Clinical value of soluble urokinase type plasminogen activator receptors in chronic kidney disease

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Abstract
Chronic kidney disease (CKD) will progress to end stage without treatment, the decline off renal function may not linear. A sensitive marker such as soluble urokinase-type plasminogen activator receptors (suPARs) may allow potential intervention and treatment in earlier stages of CKD.

Objectives: This study was designed to measure plasma (suPAR) in patients with CKD with different stages and to find its correlation with the disease severity.

Methods: This study was conducted on 114 subjects, 84 were patients with different stages and different causes of CKD, and 30 healthy subjects as controls. Blood urea, serum creatinine, serum high-sensitive C-reactive protein, estimated glomerular filtration rate, and 24 hours proteinuria were measured, renal biopsy was done for all patients, and plasma (suPAR) was measured using enzyme-linked immunosorbent assay.

Results: suPAR plasma levels were significantly higher in patients with CKD (7.9 ± 3.82 ng/mL) than controls (1.76 ± 0.77 ng/mL, P < .001). suPAR correlated with the disease severity. In stage 1 to 2 group, it was 3.7 ± 1.5 ng/mL in stage 3 to 4, it was 10.10 ± 1.22 ng/mL, and in stage 5 group, it was 12.34 ± 0.88 ng/mL; the difference between the 3 groups was highly significant (P < .001). A cutoff point 2.5 ng/mL of suPAR was found between controls and stage 1 group. According to the cause of CKD, although patients with obstructive cause and those with focal glomerulosclerosis had the higher levels 9.11 ± 3.32 ng/mL and 8.73 ± 3.19 ng/mL, respectively, but there was no significant difference between patients with CKD according to the cause of the CKD.

Conclusion: Plasma (suPAR) increased in patients with CKD and correlated with disease severity.

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, FSGS = focal segmental glomerulosclerosis, hs-CRP = high-sensitive C-reactive protein, suPAR = soluble urokinase-type plasminogen activator receptor.

Keywords: chronic kidney disease, focal segmental glomerulosclerosis, soluble urokinase type plasminogen activator receptors

1. Introduction
Soluble urokinase-type plasminogen activator receptor (suPAR) is the soluble form of urokinase plasminogen activator receptor (uPAR) which is a membrane bound receptor; this cell surface uPAR can be shed by several proteases leaving it devoid of glycosylphosphatidylinositol anchors to generate a soluble form. SuPAR has stable 3 domain (D1, D2, D3) structure that retains most of uPAR activities, which are involvement in cellular attachment, motility, and migration through its interaction with integrins.[1,2] Urokinase plasminogen type activator receptors is expressed in different cell types including neutrophils, monocytes, macrophages, activated T-lymphocytes, endothelial cells, and kidney podocytes.[3] uPAR regulates the plasminogen activation system by binding urokinase (uPA) and its zymogen form.[4,5] suPAR has many types of receptors; the most common known receptor is αvβ3 integrin; activation of αvβ3 integrin on podocytes leads to activation of guanosin triphosphate hydrolyzing enzyme (GTPase Rac1), which causes podocytes foot process (FP) motility and effacement.[6] In addition to interaction with integrins, suPAR initiates signaling transduction in cooperation with other trans-membrane proteins such as caveolin and G-protein-coupled receptors.[7] suPAR circulates in blood and present in other body fluids as cerebrospinal fluid, saliva, and urine.[8] It has been identified in various pathologic conditions like cancer,[9] cardiovascular disease,[10] and chronic kidney disease (CKD). Both uPA and...
uPAR is significantly upregulated in renal cortex and in all types of glomerular cells including podocytes.\(^{[11,12]}\)

The 1st indicator of a predictive function for suPAR in CKDs is derived from the work of Hayek and coworkers who validated a longitudinal association of baseline suPAR level with decline in estimated glomerular filtration rate (eGFR) and incident CKD in a cohort study of patients with cardiovascular disease.\(^{[13]}\)

In clinical practice, strategies of screening for kidney diseases are limited; proteinuria (PTN) and decline in the eGFR are exceptionally insensitive indexes of early injury and have constrained usefulness in mass screening of CKD. Hence, more sensitive biomarkers are required to identify patients at danger earlier in the disease process to prevent the progression of CKD to end-stage renal failure.

To our knowledge, until now, there is no study had investigated plasma suPAR level in Egyptian patients with CKD; hence, we aimed to evaluate the clinical value of suPAR in Egyptian patients with CKD with different causes and different stages of the disease.

### 2. Subjects and methods

This study was carried on 114 subjects, 84 were patients with CKD with different stages and different causes of the disease. Their age was 51.02 ± 11.57, with range of 22 to 68. Females were 45 (53.6%), while males were 39 (46.4%). They were divided according to the stages of the disease into 3 subgroups: stage 1 to 2 group (n = 34, 40.47%), stage 3 to 4 group (n = 34, 40.47%), and stage 5 group (n = 16, 19.21%). The causes of CKD of the studied patients included diabetic nephropathy (n = 35, 41.7%), hypertensive nephropathy (n = 17, 20.2%), and obstructive nephropathy (n = 10, 11.9%). Patients with CKD with cardiovascular complication were n = 35, 41.7% and those without cardiovascular complications were n = 49, 58.3%. All these descriptive data are shown in Table 1. They were selected from patients with CKD who admitted to Internal Medicine Department in AL-Zahraa Hospital, Al-Zahar University, Cairo, Egypt, in a period from March 31 to September 31, 2018, diagnosis and staging based on National Kidney Foundation. K/DOQI clinical practice guidelines for CKD (2002).\(^{[14]}\) Because suPAR cannot cross the dialysis membrane and its plasma concentration may increase after dialysis session,\(^{[5]}\) we prefer to choose stage 5 patients who did not undergo dialysis before their involvement in the current study.

The control group was 30 ethnically, age, sex, and body mass index (BMI) matched healthy individuals. The age was 51.47 ± 10.42, ranged from 28 to 67 years. Females were 7 (56.7%), while males were 13 (43.3%).

The eGFR was calculated using CKD Epi formula.\(^{[11]}\) Serum creatinine, blood urea, and 24 hours protein in urine (24 hours PTN) were measured for all patients with CKD and controls. Kidney biopsy was taken from all patients and examined pathologically to ensure FSGS diagnosis.

Exclusion criteria include: cancer, systemic infection, and history of active inflammatory disease.\(^{[9,16]}\) Also some cases in stage 5 were excluded because they undergo dialysis. The protocol of this study was approved by the medical ethics committee in the faculty and written informed consent was obtained from all patients and healthy controls.

Sample preparation: Ten milliliters of venous blood were collected from each subject and divided into 2 tubes. Five milliliters were evacuated in sterile plain tube to obtain serum for estimation of serum high-sensitive C-reactive protein (hs-CRP) by enzyme-linked immunosorbent assay (ELISA) according to DRG International Inc (Kono Biotech Co., Ltd, Zhejiang, PRC) (hs-CRP = high-sensitive C-reactive protein, PTN = proteinuria, SD = standard deviation, suPAR = soluble urokinase plasminogen activator receptor).

Data preparation: Ten milliliters of venous blood were collected from each subject and divided into 2 tubes. Five milliliters were evacuated in sterile plain tube to obtain serum for estimation of serum high-sensitive C-reactive protein (hs-CRP) by enzyme-linked immunosorbent assay (ELISA) according to DRG International Inc (Kono Biotech Co., Ltd, Zhejiang, PRC) (hs-CRP = high-sensitive C-reactive protein, PTN = proteinuria, SD = standard deviation, suPAR = soluble urokinase plasminogen activator receptor).

| Sex        | Females | 45 (53.6%) |
|------------|---------|------------|
| Males      | 39 (46.4%) |

| Age        | Mean ± SD | 51.02 ± 11.57 |
|------------|-----------|---------------|
| Range      | 22–68     |

| BMI        | Mean ± SD | 24.30 ± 1.71 |
|------------|-----------|--------------|
| Range      | 21–28     |

### Table 1

Descriptive and laboratory data for CKD patient group.

| CKD patient group | n = 84 |
|-------------------|--------|
| Sex               |        |
| Females           | 45 (53.6%) |
| Males             | 39 (46.4%) |
| **Age**           |         |
| Mean ± SD         | 51.02 ± 11.57 |
| Range             | 22–68   |
| **BMI**           |         |
| Mean ± SD         | 24.30 ± 1.71 |
| Range             | 21–28   |
| **Causess**       |         |
| Diabetess         | 31 (26.9%) |
| FSGS              | 26 (31.0%) |
| Hypertension      | 17 (20.2%) |
| Obstructive       | 10 (11.9%) |
| **Blood urea, mg/dL** |        |
| Mean ± SD         | 103.49 ± 59.97 |
| Range             | 14–200  |
| **Serum creatinine, mg/dL** |     |
| Mean ± SD         | 3.59 ± 2.68 |
| Range             | 0.5–11.8 |
| **eGFR, mL/min/1.73 m²** |        |
| Mean ± SD         | 52.99 ± 38.44 |
| Range             | 5–119   |
| **24 hrs PTN, mg/dL** |         |
| Mean ± SD         | 1474.12 ± 1720.24 |
| Range             | 100–7000 |

| **Cardiac patients** |        |
| Without card. comp. | 49 (58.3%) |
| With card. comp.    | 35 (41.7%) |
| **hs-CRP, mg/L**    |         |
| Mean ± SD           | 3.87 ± 1.98 |
| Range               | 1.1–7.4  |
| **suPAR, ng/mL**    |         |
| Mean ± SD           | 7.93 ± 3.82 |
| Range               | 2.1–15.6 |

| **Descriptive and laboratory data for CKD patient group.** |        |
|-----------------------------------------------------------|--------|
| **Sex**                                                   |        |
| Females                                                   | 45 (53.6%) |
| Males                                                     | 39 (46.4%) |
| **Age**                                                   |         |
| Mean ± SD                                                 | 51.02 ± 11.57 |
| Range                                                     | 22–68   |
| **BMI**                                                   |         |
| Mean ± SD                                                 | 24.30 ± 1.71 |
| Range                                                     | 21–28   |
| **Causess**                                               |         |
| Diabetess                                                 | 31 (26.9%) |
| FSGS                                                      | 26 (31.0%) |
| Hypertension                                              | 17 (20.2%) |
| Obstructive                                               | 10 (11.9%) |
| **Blood urea, mg/dL**                                    |        |
| Mean ± SD                                                 | 103.49 ± 59.97 |
| Range                                                     | 14–200  |
| **Serum creatinine, mg/dL**                               |         |
| Mean ± SD                                                 | 3.59 ± 2.68 |
| Range                                                     | 0.5–11.8 |
| **eGFR, mL/min/1.73 m²**                                  |         |
| Mean ± SD                                                 | 52.99 ± 38.44 |
| Range                                                     | 5–119   |
| **24 hrs PTN, mg/dL**                                    |         |
| Mean ± SD                                                 | 1474.12 ± 1720.24 |
| Range                                                     | 100–7000 |
| **Cardiac patients**                                     |        |
| Without card. comp.                                       | 49 (58.3%) |
| With card. comp.                                          | 35 (41.7%) |
| **hs-CRP, mg/L**                                          |         |
| Mean ± SD                                                 | 3.87 ± 1.98 |
| Range                                                     | 1.1–7.4  |
| **suPAR, ng/mL**                                          |         |
| Mean ± SD                                                 | 7.93 ± 3.82 |
| Range                                                     | 2.1–15.6 |
range and percentages. The evaluation between groups concerning qualitative data used to be carried out through the use of Chi-squared test. The contrast between 2 groups involving quantitative statistics was done by the use of independent t test, while the comparison between more than 2 groups involving quantitative facts with parametric distribution had been performed through the usage of 1-way analysis of variance accompanied by using posthoc analysis using least significance difference test. Pearson correlation coefficients have been used to determine the correlation between 2 quantitative parameters in the same group. Receiver-operating characteristic curve was used to verify the best cutoff point with its sensitivity, specificity, positive predictive value, negative predictive value, and area under curve (AUC). The P-value used to be considered significant as the following:

1. $P > .05$: nonsignificant (NS)
2. $P < .05$: significant (S)
3. $P < .01$: highly significant (HS)

### 3. Results

Descriptive and laboratory data of patients with CKD are shown in Table 1. Comparison between control group and CKD patient group showed that there were nonsignificant differences in age, sex ratio distribution, and BMI, but there were highly significant differences in blood urea, serum creatinine, eGFR, 24 hours PTN, and hs-CRP, as shown in Table 2. The highly significant difference in suPAR plasma level also found between control group and patients with stage 1 CKD (a very early stage of CKD), although there were nonsignificant differences between the 2 groups as regard serum creatinine, blood urea, and eGFR, as shown in Table 3.

| Variables | Control group n = 30 | CKD group n = 84 | T-value | P-value | Sig. |
|-----------|---------------------|-----------------|---------|---------|------|
| Sex       |                     |                 |         |         |      |
| Females   | 17 (56.7%)          | 45 (53.6%)      | 0.085   | .770    | NS   |
| Males     | 13 (43.3%)          | 39 (46.4%)      |         |         |      |
| Age, yrs  |                     |                 |         |         |      |
| Mean ± SD | 51.47 ± 10.42       | 51.02 ± 11.57   | 0.184   | .854    | NS   |
| Range     | 26–67               | 22–68           |         |         |      |
| BMI, kg/m²|                     |                 |         |         |      |
| Mean ± SD | 24.07 ± 1.48        | 24.30 ± 1.71    | 0.190   | .931    | NS   |
| Range     | 22–28               | 21–28           |         |         |      |
| Blood urea, mg/dL |                  |                 |         |         |      |
| Mean ± SD | 25.40 ± 10.70       | 103.49 ± 59.97  | -7.073  | .001    | HS   |
| Range     | 12–45               | 14–200          |         |         |      |
| Serum creatinine, mg/dL |               |                 |         |         |      |
| Mean ± SD | 0.70 ± 0.11         | 3.59 ± 2.68     | -5.888  | .001    | HS   |
| Range     | 0.5–0.9             | 0.5–11.8        |         |         |      |
| eGFR, mL/min/1.73 m² |             |                 |         |         |      |
| Mean ± SD | 108.40 ± 10.50      | 52.99 ± 38.44   | 7.772   | .001    | HS   |
| Range     | 94–120              | 5–119           |         |         |      |
| 24 hrs PTN, mg/dL |                |                 |         |         |      |
| Mean ± SD | 108.10 ± 9.79       | 1474.12 ± 1720.24 | -4.337 | .001    | HS   |
| Range     | 80–120              | 100–7000        |         |         |      |
| hs-CRP, mg/L |                |                 |         |         |      |
| Mean ± SD | 1.90 ± 0.45         | 3.87 ± 1.98     | -5.375  | .001    | HS   |
| Range     | 1.2–8               | 1.1–7.4         |         |         |      |
| suPAR, ng/mL |                |                 |         |         |      |
| Mean ± SD | 1.76 ± 0.77         | 7.93 ± 3.82     | -8.758  | .001    | HS   |
| Range     | 0.6–2.9             | 2.1–13.6        |         |         |      |

**Table 2**

Comparison between control group and CKD patient group regarding the studied parameters included plasma suPAR level.

| Variables | Control group n = 30 | Stage 1 n = 20 | T-value | P-value | Sig. |
|-----------|---------------------|---------------|---------|---------|------|
| Age, yrs  |                     |               |         |         |      |
| Mean ± SD | 51.47 ± 10.42       | 50.20 ± 10.03 | 0.427   | .671    | NS   |
| Range     | 26–67               | 29–66         |         |         |      |
| Sex       |                     |               |         |         |      |
| Females   | 17 (56.7%)          | 10 (50.0%)    | 0.215   | .643    | NS   |
| Males     | 13 (43.3%)          | 10 (50.0%)    |         |         |      |
| BMI, kg/m²|                     |               |         |         |      |
| Mean ± SD | 25.07 ± 1.48        | 24.65 ± 1.76  | 0.470   | .640    | NS   |
| Range     | 22–28               | 22–28         |         |         |      |

**Table 3**

Comparison between control group and patients with stage 1 CKD regarding all parameters.

| Variables | Control group n = 30 | Stage 1 n = 20 | T-value | P-value | Sig. |
|-----------|---------------------|---------------|---------|---------|------|
| Age, yrs  |                     |               |         |         |      |
| Mean ± SD | 51.47 ± 10.42       | 50.20 ± 10.03 | 0.427   | .671    | NS   |
| Range     | 26–67               | 29–66         |         |         |      |
| Sex       |                     |               |         |         |      |
| Females   | 17 (56.7%)          | 10 (50.0%)    | 0.215   | .643    | NS   |
| Males     | 13 (43.3%)          | 10 (50.0%)    |         |         |      |
| BMI, kg/m²|                     |               |         |         |      |
| Mean ± SD | 25.07 ± 1.48        | 24.65 ± 1.76  | 0.470   | .640    | NS   |
| Range     | 22–28               | 22–28         |         |         |      |

The SuPAR plasma level was significantly higher in CKD patient group ($7.93 ± 3.82$ ng/mL) with a range of 2.1 to 13.6 ng/mL than controls ($1.76 ± 0.77$ ng/mL) with a range of 0.6 to 2.9 ng/mL ($P < .001$), as shown Table 2. The highly significant difference in suPAR plasma level also found between control group and patients with stage 1 CKD (a very early stage of CKD), although there were nonsignificant differences between the 2 groups as regard serum creatinine, blood urea, and eGFR, as shown in Table 3.

Also, suPAR plasma level varies between the CKD patient subgroups. In stage 1 to 2 group, it was $3.70 ± 1.50$ ng/mL with a range of 2.1 to 6.9 ng/mL; in stage 3 to 4 group, it was $10.10 ± 1.22$ ng/mL with a range of 6.8 to 11.7 ng/mL; and in stage 5 group, it was $12.34 ± 0.88$ ng/mL with a range of 10.8 to 13.6 ng/mL, the difference between the 3 subgroups was highly significant ($P < .001$), as shown in Table 4; also posthoc analysis showed high significant difference ($P < .001$) between each 2 groups (Table 5).

We found a cutoff point for suPAR plasma level between 24 hrs PTN, mg/dL.

| Mean ± SD | 1.76 ± 0.77         | 3.66 ± 1.40   | -6.181  | .001    | HS   |
| Range     | 0.6–2.9             | 2.1–5.9       |         |         |      |
Significantly higher than its level in controls, a highly significant finding a more sensitive marker out such as suPAR which is strongly and independently associated with the development of future kidney disease is of a great benefit.[18]

In patients with CKD, suPAR correlated positively with age, blood urea, serum creatinine, 24 hours PTN, and hs-CRP, but correlated negatively with BMI, eGFR, as shown in Table 9. In the control group, suPAR correlated positively with 24 hours PTN, but correlated negatively with eGFR, as shown in Table 10.

### 4. Discussion

The CKD affects about 800 million subjects all over the world, and the number is rising. Treatment of kidney disease is further hampered by the often late diagnosis, so finding a more sensitive marker out such as suPAR which is strongly and independently associated with the development of future kidney disease is of a great benefit.[18]

In this study, plasma level of suPAR in patients with CKD was significantly higher than its level in controls, a highly significant

### Table 4

Comparison between CKD patient subgroups regarding all parameters including suPAR.

| Parameters                | Stages 1–2 | Stages 3–4 | Stage 5 | T-value | P-value | Sig. |
|---------------------------|------------|------------|---------|---------|---------|------|
| **Sex**                   |            |            |         |         |         |      |
| Females                   | 18 (62.9%) | 17 (50.0%) | 10 (62.5%) | 0.780 | .854    | NS   |
| Males                     | 16 (47.1%) | 17 (50.0%) | 6 (37.5%)  |       |         |      |
| **Age, yrs**              |            |            |         |         |         |      |
| Mean ± SD                 | 48.68 ± 10.17 | 50.53 ± 13.54 | 57.06 ± 7.62 | 2.130 | .101    | NS   |
| Range                     | 22–66      | 23–68      | 39–66   |         |         |      |
| **BMI, kg/m²**            |            |            |         |         |         |      |
| Mean ± SD                 | 24.97 ± 1.64 | 23.91 ± 1.71 | 23.69 ± 1.40 | 5.190 | .002    | HS   |
| Range                     | 22–28      | 21–28      | 22–26   |         |         |      |
| **Cause**                 |            |            |         |         |         |      |
| Diabetes                  | 15 (44.1%) | 9 (26.5%)  | 7 (43.8%) | 4.106 | .662    | NS   |
| FSGN                      | 10 (29.4%) | 12 (35.3%) | 4 (25.0%) |         |         |      |
| Hypertension              | 7 (20.6%)  | 7 (20.6%)  | 3 (18.8%) |         |         |      |
| Obstructive               | 2 (6.9%)   | 6 (17.0%)  | 2 (12.5%) |         |         |      |
| **Blood urea, mg/dL**     |            |            |         |         |         |      |
| Mean ± SD                 | 45.44 ± 30.78 | 123.92 ± 39.77 | 164.50 ± 37.86 | 125.994 | .001    | HS   |
| Range                     | 14–120     | 60–190     | 124–200 |         |         |      |
| **Serum creatinine, mg/dL** |             |            |         |         |         |      |
| Mean ± SD                 | 1.22 ± 0.74 | 3.91 ± 1.07 | 7.96 ± 1.62 | 263.430 | .001    | HS   |
| Range                     | 0.5–2.5    | 2.3–6      | 5.9–11.8 |         |         |      |
| **eGFR, mL/min/1.73 m²**  |            |            |         |         |         |      |
| Mean ± SD                 | 95.26 ± 18.93 | 31.00 ± 10.66 | 9.88 ± 3.12 | 338.914 | .001    | HS   |
| Range                     | 60–119     | 17–65      | 5–14    |         |         |      |
| **24 hrs PTN, mg/dL**     |            |            |         |         |         |      |
| Mean ± SD                 | 276.94 ± 282.9 | 2152.65 ± 1506 | 2576.25 ± 2235 | 28.342 | .001    | HS   |
| Range                     | 100–1000   | 150–7000   | 180–7000|         |         |      |
| **CKD patients with cardiac disease** |           |            |         |         |         |      |
| Without                   | 25 (73.5%) | 17 (50.0%) | 7 (43.8%) | 5.602  | .061    | NS   |
| With                      | 9 (26.5%)  | 17 (50.0%) | 9 (56.3%) |         |         |      |
| **hs-CRP, mg/L**          |            |            |         |         |         |      |
| Mean ± SD                 | 2.51 ± 1.48 | 4.41 ± 1.86 | 5.65 ± 1.07 | 36.770  | .001    | HS   |
| Range                     | 1.1–6.7    | 1.5–7.4    | 3.6–7.2 |         |         |      |
| **suPAR, ng/mL**          |            |            |         |         |         |      |
| Mean ± SD                 | 3.70 ± 1.50 | 10.10 ± 1.22 | 12.34 ± 0.88 | 464.035 | .001    | HS   |
| Range                     | 2.1–6.9    | 6.8–11.7   | 10.8–13.6|         |         |      |

BMI = body mass index, CKD = chronic kidney disease, card. Comp. = cardiac complications, eGFR = estimated glomerular filtration rate, HS = high significant, n = number, NS = nonsignificant, PTN = proteinuria, SD = standard deviation, Sig. = significant, suPAR = soluble urokinase plasminogen activator receptor. Significant at P < .05.

| P1 | P2 | P3 |
|----|----|----|
| 0.001 | 0.001 | 0.001 |

P1 = stage 1–2 vs stage 3–4, P2 = stage 1–2 vs stage 5, P3 = stage 3–4 vs stage 5.
difference in suPAR plasma level also found between control group and patients with stage 1 CKD, although there was nonsignificant difference between the 2 groups as regard serum creatinine, blood urea, eGFR, this finding supports that suPAR is more sensitive than other parameters. Also we found a cutoff point for suPAR between controls and stage 1 group as early stages of renal disease which was 2.5ng/mL. This cutoff point had 80% sensitivity, specificity 73.3%, negative predictive value (66.7). The OR had 80% sensitivity, specificity 73.3%, negative predictive value (66.7). The OR = 9.33, 95% CI = 2.43 to 35.83, \( P = .001 \), that means suPAR may be a reliable marker help in diagnosis of CKD in very early stages especially in risky patients.

In a large cohort prospective study, suPAR can precede microalbuminuria and can be a predictive marker in very early stages of diabetic nephropathy.\(^{19}\)

In this study, plasma suPAR increased with increasing stages of the disease that means the plasma levels of suPAR correlates with the disease severity. This was in accordance with Sinha et al who demonstrated serum suPAR levels in various clinical categories of proteinuric CKD disease and they found values for suPAR in CKD stage 1 to 3 were higher than in controls, and values of suPAR in CKD stage 4 to 5 were higher than stage 1 to 3 or healthy controls.\(^{20}\)

Wu et al examined serum samples for suPAR and renal tissue for suPAR in various common kidney diseases and they found the serum level of suPAR increased in all types of kidney diseases and the suPAR correlates with the stage of diabetic nephropathy staging.\(^{21}\) So, it has prognostic value in CKD.

As regard the cause of CKD, although there was nonsignificant difference between different causes of the disease involved in this study, the obstructive cause and FSGS had the higher levels. Obstructive renal disease may interfere with suPAR excretion in the urine resulting in retention of suPAR to blood. Also suPAR had identified as a causal factor for FSGS.\(^{22}\) It was suggested that elevation of circulating suPAR in FSGS might reflect a secondary effect of immune activation in FSGS.\(^{23,24}\) Although suPAR increases in different renal disease but it cannot distinguish between them.

In the present study, plasma suPAR correlated negatively with eGFR in both patients with CKD and controls. This was the most obvious finding many studies that investigated suPAR in different renal diseases.\(^{19,20,24}\)

Also, Hayek et al had the same finding, but they suggested that elevated suPAR in CKD and its negative correlation with eGFR may not due to decrease in renal clearance but there may be other pathogenic mechanisms.\(^{13}\)

Meijers et al had concluded that eGFR was the strongest determinant of suPAR and they suggested that circulating suPAR levels are strongly affected by renal function and cannot

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### Table 6
Receiver operating characteristic curve for soluble urokinase plasminogen activator receptor level as a predictor for patients with stage 1 chronic kidney disease.

| Cutoff point | AUC  | Sensitivity | 95% CI sensitivity | Specificity | 95% CI specificity | +PV  | –PV  |
|-------------|------|-------------|--------------------|-------------|--------------------|------|------|
| >2.5        | 0.886| 80.00       | 56.3–94.3          | 73.33       | 54.1–87.7          | 66.7 | 84.6 |

AUC = area under the curve, CI = confidence interval, PV = predictive value.

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### Table 7
Odds ratio between controls and patients with stage 1 chronic kidney disease.

| Cutoff point | Odds ratio | 95% CI | Z-statistics | P-value |
|-------------|------------|-------|--------------|---------|
| >2.5        | 9.33       | 2.43–35.83 | 3.254       | .001    |

CI = confidence interval.
Table 9
Correlation of suPAR with all parameters in chronic kidney disease patient group.

| Variables        | R   | P-value | Sig. |
|------------------|-----|---------|------|
| Age              | 0.23 | .034    | S    |
| BMI              | -0.30 | .005   | HS   |
| Serum urea       | 0.77 | .001    | HS   |
| Serum creatinine | 0.87 | .001    | HS   |
| eGFR             | -0.89 | .001   | HS   |
| 24 hrs PTN       | 0.72 | .001    | HS   |
| hs-CRP           | 0.48 | .001    | HS   |

BMI = body mass index, eGFR = estimated glomerular filtration rate, HS = high significant, hs-CRP = high-sensitive C-reactive protein, NS = non-significant, PTN = proteinuria, S = significant, Sig. = significance, suPAR = soluble urokinase plasminogen activator receptors. Significant at P < .05.

distinguish between different nephropathies for any given level of eGFR.[25]

As suPAR has molecular weight of 20 to 50 kDa, it is subjected to glomerular filtration and can be secreted in the urine, and this may explain negative correlation between suPAR and eGFR. We think that there is closed circle between suPAR and eGFR that means decrease in eGFR will result in increase in suPAR which in turn will affect kidney functions.

In this study, we found that plasma suPAR positively correlated with PTN in all patients with CKD and controls, this was in accordance with Musetti et al who noted that suPAR was inversely associated with eGFR and directly associated with PTN, they suggest that suPAR is involved in the pathogenesis of PTN through a pathway shared by a wide spectrum of nephropathies.[24]

Podocytes are highly specialized structure and they are important component of the glomerular filtration barrier that prevents the excretion of albumin into urine. These visceral epithelial cells of the glomerular tuft contains a cell body, major process that extended outwards and distal FP that surrounds glomerular capillaries. Damage to the structure and functional components of podocytes results in the effacement of FP, also referred to podocyte fusion or retraction.

The detachment of podocytes from glomerular basement membrane causes leakage of protein in urine. suPAR activates integrins avβ3 presents in podocytes results in changes in podocytes actin cytoskeleton shifting it from stationary phenotype to mobile phenotype which causes FP effacement and podocytes migration leading to PTN. This mechanism is the main mechanism involved in FSGS.[26]

Other mechanism is through expression of shingomyelinase-like phosphodiesterase 3b (SMPDL-3b) which is high in diabetic nephropathy shifting suPAR-mediated podocyte injury from migratory podocytes which occurs FSGS to an apoptotic phenotype which occurs in diabetic nephropathy that means the effect of suPAR on podocytes function may be modulated by many pathways in a disease-specific manner.[19]

However, further studies are needed to identify the exact role of suPAR in PTN, as it was noted that in various inflammatory conditions, increase in suPAR levels was not associated with PTN,[27] this observation may be due to the presence of suPAR alone is not sufficient to produce PTN, or may be PTN depends on the source of suPAR in the body.

Surprisingly, in this study, patients with CKD with cardiovascular complications had higher plasma suPAR level than those without cardiovascular complications, but the difference was non-significant. This finding is contrary to Walzal et al[5] who observed a significantly higher baseline suPAR level in hemodialysis patients with diagnosed heart failure and in patients with history of cardiovascular disease. Also, Meijers et al[23] found that suPAR level was directly and significantly associated with cardiovascular events with mild to moderate kidney disease. Furthermore, Eapen et al who found that suPAR levels elevated in patients with adverse cardiovascular events with or without CKD,[24]

In this study, plasma suPAR correlated positively with hs-CRP that suggests role of inflammation in suPAR production,[29,30] or may be due to an inflammatory role of suPAR in CKD.[13]

Also, suPAR correlates positively with age in CKD patient group which was in accordance with Florquin et al[31] but Bock et al[32] had found that there was inverse correlation between suPAR with the age. All findings of this study clarified the clinical value of suPAR measurement in patients with CKD, but larger sample size, and prospective studies are needed to ensure our findings.

5. Conclusion

Plasma (suPAR) increased in patients with CKD and correlated with disease severity. Measurement of suPAR gives chance for early stratification of patients with CKD in their disease course and allows targeting of early treatment.

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