The Hype Cycle for Soluble Urokinase Receptor in FSGS: Passing the Trough of Disillusionment?

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Activation of the podocyte urokinase receptor signaling pathway leads to foot process effacement and proteinuria (1). In a similar fashion, certain— but not all— serum soluble urokinase receptor (suPAR) splice variants in mice cause foot process effacement, proteinuria, and FSGS-like glomerulopathy (2,3). These observations fueled speculation on suPAR as the circulating factor causing FSGS. Clinical studies showed elevated suPAR concentrations in patients with primary FSGS compared with healthy individuals and patients with minimal changes disease (MCD) and that a threshold of 3000 pg/ml might distinguish FSGS from other glomerulopathies (4).

The initial enthusiasm about the use of suPAR as a diagnostic biomarker of FSGS was significantly dampened resultant to a series of mostly clinical studies. First, serum suPAR concentrations could not discriminate patients with primary versus secondary FSGS or patients at risk of recurrent FSGS after kidney transplantation (5–7). Second, studies looking at determinants of serum concentrations identified kidney function to be one of the most important determinants of suPAR (8,9). This argues against the use of an absolute suPAR concentration cutoff as a biomarker for underlying FSGS. Third, in patients with mild to moderate CKD, suPAR concentrations show a direct graded association with higher risk for new-onset cardiovascular disease (10), which is in line with numerous studies in various non-CKD populations. These studies point to suPAR as a broad and unspecific marker of subclinical immunologic activity rather than a selective moderator of a single disease entity. In aggregate, serum suPAR cannot currently be considered a valid biomarker for primary or secondary FSGS (11).

The study by Li et al. (12) describes the relationship between suPAR concentrations and steroid responsiveness in 109 patients with biopsy-proven primary FSGS and 138 controls (healthy volunteers [n=96], patients with MCD [n=20], and patients with membranous nephropathy [n=22]). The diagnostic cutoff of 3000 pg/ml as defined in previous studies seems quite reasonable, because in this study, it corresponds to the mean +1.96 SD or around the 97.5 percentile of the distribution of serum suPAR concentrations in healthy volunteers. This threshold is exceeded in 49% of patients with FSGS, 5% of patients with MCD, and 5% of patients with membranous nephropathy, which is in line with the work by Wei et al. (4).

Although of interest, this part of the study does not help us to decide on the usefulness of suPAR as a diagnostic marker. Most importantly, patients with eGFRs below 40 ml/min per 1.73 m² at baseline were excluded. This may have filtered out the significant effects of moderate to severe CKD on suPAR concentrations, thus obfuscating the observed reciprocal relationship between eGFR and suPAR concentrations seen in other studies (8,9). Also, the study population pools results from children and adults with FSGS. Li et al. (12) have partly addressed this issue by performing additional analyses in subgroups, but it remains an open question whether suPAR in young children and middle-aged adult patients actually has the same meaning. Finally, this study includes Asian patients only, whereas patients included in previous studies were of predominantly Caucasian and African-American ancestry. Racial differences in suPAR concentrations have been noted (13), but whether race is a decisive factor in patients with the nephrotic syndrome has not been studied to date.

A great strength and discriminatory feature of the Nanjing cohort in the study by Li et al. (12) is the standardized prospective follow-up of patients. All patients with FSGS were seen at fixed time points, resulting in complete clinical follow-up data and blood results at 6 months for 84 patients. For evaluation of the prognostic value of baseline suPAR concentration on steroid responsiveness, a novel cutoff value was defined (3400 pg/ml) on the basis of the receiver operating characteristic curve analysis. Patients with high suPAR (≥3400 pg/ml) were more likely to show reduction of suPAR concentrations over time and far more likely to reach complete remission (CR; CR=76%) compared with patients with low (<3400 pg/ml) suPAR (CR=28%).

The former should come as no surprise, because it at least partially can be explained by the regression to the mean phenomenon. The latter is, however, of great interest, because it suggests that high suPAR concentrations are indicative of steroid responsiveness. This observation, however, is at odds with a recent study showing equal suPAR in patients with steroid-resistant and steroid-sensitive idiopathic FSGS (8). One potential explanation for these discrepant results could be the exclusion of patients with low eGFR in the Nanjing cohort in the work by Li et al. (12). This raises the hypothesis that suPAR is elevated in patients with FSGS and patients with advanced CKD. In other words,
suPAR may be useful as a diagnostic marker in patients with reasonably preserved kidney function, whereas selectivity of suPAR as an FSGS biomarker is lost in patients with more advanced stages of CKD. Whether suPAR discriminates FSGS in patients with preserved GFR remains an open question.

How should we proceed from here? Although the work by Li et al. (12) is a valuable addition to the existent literature, even more data are needed. Prolongation of follow-up in the Nanjing cohort in the work by Li et al. (12) is likely to provide us with highly relevant findings. It would be informative to have suPAR time profiles of patients reaching complete remission and eventual disease relapse later. Comparative studies in patients from different regions could help to confirm or refute racial interference in patients with FSGS. Mechanistic studies should be designed to understand the renal handling of suPAR, including the effects of the GFR on renal clearance. Additionally, a grouping of the published studies, which for the most part, are cross-sectional, monocentric, and/or of small size, is needed. A meta-analysis could be of great help to test the hypothesis that suPAR concentrations in patients with FSGS and other causes of nephrotic syndrome do not overlap over the entire range of GFR (Figure 1).

In conclusion, the work by Li et al. (12) adds another piece to the suPAR puzzle but fails to complete it. Until we have a better picture of what this puzzle should look like, we do not recommend implementation of suPAR measurements into routine clinical practice.

Disclosures

B.M. reports having received travel grants from Amgen, consultancy and/or lecture fees from Bellco and Menarini, and study grant support from Baxter. B.S. reports having received travel grants and lecture fees from Shire.

References


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Relationship between Serum Soluble Urokinase Plasminogen Activator Receptor Level and Steroid Responsiveness in FSGS,” on pages 1903–1911.