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Targeting Tubulointerstitium to Predict Kidney Outcomes in Childhood Nephrotic Syndrome

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In this issue of *KI Reports*, Gipson *et al.*[1] provide the first evidence for the potential applicability of urinary epidermal growth factor (uEGF) to predict kidney function in children with nephrotic syndrome. Their analysis included 191 children from the National Institutes of Health–sponsored Nephrotic Syndrome Study Network (NEPTUNE Cohort) (62% with a kidney biopsy; 26% with focal segmental glomerulosclerosis [FSGS]) with a median follow-up of 2.5 years. Mixed linear modeling with time-interactions was applied to investigate the effect of different variables on the estimated glomerular filtration rate (eGFR) slope. After adjustment for other risk factors at study entry (age, race, diagnosis, proteinuria) halving of uEGF/creatinine (Cr) ratio was associated with an eGFR decline of 2.0 ml/min per 1.73 m^2 per year. This effect was retained after excluding nonbiopsied patients and when adjusting the analysis for biopsy characteristics (interstitial fibrosis, global sclerosis). In addition, the authors investigated whether uEGF could aid in predicting response to immunosuppressive therapy. However, the analysis did not show any relationship of uEGF with steroid sensitivity at either baseline or at 1-year follow-up.

Caution always should be taken whenever interpreting novel findings of biomarker performance to consider both potential confounding and clinical relevance. Ideally, a novel biomarker should demonstrate ability to predict the development of hard or intermediate clinical endpoints (such as end-stage kidney disease [ESKD] or chronic kidney disease [CKD] progression) and provide complementary information to the existing risk models. The latter has been successfully demonstrated by controlling for a variety of baseline risk factors. The availability of comprehensive information about other risk factors at baseline, in particular the APOL1 genotype, is indeed the most important strength of this study and allows elucidation of the independent predictive value of uEGF. However, because of the slowly progressive course and much lower event rate compared with other CKD populations, modeling the risk of hard clinical endpoints would require very long follow-up and pose many practical challenges. Because of the generally lower risk of ESKD in pediatric nephrotic syndrome, even the risk of mild-to-moderate kidney function decline could be considered a relevant concern in the daily practice of pediatric nephrologists.

uEGF has recently emerged as a highly promising biomarker of CKD progression, largely because of several lines of robust biological, mechanistic, and clinical evidence. First, uEGF was identified as a biomarker of kidney function decline by following an unbiased and exploratory tissue transcriptomics–driven approach where it demonstrated best performance among 72 candidate genes.[2] These findings were well supported by the known biological role of the epidermal growth factor (EGF) pathway in modulating kidney injury and repair.[3] Indeed, urine levels of EGF correlate strongly with intrarenal EGF mRNA expression and also are closely related to histological interstitial fibrosis/tubular atrophy scores.[2] This suggests that lower levels of uEGF may serve as a surrogate measure of reduced functional tubular mass, an indicator of progressive renal injury. None of the conventional biomarkers used to predict kidney function (e.g., proteinuria, hypertension) specifically targeted chronic tubulointerstitial injury, a nearly universal common pathway of CKD progression. Therefore, uEGF appears as an excellent candidate to fill the

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existing gaps in modeling the risk of progressive kidney function decline.

Initial clinical evidence about the predictive performance of uEGF was derived from a large analysis of 3 large independent cohorts of adults with glomerular CKD (Clinical Phenotyping Resource and Biobank Core [C-PROBE], NEPTUNE, and Patients with Immunoglobulin A Nephropathy from Peking University First Hospital, China [PKU-IgAN]). The findings revealed improved risk discrimination by adding uEGF to prediction models for CKD progression based on eGFR and proteinuria.[2] Recently, our group performed a similar analysis to investigate the potential use of uEGF in the pediatric CKD population, in which nonglomerular kidney diseases (congenital anomalies of kidney and urinary tract) are predominant. The analysis of the large Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study Cohort (n = 623; 70% with congenital anomalies of kidney and urinary tract) showed improvement of predictive model performance across all underlying disease groups when uEGF was included among conventional risk factors.[4] Similar findings were made in children with Alport syndrome, in whom uEGF improved the prognostic discrimination between progressors and nonprogressors in addition to proteinuria and baseline eGFR.[5] Altogether, growing evidence suggested uEGF as a universal independent risk biomarker for CKD progression irrespective of age or primary renal diagnosis.

The availability of previous studies of uEGF in different pediatric cohorts offers an opportunity to compare absolute values of uEGF/Cr among children with kidney disease of various etiology and with healthy controls. It is interesting to note that uEGF/Cr values in the overall cohort of children with nephrotic syndrome appear to be comparable to those of healthy children. Surprisingly, uEGF/Cr levels seem to be even higher in the subgroup of nephrotic children who did not undergo a kidney biopsy than those of healthy controls.[5] Although substantially lower in children with FSGS, uEGF/Cr levels in this group did not reach even those of the highest quartile of children with CKD (the 4C Study Cohort).[4] Such comparisons should be interpreted cautiously because of the significant inverse relationship between age and uEGF levels that has been demonstrated in previous pediatric studies.[4,5] Moreover, matching of other baseline characteristics should be performed to allow direct comparisons. These notions, although speculative, may still suggest negligible tubulointerstitial damage at study entry, at least in a certain proportion of the children studied by Gipson *et al.*[1]

Children with nephrotic syndrome represent a unique population of patients with kidney disease. Compared with other risk groups (e.g., congenital anomalies of kidney and urinary tract, adult glomerulopathies) children with nephrotic syndrome have a substantially lower risk of progressive kidney function decline. In particular, children with steroid-sensitive nephrotic syndrome are generally expected to follow a favorable disease course with excellent renal outcomes. This is well illustrated by the findings of a study by Carter *et al.*,[6] published in the current issue of *KI Reports*. The overall incidence of ESKD among 631 children with idiopathic nephrotic syndrome was less than 2%, and approximately 1% in those with initial steroid sensitivity. Of 301 patients with available follow-up data, almost 78% were disease-free at the age of 18 years.[6] However, those with steroid resistance (steroid-resistant nephrotic syndrome) are at a much higher risk of kidney function impairment. During a median 3.7 years of follow-up, 7% of the children from the Carter *et al.*[6] study developed ESKD. Longer-term data from the multicenter PodoNet Registry showed that 58% of children with steroid-resistant nephrotic syndrome had preserved renal function at 10 years, with even worse 10-year renal survival (ESKD-free) in children with multidrug resistance (43%), genetic disease (27%), and FSGS (52%).[7]

Prediction of kidney function decline in the pediatric nephrotic syndrome population may be particularly challenging, as such children frequently have normal kidney function at baseline and demonstrate slow progression rates. Risk stratification ideally should start at disease onset and should be based on models incorporating available clinical data and biomarker results. The study by Carter *et al.*[6] addressed this issue by exploring whether certain clinical and self-reported characteristics at the onset of childhood idiopathic nephrotic syndrome could be predictive of the disease course and kidney outcomes. Such models using easily obtainable data would significantly improve informed decision making and family counseling at the earliest disease stage. However, none of the models comprising baseline data, including initial steroid sensitivity, were predictive of short- or long-term remission, frequent relapses, requirement of second-line therapy, or ESKD.[6] Biomarker research in children with nephrotic syndrome is also scarce and mainly focused on predicting steroid sensitivity or identifying children with FSGS. Although certain biomarkers targeting different pathways of kidney injury (e.g., kidney injury

molecule-1, soluble urokinase plasminogen activating receptor, transforming growth factor-beta) have shown promising results,[8] no clear prediction models or prognostic biomarkers of long-term kidney function have been established or even implemented in clinical practice to date. Therefore, the study by Gipson *et al.*[1] fills an important and unaddressed research gap in pediatric nephrotic syndrome.

In vitro and *in vivo* studies have demonstrated detrimental effects of chronic proteinuria on the tubulointerstitial compartment. These include but are not limited to the induction of interstitial inflammation and activation of apoptotic pathways and the complement system in the tubules, eventually resulting in interstitial fibrosis/tubular atrophy.[9] Based on its known association to the tubulointerstitial injury, uEGF might indeed mirror the prevailing degree of such secondary damage in proteinuric glomerulopathies which is a critical determinant of long-term survival. However, it is important to note the high proportion of patients in the cohort studied by Gipson *et al.*,[1] in particular those with minimal change disease and steroid-sensitive nephrotic syndrome, who are generally not expected to develop CKD progression. Indeed, the eGFR slope of children who did not have a biopsy performed (1.0 ml/min per 1.73 m^2) or those with minimal change disease (−2.3 ml/min per 1.73 m^2) suggests minimal risk of renal function decline compared with FSGS (−5.4 ml/min per 1.73 m^2). It is therefore questionable whether modeling the risk of kidney function decline is actually relevant to all studied patients and whether the effect of uEGF would be even larger if only the patients with higher expected risk of progressive kidney disease were considered.

Overall, the findings of the present study provide several important points. First, it is the first study to suggest a biomarker effectively predicting kidney function decline in children with nephrotic syndrome. Given the paucity of evidence about risk prediction in this population, this is an important step toward developing standardized risk models to predict kidney function decline. Such models would facilitate informed decision making when treatment and follow-up decisions are made. Second, it further expands the use of uEGF to kidney disease populations in which CKD progression is far less likely compared with more progressive kidney disorders. Last, the increasing evidence on the importance of EGF for renal function decline in a wide spectrum of different renal disorders opens the gate to future therapeutic studies targeting EGF and its receptor pathway to attenuate chronic kidney injury and risk of ESKD development. Studies with larger sample sizes and longer follow-ups accompanied by establishing standardized uEGF/Cr cutoff values will be needed to start the implementation of uEGF in routine patient care and should be undertaken in the near future.

DISCLOSURE

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