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Plasma soluble urokinase receptor levels are increased but do not distinguish primary from secondary focal segmental glomerulosclerosis

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In this study, we measured soluble urokinase receptor levels, a possible permeability factor, in the plasma of patients with primary focal segmental glomerulosclerosis (FSGS) and determined their association with clinical and pathological data in 74 patients with primary FSGS. Healthy donors and patients with minimal change disease, membranous nephropathy, and secondary FSGS were used as controls. The plasma-soluble urokinase receptor levels, measured by commercial ELISA kits, of patients with primary FSGS (median: 2923, interquartile range 2205–4360 pg/ml) were significantly higher than those of patients with minimal change disease (median 2050 pg/ml), membranous nephropathy (median 2029 pg/ml), and normal individuals (median 1739 pg/ml). There was no significant difference in plasma-soluble urokinase receptor levels between the 74 patients with primary and 14 patients with secondary FSGS. The soluble urokinase receptor levels increased in the order of tip variant, to a not otherwise specified variant and a cellular variant. The soluble urokinase receptor levels were significantly but negatively correlated with creatinine clearance at presentation but positively correlated with crescent formation in patients with primary FSGS. During follow-up, receptor levels decreased significantly in patients with complete remission. Thus, plasma-soluble urokinase receptor levels did not differentiate primary and secondary FSGS, and although significantly elevated in FSGS, they showed considerable overlap with other glomerular diseases.

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Focal segmental glomerulosclerosis (FSGS) is an important cause of steroid-resistant nephrotic syndrome in children and adults. FSGS can be divided into primary and secondary forms. The cause of secondary FSGS may be linked to genetic variations, drug toxicity, viruses, metabolic diseases, and so on. The etiology and pathophysiology of primary FSGS is still unknown. During the past 20 years, a consensus has been reached that the podocyte may have a key role in the initiation and progression of the lesion observed in FSGS[1,2] and the primary FSGS is regarded as a podocytopathy. However, substantial evidences suggest that primary FSGS may not only be a kidney disease, but also a systemic disorder in which podocytes may act as effector cells. It has been found that FSGS may recur in some patients after kidney transplantation,[3] and some patients with FSGS are successfully treated with plasmapheresis.[4] Therefore, a hypothesis that circulating permeability factors may involve in the pathogenesis of FSGS is fairly attractive.[5,6] Recently, Wei *et al.*[7] studied a group of FSGS patients with kidney transplantation and found that soluble urokinase receptor (suPAR) might be the most likely pathogenic circulating permeability factor. In our study, we measured plasma suPAR levels in a variety of primary glomerular diseases including primary FSGS with various pathological variants; their clinical and pathological associations were further analyzed.

RESULTS

Demographic and clinical characteristics of patients with primary FSGS

The median age of the 74 FSGS patients was 29 years, ranging from 13 to 84 years. Of these, 50 were men and 24 were women. Their demographic, clinical, and pathological data are listed in Table 1. Of the 74 patients, 73 had nephrotic syndrome (98.6%), 18 had acute kidney injury (24.3%), and

53 had microscopic hematuria (71.6%). Their median 24-h urine protein was 7.6 (interquartile range (IQR) 5.3–13.1) g per 24 h. The mean serum albumin was 21.6 ± 7.2 g/l. The median serum creatinine was 93.0 (IQR 64.5–159.5) μmol/l at presentation.

The plasma suPAR levels in patients with primary FSGS and controls

The plasma suPAR levels of patients with primary FSGS, minimal change disease, membranous nephropathy, secondary FSGS, and normal subjects are shown in Table 2 and Figure 1. The plasma suPAR levels of patients with primary FSGS (2923, IQR 2205–4360 pg/ml) were significantly higher than those of patients with minimal change disease (2050, IQR 1813–2249 pg/ml, $P<0.001$), membranous nephropathy (2029, IQR 1512–2715 pg/ml, $P<0.001$), and normal controls (1739, IQR 1576–2063 pg/ml, $P<0.001$). There was no significant difference in the plasma suPAR levels between patients with primary FSGS and those with secondary FSGS (2639, IQR 1945–3166 pg/ml, $P=0.171$).

Of the 14 patients with secondary FSGS, the plasma suPAR level was 2512 pg/ml for the patient with pre-eclampsia, 1890 pg/ml for the patient with Kimura disease, 2138 and 2333 pg/ml for the two patients with obesity, 3082 and 1519 pg/ml for the two patients with Alport syndrome, and 2813 (IQR 2164–3427) pg/ml for the median plasma suPAR level of the eight patients without identifiable factors.

Table 1 | The demographic and clinical parameters of patients with primary FSGS

Parameter	$n=74$
Age (years; median, range)	29, 13–84
Gender (male/female)	50/24
Nephrotic syndrome, *n* (%)	73 (98.6%)
Acute kidney injury, *n* (%)	18 (24.3%)
Microscopic hematuria, *n* (%)	53 (71.6%)
24-h urine protein (g per 24 h; median, IQR)	7.6, 5.3–13.1
Albumin (g/l; mean ± s.d.)	21.6 ± 7.2
Serum creatinine at presentation (μmol/l; median, IQR)	93.0, 64.5–159.5
Percentage of sclerosis in glomeruli (%; mean ± s.d.)	17.9 ± 16.3
Percentage of segmental sclerosis in glomeruli (%; mean ± s.d.)	11.1 ± 11.4
Percentage of global sclerosis in glomeruli (%; mean ± s.d.)	2.2 ± 5.3
Crescent formation, *n* (%)	11 (14.9%)

Abbreviations: FSGS, focal segmental glomerulosclerosis; IQR, interquartile range.

The plasma suPAR levels in patients with primary FGGS with different pathological variants

We compared the plasma suPAR levels among different histopathological variants of patients with primary FSGS. As shown in Figure 2, the plasma suPAR levels increased in the order of tip, not otherwise specified (NOS), and cellular variant (2323, IQR 2038–2665 pg/ml; 3216, IQR 2519–4762 pg/ml; 3270, IQR 2338–5438 pg/ml, respectively). As there were only a few cases with perihilar variant, collapsing variant, and advanced FSGS, statistical analysis was not performed for them. The plasma suPAR levels were 1201 and 2755 pg/ml for the two patients with perihilar variant, 3123 pg/ml for the patient with collapsing variant, and 3099 and 10337 pg/ml for the two patients with advanced FSGS.

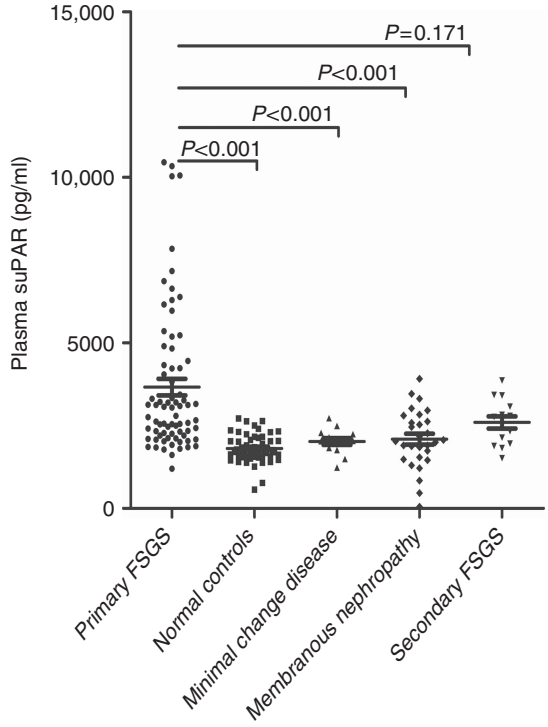

Figure 1 | Plasma soluble urokinase-type plasminogen activator receptor (suPAR) levels among patients with primary focal segmental glomerulosclerosis (FSGS), normal subjects, and patients with minimal change disease, membranous nephropathy, and secondary FSGS.

Table 2 | The demographic data and plasma suPAR levels of patients and controls

	Primary FSGS	Minimal change disease	Membranous nephropathy	Secondary FSGS	Normal controls
Numbers of subjects	74	14	29	14	56
Age (median, range)	29, 13–84	42, 17–71	50, 33–79	38, 14–46	36, 21–47
Gender (male/female)	50/24	7/7	18/11	5/9	33/23
Plasma suPAR (pg/ml) (median, IQR)	2923, 2205–4360	2050, 1813–2249	2029, 1512–2715	2639, 1945–3166	1739, 1576–2063

Abbreviations: FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; suPAR, urokinase-type plasminogen activator receptor.