered in our investigation that suPAR can forecast DN. **Wang *et al.*** [20] discovered that serum suPAR is a significant independent contributor to DN, which is comparable to our results. In order to investigate the threshold suPAR value to identify the early stages of DN, ROC analysis was further utilised. SuPAR's 499.33 cutoff value was the best one for predicting early DN. In line with this, the AUC was 0.763 (95% CI: 0.663-0.863). It had a 0.497 Youden index, a sensitivity of 0.547, and a specificity of 0.950.

Also, SuPAR demonstrated an AUC of 0.92 (95% CI:0.56-0.95) as a predictor for CKD stage G3b-5 and 0.74 (95% CI:0.53-0.93) as a marker for DN class IV, according to **Lupuş oru *et al.*** [19]**.**

We stated in the current study that urine nephrin can forecast DN. According to **Veluri and Mannangatti**[18]**,** urine nephrin had a statistically significant AUC of 0.993 and sensitivity and specificity ranged between 100% and 93%, respectively (p <0.0001). Nephrin had an overall predicted probability of 96% in individuals with DN, according to **Kostovska *et al.*** [17] who conducted a ROC analysis.

Similar to our findings, **Wang *et al.*** [22] studied of 21 cases with biopsy-proven DN and 9 healthy controls. Their research revealed that there was no relationship between urinary nephrin and baseline clinical indicators (sex, age, serum creatinine, urine protein, estimated GFR). Contrarily, **Veluri and Mannangatti** [18] found that urine nephrin

had a strong negative association with eGFR and a substantial positive association with urinary ACR and HbA1c (r=-0.539, p < 0.0001).

Nephrin can be utilised as an early indicator of DN by looking for it in urine. In diabetic subjects with microalbuminuria and macroalbuminuria, and 54% of those with normoalbuminuria, nephronuria was discovered to be present [(8)].

Urinary ACR and urine nephrin were used as independent variables in a univariate linear regression analysis, which revealed a significant inverse relationship between them and eGFR. Urinary nephrin and urine ACR were studied as dependent and independent variables, respectively, and a direct correlation was found. The scatter plots demonstrated an association between urine nephrin, urinary ACR, and eGFR (r=0.87, 0.65, and 0.66, correspondingly; p=0.001). Nephrin is therefore indicated as being a better diagnostic for the diagnosis of DN than urine ACR based on these findings [(18)].

CONCLUSIONS

In the context of T2DM patients, serum suPAR and urinary nephrin have been demonstrated to be associated with a higher sensitivity and specificity compared to microalbuminuria in early detection of DN. suPAR can significantly predict diabetic nephropathy with cutoff > 82.3, at which sensitivity and specificity were 97.1% and 68.6%, respectively. Urinary nephrin can significantly predict DN with cutoff > 10.8, at which sensitivity and specificity were 80% and 68.6%, correspondingly.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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