

Proteinuria: Not a Small Problem in the Little Ones

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Our current state of knowledge regarding the predictive value and pathomechanistic importance of proteinuria in progressive renal failure has been established mostly by studying glomerular disorders usually acquired in adult life, such as diabetic or IgA nephropathy. Chronic kidney disease (CKD) in children is caused by a quite different spectrum of underlying disorders. At least 60% of children with CKD have a variety of hypo- and dysplastic malformations of the kidneys commonly associated with refluxive or obstructive uropathies and termed “congenital anomalies of the kidneys and urinary tract” (CAKUT). Primary glomerulopathies account for only 15 to 20% of pediatric CKD cases and comprise mainly inherited structural disorders of the podocytes. The rest of the spectrum is formed by various rare disorders, including hereditary kidney disorders such as nephronophthisis or Alport syndrome; systemic diseases involving the kidneys, such as hemolytic uremic syndrome, lupus erythematosus, cystinosis, and oxalosis; and development of CKD after peri- or postnatal acute kidney injury.

Few studies have addressed the prevalence, extent, covariates, and prognostic value of proteinuria in this heterogeneous pediatric population. In this issue of *CJASN*, Wong *et al.* (1) characterize proteinuria in a large, unselected pediatric cohort followed in the Chronic Kidney Disease in Children (CKiD) Study. Their report is remarkable for a large sample size and high methodologic quality applied in a multicenter effort, including GFR assessments by iohexol clearance and centralized proteinuria measurements. The cross-sectional analysis at time of enrollment revealed that 75% of pediatric patients with stages 2 through 4 CKD exhibit some degree of proteinuria, although only 14% reach the nephrotic range. Notably, in 81% of the children with “significant” and 52% of those with nephrotic-range proteinuria, CKD was due to nonglomerular disorders, although absolute urinary protein/creatinine levels were 140% higher on average in patients with glomerular diagnoses. Hence, the data provided by Wong *et al.* provide demographic evidence that the majority of children with proteinuria have nephropathies that do not primarily affect the glomerulus. Although the authors did not provide a more detailed analysis of the relative degree of proteinuria in indi-

vidual nonglomerular nephropathies, it can be assumed that the bulk of patients had CAKUT-type disorders.

Irrespective of the nature of the underlying disease, the most important predictor of proteinuria was a low level of GFR. The cross-sectional nature of this study does not allow differentiation of whether heavy proteinuria caused a more rapid progression of CKD or whether proteinuria generally tends to increase with advancing CKD; however, several prospective observational studies of children have provided evidence for an independent link between proteinuria and progression even in children with nonglomerular nephropathies (2–4). As in adult nephropathies, the renal risk conferred by even moderate proteinuria in this population seems to be independent of those of a low baseline GFR and a high BP. Progression of renal failure in these children tends to occur in the second decade of life after an initial period of stable or even increasing GFR. Children who are born with a critically reduced nephron number can be considered an experiment of nature to test Brenner’s hypothesis. That such children tend to develop proteinuria and progressive renal failure even in the absence of active, disease-related damage to renal tissues lends support to the concept of a gradual self-destruction of hyperfiltering nephrons over time.

An as-yet-open question is whether renin-angiotensin system (RAS) antagonists, by virtue of their antiproteinuric properties and on top of their antihypertensive potential, will provide a specific renoprotective benefit to children with nonglomerular disorders. The lack of difference in proteinuria in patients with and without RAS antagonist treatment noted by Wong *et al.* in nonglomerular disorders is very likely to be due to bias by indication. Moreover, the degree of proteinuria is substantially lower in nonglomerular than in glomerular disorders, and the proteinuria reduction achieved by RAS blockade is only partial. Hence, the sensitivity of detecting an antiproteinuric effect of RAS blockade in this population will be limited in a cross-sectional survey. In the prospective ESCAPE trial, the angiotensin-converting enzyme inhibitor (ACEI) ramipril, administered at a standardized dosage, was demonstrated to lower proteinuria, expressed as percentage reduction, equally effectively in children with glomerular and nonglomerular disease (5).

The crucial question that still remains to be answered is whether the short-term antiproteinuric effect of ACEI will translate into improved long-term renal survival in children with CKD, and, if so, which subsets of this heterogeneous population will benefit most. In children with gross proteinuria as a result of glomerular disorders, it may be appropriate to assume similar renoprotective efficacy if RAS antagonists as in nephrotic adults, although a child

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with an inherited structural podocyte defect may not necessarily benefit as much as an adult with acquired diabetic nephropathy. There is even more uncertainty with respect to the nonglomerular disorders: The nephroprotective efficacy of RAS antagonists has not been demonstrated by randomized trial evidence in children. A retrospective analysis of the Italkid registry did not find a significant renal survival benefit in children who had renal hypodysplasia and were receiving ACEI, but the administered dosages were unknown and bias by indication was likely (3). The prospective, randomized Effect of Strict Blood Pressure Control and ACE Inhibition on CKD Progression in Pediatric Nephropathies (ESCAPE) trial, which evaluated the nephroprotective effect of intensified BP control in a large group of children with CKD, was not designed to test the nephroprotective efficacy of RAS blockade, because all patients received the same fixed dosage of an ACEI and no untreated control group was followed. Of note, preliminary analyses from that trial suggested that residual proteinuria on treatment remained quantitatively predictive of renal failure progression (6).

Should all children with CKD receive a RAS antagonist or only those with established proteinuria, and what is the critical level justifying long-term treatment? Even if we assume nephroprotective efficacy of RAS blockade in pediatric nephropathies, it is unclear at which stage of CKD treatment should be initiated. In nonglomerular disorders, proteinuria and progression rates are usually low in stage 2 CKD and increase in a nonlinear manner once a critical number of nephrons has been lost (1,3). Hence, one could argue that children with advanced CKD might benefit most from RAS blockade. Conversely, preventive therapy might be more efficacious in hyperfiltering kidneys with congenitally reduced nephron mass than secondary intervention when severe secondary nephron loss has already occurred. Another problem is the largely unknown safety profile and dosing requirements of most RAS antagonists in children with advanced CKD.

The choice of strategy is facilitated in children with renal hypertension associated with mild to moderate CKD. In this subgroup, comprising at least 30 to 40% of all children with CKD (7), good safety data are available and the threshold to use ACEI and angiotensin receptor blockers as first-choice antihypertensive agents irrespective of the prevailing degree of proteinuria should be minimal.

Another interesting observation in the study of Wong *et al.* is the seeming variation of proteinuria with the ethnic background. According to the multivariate analysis, white individuals seem to exhibit lower proteinuria than other ethnicities at any given GFR, irrespective of the underlying type of disease. Consistent with results of interracial studies in healthy adults and children (8,9), this observation points to potential genetic differences between ethnic groups in the regulation of renal protein handling. Such genetic disposition may contribute, independent of environmental factors, to the faster CKD progression and higher incidence of ESRD in nonwhite populations. The search for the genetic variants

underlying this variation will be one of the most fascinating aspects of renal research in the years to come.

The report by Wong *et al.* in this issue of *CJASN* draws attention to the important unsolved issue of proteinuria in pediatric CKD. Extensive multicenter efforts and long-term prospective studies will be needed to establish efficacious nephroprotective strategies for this small patient group, which comprises less than 1% of the total CKD population. With pharmaceutical industry interest in this population being minimal, the formation of study consortia devoted to pediatric CKD such as CKiD in the United States and ESCAPE in Europe raises hope that the low disease prevalence eventually will not preclude the development of an evidence base for pharmacologic nephroprotection in children.

Disclosures

None.

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See related article, “Association of Proteinuria with Race, Cause of Chronic Kidney Disease, and Glomerular Filtration Rate in the Chronic Kidney Disease in Children Study,” on pages 812–819.