Hypertension in Children With Chronic Kidney Disease
A Call to Action
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In this issue of Hypertension, Flynn et al report novel findings from the Chronic Kidney Disease in Children (CKiD) study on the prevalence of elevated blood pressure in a cohort of children with chronic kidney disease (CKD).1 CKiD is a well-characterized, cohort study to identify risk factors for kidney disease progression in children. It includes 540 children ages 1 to 16 years with CKD (estimated glomerular filtration rate 30 to 75 mL/min per 1.73 m²).2 In this article from the CKiD, the authors report characteristics associated both with high blood pressure and uncontrolled hypertension in children with CKD. The authors used the following definitions: prehypertensive, age-specific blood pressure ≥90th and <95th percentile and hypertensive blood pressure as ≥95th percentile. The presence of hypertension was defined as having either a systolic blood pressure or diastolic blood pressure ≥95th percentile or both a self-reported history of high blood pressure and current treatment with antihypertensive medications. Using these definitions, the authors report a very high prevalence of hypertension (54%) in this cohort. In adjusted analyses, black race was significantly associated with higher blood pressure levels. Among 275 children receiving antihypertensive medications, the authors also reported that 98 (36%) had uncontrolled hypertension. In adjusted analyses, use of angiotensin-converting enzyme inhibitors (ACEIs) was associated with better hypertension control.

What makes this study important? To readers familiar with the hypertension literature in adults, these findings may not seem at all surprising. In adults, hypertension is common among persons with CKD, and hypertension prevalence is higher in blacks than whites. A large proportion of adults with CKD and hypertension remain uncontrolled despite the use of antihypertensives, and ACEIs are recommended as the preferred agent for most patients with CKD and hypertension. The interesting aspect of this study in children is that hypertension among children with CKD has not been well characterized previously, and the management of hypertension in children with CKD is uncertain. Some evidence does suggest that improved blood pressure control may attenuate progression of CKD, but the epidemiology in this field is rather limited.3 In the remainder of this editorial, we offer a brief overview of the public health problem of hypertension in children, an analysis of the key findings of this article, and a comment on the challenges of practicing medicine without clear guidance from hard evidence.

First, this study highlights the growing problem of hypertension in children. Recent reports show that the prevalence of hypertension among children and young adults is rising and may be related to obesity; similarly, the prevalence of type 2 diabetes and impaired fasting glucose are also on the rise among children and young adults.5 It is expected that the prevalence of hypertension among children with CKD would be higher than the general pediatric population; however, the finding that over half of children with CKD met this definition of hypertension in CKiD is astounding. Given the increasing prevalence of obesity, diabetes, and hypertension in children, this problem is likely to escalate as a public health disaster with downstream effects on the incidences of cardiovascular and kidney disease.

Second, the finding that black race was associated with higher blood pressure mirrors the adult hypertension literature. The fact that these racial disparities in prevalence and control of hypertension are present at such young ages raises questions of genetic predisposition of blacks to hypertension. Interestingly, studies have reported higher prevalence of mutations associated with hypertension among blacks.6 Several other mechanisms have been proposed to explain the pathogenesis of hypertension development in blacks, including lower nephron number at birth, lower birth weight,7 and genetic variations in aldosterone synthase or in regulators of the sympathetic nervous system.8 It is also likely that differences in socioeconomic status are important in partially explaining the observed racial differences and that gene–environment interactions may be involved in the pathogenesis of hypertension in blacks.

A third important aspect of this study was the relatively poor rate of controlled blood pressure among children on antihypertensives and the association of ACEI use with better hypertension control. As the authors point out, despite recommendations and guidelines, hypertension control among those with CKD remains a challenge in clinical practice. This has been reported in the adult literature,9 and the reasons for the gap between guidelines and outcomes remain unclear. Because these participants were on therapy, recognition of hypertension was not the culprit. Possibilities include poor compliance, inadequate

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aggression of treating clinicians, or physiological refractoriness to therapy. Interestingly, approximately 55% of the cohort was being treated with ACEI/angiotensin receptor blockers and these agents were associated with higher rates of blood pressure control in this study. CKiD is not a trial, so we cannot discern whether or not the ACEI use was causally related to improved blood pressure control, but this class of drugs has been shown to attenuate progression of CKD among adults with proteinuria and with CKD. Less is known about the possible beneficial effects of this class of drugs in children with CKD. However, current K/DOQI guidelines recommend the use of these drugs in children with CKD (www.kidney.org/professionals/KDOQI/guidelines_bp/guide_13.htm).

The mention of treatment guidelines brings us to the most important issue of this study: hypertension in children with CKD is a growing public health problem, but the evidence for treatment lags far behind. In adults, we have good evidence that control of blood pressure attenuates kidney function decline, and that ACEI/angiotensin receptor blockers are the first-line agents for the treatment of hypertension in CKD. Should we assume that pediatric kidney disease is pathophysiologically similar enough to adult CKD that we can extrapolate the evidence; or, on the contrary, is the adult literature of little value to the treatment of children with CKD? As clinicians, we are commonly faced with the need to extrapolate treatments that are documented to be beneficial in one population to other types of patients. This is of particular importance in chronic diseases such as hypertension and CKD, in which many treatment strategies have not been adequately studied in minorities, women, or the elderly. Randomized clinical trials, our gold standard for evidence-based practice, tend to have inadequate representation of these subgroups of patients as well as those who have the greatest comorbidity.

So, what should the pediatrician do? It seems to us that pediatric providers are faced with a philosophical challenge in deciding on a treatment plan for hypertension in children with CKD. One can take a nihilistic approach and refrain from aggressive treatment of blood pressure in children given the paucity of data for beneficial effects of blood pressure-lowering in pediatric kidney disease. On the other hand, one can extrapolate from the adult literature with the assumption that certain pathophysiological mechanisms are likely to be shared among adults and children with CKD, and the beneficial effects of treating hypertension are likely to be substantial in children with CKD. This decision is critical; the stakes for patients are very high; and pediatric providers will be faced with this conundrum for decades to come.

It may be informative to review the steps that would be required to develop an evidence-based treatment plan for hypertension among children with CKD. First, we need observational evidence that high blood pressure is associated with progression of kidney disease in large, multicentric cohorts of children with all stages of CKD. Second, we would need demonstrations from clinical trials that aggressive treatment of blood pressure reduces the incidence of end-stage renal disease in the pediatric population. Third, randomized clinical trials would need to compare the effects of ACEI/angiotensin receptor blockers and other antihypertensives on kidney disease progression across a multitude of kidney disease stages and etiologies. Even beyond initial therapies, it is likely that children, like adults, will need more than one drug to control blood pressure. Thus, evidence would need to accumulate on the best combination of drugs to treat hypertension in children with CKD. In addition, the long-term effects of these drugs in children need to be evaluated.

Given that it would take decades of research before these questions could possibly be answered and the pediatric population continues to become more obese, to have higher blood pressure levels, and to have higher cardiovascular risk at younger ages, we believe that there is a great danger to inaction. The prevalence of CKD in children is likely to rise along with its associated cardiovascular complications. We hypothesize that hypertension in children with CKD is pathophysiologically similar enough to adults that blood pressure control would be beneficial. Unlike adults with CKD who disproportionately die before end-stage renal disease onset, children with CKD are more likely to reach end-stage renal disease; thus, renal preservation is essential. We forecast that failure to treat hypertension aggressively in the setting of CKD will result in preventable complications. Given the expense and time needed for adequate randomized control trials, ongoing observational studies in children with CKD will be an essential asset for accruing evidence on the effectiveness and safety of antihypertensive agents. Although the pediatric community will ultimately have to decide, we believe that active, intensive measures to treat hypertension in children with CKD should be part of clinical practice. As a well-characterized cohort of children with CKD, the CKid study will be an invaluable tool to answer many of these questions, and we look forward to their longitudinal findings.

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References


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