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Blood pressure in children with chronic kidney disease: Lessons learned from the Chronic Kidney Disease in Children Cohort Study

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Abstract

Cardiovascular disease (CVD) is common amongst children and adolescents with chronic kidney disease (CKD) and end-stage kidney disease (ESRD). However, the early accrual of CVD risk factors in children with CKD has not been well studied. The Chronic Kidney Disease in Children (CKiD) Study, a multicenter, prospective cohort study of children with mild-to-moderate CKD at study entry counts among its primary aims investigation of the drivers of CVD risk in this population. As the most prevalent CVD risk factor in children with CKD, blood pressure (BP) has been a major focus of investigation for the CKiD Study Group. Over the first 15 years of the study, landmark publications have better defined the prevalence of hypertension, the frequency with which it is under-recognized and thus undertreated, and the consequences of elevated BP in this cohort. The purpose of this review is to summarize the contributions made by the CKiD Study in advancing knowledge of BP in this high-risk population, and to highlight areas in need of further study.

Keywords

Children; Chronic kidney disease; Cardiovascular disease; CKiD; Hypertension; risk factors; progression

Introduction

Chronic kidney disease (CKD) is well-established as a high-risk condition for development cardiovascular disease (CVD), and CVD is in fact the leading cause of death in patients with

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end-stage renal disease (ESRD), accounting for nearly 50% of deaths in adults with ESRD [1]. The data are more alarming for young CKD patients, as CVD-specific mortality rates in children and young adults with ESRD are increasing over time [2] and are up to 1000 times higher than in comparably aged populations without CKD [3]. CVD further accounts for much of the excess mortality in adult survivors of childhood-onset ESRD, and has been found to be responsible for 30–40% of deaths among these patients [4]. In 2003, the National Institutes of Health established the Chronic Kidney Disease in Children (CKiD) study [5]. Improving the understanding of the prevalence and the evolution of both traditional and novel cardiovascular risk factors in children with CKD is among the study's primary aims. A summary of the CKiD study visit schedule and laboratory/imaging periodicity has been published previously [5]. To date, over 1000 children have completed at least one study visit at over 50 sites across the US and Canada, and over 30 papers have been published on various aspects of CVD in this cohort. The purpose of this educational review is to summarize the contributions of the CKiD Study to the understanding of hypertension in pediatric CKD patients, and its impact on overall CV health and CKD progression in this population of uniquely at-risk children.

Hypertension Prevalence

Prior to the inception of CKiD, few studies had rigorously examined the prevalence of hypertension in large cohorts of children with CKD, nor was the association between severity of hypertension and development of progressive kidney damage well quantified, though NAPRTCS data suggested that hypertension was common [6] and likely associated with more rapid deterioration of kidney function [7]; another smaller study, primarily focused on the impact of protein intake on CKD progression, had also previously indicated increased risk for progression of CKD in children with higher systolic blood pressure (BP) [8]. One of the first CKiD publications was a report of casual BP measurements taken at the initial/baseline study visit [9]. In total, 54% of children in the cohort had either hypertensive range BP (either systolic or diastolic BP equal to or exceeding 95th percentile values for age, gender, and height) or had a documented history of hypertension plus current antihypertensive medication use. More worrisome was the finding that uncontrolled and/or unrecognized hypertension was common. Among study participants who reported taking antihypertensive medications, 35% had BP above the 90th percentile, and among the 37% of study participants who had an elevated systolic or diastolic BP at time study entry, nearly 40% were prescribed no antihypertensive medication.

CKiD has further allowed the investigation of the comparability of auscultatory and oscillometric casual BP readings, detailed in a 2012 publication by Flynn et al. [10]. This study demonstrated that (in a highly standardized research clinic environment) oscillometric readings were, on average, higher than auscultatory readings (by 9/6 mmHg) and resulted in misclassification of BP in a substantial percentage of patients, underscoring the importance and continued relevance of auscultatory BP measurement as standard of care in this population.

The understanding of the prevalence of hypertension in this population was subsequently refined with publication of initial 24-hour ambulatory BP monitoring (ABPM) results in the

cohort [11], which demonstrated that 44% of the CKiD cohort had normal BP (both normal casual BP and normal ABPM), 4% had white-coat hypertension (elevated casual BP with normal ABPM), 37% had masked HTN (normal casual BP with abnormal ABPM), and 15% "confirmed" hypertension (elevated casual BP with abnormal ABPM). These rates stand in stark contrast to findings described in cohorts of children without renal disease, in whom rates of white coat hypertension are reported to approach 50% (among children being evaluated for elevated casual BP) [12, 13], and in whom masked hypertension is far less common, found in only around 6% of unselected children evaluated with ABPM [14]. Self-report of use of an ACE inhibitor was found to be significantly associated with higher odds of having normal BP.

The high prevalence of masked hypertension observed in the cohort led to the additional question of whether there are patients in whom casual BP readings are so low as to accurately predict low risk for masked hypertension. Mitsnefes et al. investigated this in a recent publication [15]; among the 506 patients with a normal (<90 percentile) casual BP, indeed those with the lowest level (<25th percentile) of casual BP had the lowest rates of masked hypertension. However, it is important to note that even among this group of patients, with seemingly very well controlled BP as assessed in clinic, the frequency of abnormal mean wake or sleep BP ranged from 2–7%, and elevated BP load (i.e.>25% of ABPM readings above 95th percentile) was observed in 6–16%. Further, as 25th percentile limits for BP are not readily available without the use of specialized calculators, routine clinical use of this threshold as a casual BP limit at which management is to be modified could be cumbersome.

In the years following publication of the early CKiD BP data, which illustrated clearly that children with CKD were not achieving recommended BP targets, one might have speculated that BP control in children with CKD overall, and specifically within the CKiD cohort, would improve. Unfortunately, the longitudinal data from the CKiD cohort demonstrate this is not the case. A recent publication comparing casual BP and ABPM data from the period of 2005–2008 to that from 2010–2013 demonstrates clearly that hypertension remains under-recognized and undertreated, with essentially no change in rates of uncontrolled HTN as assessed by casual BP (17% in the recent period versus 18% in the early cohort), and with worsening in rates of masked HTN (49% vs 37%) on ABPM [16]. What CKiD cannot answer, of course, is what the underlying reasons for lack of improvement over time may be. One might speculate that lack of improvement in BP in the cohort may reflect lack of routine utilization of ABPM in clinical practice (thus leading to non-diagnosis of masked hypertension), for any of many reasons: physician non-adherence to clinical practice guidelines for ABPM use, poor patient adherence to MD recommendations for ABPM (inconvenience, discomfort of study), or restricted ability/inability to offer ABPM routinely due to either the expense of the equipment or to limits in reimbursement. In this regard, CKiD's work in the area of hypertension has recently informed publication of American Academy of Pediatrics recommendations for routine/annual ABPM in children with CKD [17]. Poor rates of control may alternatively reflect that hypertension control in children with CKD may simply be difficult to achieve, either because of medication non-adherence, medication side effects that limit use of specific antihypertensive medications, or other issues.

Correlates of hypertension

In the early, cross-sectional examination of BP in the first CKiD cohort, it was observed that being on antihypertensive medication, specifically an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), was associated with higher likelihood of controlled BP. Boys, and those with a shorter duration of CKD, were also observed to be more likely to have poor BP control. There were significant racial disparities observed within the cohort, with black children 63% more likely to have elevated systolic BP and 79% more likely to have elevated DBP than white children; this is despite the fact that all participants were known, at time of enrollment, to be regularly receiving CKD care at tertiary care pediatric nephrology centers across the US & Canada [9].

In a separate analysis, primarily focused on associations between proteinuria and longitudinal BP control, children with nephrotic range proteinuria (spot urine protein:creatinine ratio >2 mg/mg) were least likely to achieve control of BP over time (relative sub-hazard (RSH) 0.19). Racial disparities were observed in this longitudinal data analysis which mirrored those seen in the cross-sectional data, with black children also less likely to achieve BP control than white children (RSH 0.42). Children with lower baseline eGFR <40 mL/min/1.73m^2 were also more likely to have poor BP control (RSH 0.58) [18]. These associations were found to be consistent in longitudinal data analysis as well, with prevalent renin angiotensin II-aldosterone system (RAAS) blocker users being both less likely to have elevated BP and less likely to progress to ESRD over the time period studied (21% vs. 37% among patients not on RAAS blockade) despite those patients being older, having more proteinuria, and more likely to have glomerular disease than their counterparts not on RAAS blocking agents [19].

Data from ABPM inspecting correlates of hypertension has also demonstrated that only being on treatment with RAAS blockers (among antihypertensive medications) is associated with higher odds of having a normal 24-hour BP study [11]. In contrast to data from the non-CKD pediatric population, ABPM data from the CKID study do not show any clear association between birth history and hypertension risk [20]. Finally, in an analysis of ABPM data among children in the cohort who were not on antihypertensive medications and did not carry a pre-existing hypertension diagnosis, increased systolic BP variability was observed in study participants who were found to be hypertensive (in comparison to study peers found to have ambulatory normotension). Increased diastolic BP variability during sleep and decreased heart rate variability overall were found in the hypertensive patients as well. Systolic BP variability was higher among those with more time in follow up and with a higher percentage of total lifespan spent with CKD [21]. These data suggest that, as in adults [22], aberrant autonomic nervous system function (specifically, over-activity) may play a role in the origin and progression of CVD in this population. Clearly, further study is needed to understand how specific hypertension treatment strategies (i.e. those which reduce autonomic over-activity) may reduce long-term CVD risk in adults with childhood onset CKD.

Consequences of hypertension

Although CVD is an important long-term cause of morbidity and mortality in patients with CKD, these events rarely occur during childhood. However, the CKiD study has examined several surrogate markers of CVD that are detectable in the young, including left ventricular hypertrophy (LVH), abnormal left ventricular geometry, increased carotid intima-medial thickness (cIMT) and abnormal pulse wave velocity (PWV).

Consistently across studies in this cohort, poorly-controlled BP emerges as a strong association with LVH. The earliest data to emerge, published in 2010 by Mitsnefes et al., comprised cross-sectional observations regarding associations between LVH and data from ABPM studies in the earliest CKiD cohort [23]. In this study, LVH, defined as left ventricular mass indexed to height^2.7 >95th percentile for gender and age, was found to be present in one-third of the cohort with sustained ambulatory hypertension. However, the more striking finding of the study was that in children with moderate CKD, LVH was also seen in 20% of children who had been found to have masked hypertension, versus only 8% of normotensive children. This of course suggested that routine assessment of ambulatory BP patterns should play an important role in the routine clinical care for this population, and that it may be more important than clinic BP as a predictor of risk to accrue end organ damage.

However, there are equally compelling data that highlight the importance of casual BP control as it pertains to LVH risk. Kupferman et al. investigated the impact of casual BP control on regression of LVH in 478 CKiD participants; their analysis found that overall, the prevalence of LVH declined over the three years studied (from 16 to 11 %)[24], and that there was a clear relationship between higher systolic BP and increase in left ventricular mass index over time. ABPM data was not incorporated into this study. Notably, use of antihypertensives other than RAAS blockers at baseline again emerged as predictive of increased CVD risk, and was found to be a significant predictor of development of LVH. A more recent analysis by Ku et al., also suggests that for BP outcomes such as either progression to ESRD or development of LVH, clinic BPs may still play an important prognostic role [25]. In this analysis, clinic systolic BP was found to be a slightly stronger predictor of development of LVH than was mean wake BP on a 24 study. For ESRD risk prediction, both clinic systolic BP and mean wake BP performed similarly. Given the relative difficulty and expense of obtaining an ABPM (which may limit the frequency of study to no more than once a year even in relatively highly-resourced settings), it seems the true “message” from the CKiD cardiovascular data is that both regular, high-quality, auscultatory clinic BPs and routine ABPM have important roles to play in monitoring hypertension. Further, when treatment for hypertension is indicated, preferential use of ACE inhibitors or ARBs (if feasible) may have particularly significant long-term benefits in this population.

Examination of carotid intima-media thickness (cIMT) has emerged recently as another means by which to assess early cardiovascular disease development in children. An early (i.e. cross-sectional, at year 2 of study) evaluation of cIMT in the CKiD cohort revealed that among the study participants, median cIMT was thicker than in healthy pediatric controls

(0.43 mm vs. 0.41 mm, p for difference, 0.03). Further, in multivariable linear regression analysis, both hypertension (defined as either use of antihypertensive medication, reported history of hypertension, or mean BP at time of study visit above 95th percentile limits) and dyslipidemia were found to be independently associated with higher cIMT, by 0.04 mm (95% CI, 0.003–0.08mm) and 0.05 mm (95% CI, 0.01–0.08), respectively. Interestingly, no such associations were found with BMI, CKD etiology, or severity of renal dysfunction [26]. The conclusions that can be drawn from this finding are limited given the cross-sectional nature of the data presented; however, the CKiD protocol allows for serial assessments of cIMT (with repeat cIMT at year 6 of study at selected sites), which may allow future work to draw additional conclusions in regards to the impact of achieving BP control on markers of vascular health.

Another potential target organ effect of hypertension in CKD is vascular stiffness. Increased vascular stiffness has been linked with both CKD progression and mortality in adults with CKD [27]. However, in a study of 95 children in the CKiD cohort who underwent assessment of carotid-femoral PWV by applanation tonometry, while PWV did increase with age and BP, there were no significant differences compared to pediatric normative data for PWV [28]. This is in contrast to findings published in small pediatric cross-sectional studies, in which a relationship between higher PWV and CKD has been observed [29]. Finally, although baseline data from the 4C study demonstrated that a significant proportion (20%) of participants had increased PWV, there was no graded increase in likelihood of high PWV across stages of worsening CKD observed [30]. It is possible that the duration of CKD in the CKiD cohort was too short to see a statistically significant impact on PWV; these conflicting results highlight the importance of gathering longitudinal data from larger cohorts as is planned for the 4C study.

Importantly, the multiple areas of focus within the CKiD study (Growth/Nutrition, Neurocognitive, Cardiovascular, and Progression) have also allowed for robust investigation of the non-cardiovascular disease-related impacts of hypertension in this cohort. Lande et al. reported an association (in cross-sectional analysis) between lower performance IQ scores and increased BPs, which persisted even after controlling for a variety of demographic and disease-related variables thought likely to impact neurocognitive outcomes [31] Specifically, it appeared that observed difficulties with visuo-spatial organization and visuo-constructive ability among children with CKD may be in part related to elevated BP. A follow up cross-sectional and longitudinal analysis of the relationship between BP variability (assessed by both visit-to-visit variability of clinic BP and by standard deviation of sleep and wake BPs on 24 hour ABPM) and neurocognitive test results was published in 2016 [32]. Again, significant findings were in the realm of executive function, this time revealing an association between increased visit-to-visit systolic BP variability (BPV) and worse performance on a category switching subtest of verbal fluency (specifically, the D-KEFS Verbal Fluency Test), which is a measure of cognitive efficiency and processing speed. As some antihypertensive medications are known to reduce BPV in addition to lowering mean BP levels [33], these findings at least raise the question of whether specifically treating hypertension with medications that blunt BPV may lead to cognitive benefits in children with CKD. Notably, though, ACE inhibitors and ARBs are among the drug classes which have been observed to increase rather than decrease BPV in adults, while calcium channel

blockers (CCBs) are observed to decrease BPV, but do not share the beneficial effects on proteinuria lowering and improved renal survival that are associated with RAS blockade in this cohort. Clearly, further investigation is warranted before any change in routine treatment practices could be considered.

Perhaps obviously, the impact of hypertension on progression of CKD to ESKD is a preeminent concern in this population, and is truly the only “hard outcome” of hypertension that is readily studied in this age group. In addition to the Ku study discussed previously, and as has also been demonstrated by the ESCAPE study group [34], BP control is a major determinant of renal survival in children with CKD. The CKiD study has demonstrated clearly an association between higher BPs and more rapid progression of CKD in this cohort of children, regardless of type of CKD (i.e. glomerular disease vs. non-glomerular disease origin). Specific to glomerular disease, ill-controlled BP (i.e. BP >90th percentile as defined by the Fourth Report on Hypertension in Children [35]) was demonstrated to reduce by 67% the time to the composite event, defined as either reaching need for renal replacement therapy or reaching 50% decline in GFR [36]; among children with non-glomerular disease the impact of ill-controlled BP was somewhat less but clinically and statistically significant nonetheless, reducing time to composite event by 38%. The relationship between BP and GFR decline was further delineated in a follow up study limited to just the sub-cohort (n=522) of CKiD participants with non-glomerular CKD, which confirmed an association between higher baseline BP (specifically systolic BP z-scores) and more rapid rate of GFR decline, which persisted in multivariate analysis [37]. Interestingly, this relationship was not significantly attenuated or exacerbated by absence or presence of significant proteinuria; rather, children with either proteinuria or higher BP appeared to have similar progression of GFR decline as children with both risk factors.

Finally, it is known that hypertension associates with adverse impact on health-related quality of life (HRQoL) measures in adults. The CKiD investigators thus sought to assess, given the high prevalence of hypertension in the cohort, its impact on HRQoL in children. Interestingly, though some mild associations between elevated BP and slightly lower HRQoL scores were observed in cross-sectional univariate analysis, these did not persist in longitudinal or multivariate analyses [38]. Further, neither use of antihypertensive medications nor number of antihypertensive medications appeared to have an impact on HRQoL. The reasons for the differences between this cohort and the existing adult literature are not fully understood, but one might speculate this is because children typically have few, if any, physically limiting health effects related to hypertension or its cardiovascular comorbidities, or that CKD-related symptoms may dominate over hypertension-specific symptoms, thus masking any effect of the symptoms specific to hypertension in this particular cohort.

Conclusions

Though first measured in humans well over a century ago, BP remains a vexing problem in children with CKD. The CKiD Study has advanced the science of BP in childhood CKD in a variety of ways, both in elucidation of optimal measurement techniques and in assessment of the consequences of poor BP control. Despite this, there remain a variety of questions yet to

be answered. In particular, there remain gaps in our understanding of how best to manage BP in children with CKD in order to prevent altogether or forestall worsening of CVD precursor conditions, and in our understanding of how various end-organ effects of dysregulated BP might demand differing treatment strategies.

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Study Questions

1. In children with mild-to-moderate chronic kidney disease, what technique for in-office blood pressure measurement is considered the gold standard for classification of blood pressure status?

- **a.** Blood pressure measured manually by auscultation
- **b.** Blood pressure measured automatically by oscillometry
- **c.** Blood pressure measured automatically by ABPM
- **d.** Blood pressure measured by auscultation and by oscillometry

2. A 15-year-old girl with stage 3 chronic kidney disease undergoes ambulatory blood pressure monitoring. The study shows normal mean blood pressure while awake, elevated mean blood pressure while asleep and normal nocturnal blood pressure dipping. Based on findings from CKiD, for which of the following patterns of additional findings is the patient at highest risk?

- **a.** She would have normal carotid intima-media thickness and abnormal echocardiography
- **b.** She would have abnormal carotid initima-media thickness and abnormal pulse wave velocity
- **c.** She would have abnormal echocardiography and normal pulse wave velocity
- **d.** She would have abnormal echocardiography, abnormal carotid intima medial thickness and abnormal pulse wave velocity

3. The chances of rapid progression of chronic kidney disease in children are increased the most when what sequence of events occurs?

- **a.** Blood pressure is normal at baseline and hypertension develops two years later
- **b.** Blood pressure is elevated at baseline but is controlled with medication
- **c.** Blood pressure is normal at baseline and remains normal two years later

4. Left ventricular hypertrophy has been associated with what blood pressure pattern in children with chronic kidney disease?

- **a.** Nocturnal hypertension
- **b.** Masked hypertension
- **c.** White coat hypertension
- **d.** Pre-hypertension
- **e.** All of the above

5. In children with chronic kidney disease, increased carotid-intima thickness correlates with what other finding?

- **a.** Left ventricular hypertrophy
- **b.** Hypertension
- **c.** Nephrotic-range proteinuria
- **d.** Rapid CKD progression

Answers to questions

1-a, 2-c, 3-a, 4-e, 5-b