

# Nephrotic-range proteinuria is strongly associated with poor blood pressure control in pediatric chronic kidney disease

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Despite the importance of blood pressure (BP) control in chronic kidney disease (CKD), few longitudinal studies on its trends exist for pediatric patients with CKD. Here we longitudinally analyzed casual data in 578 children with CKD and annual BP measurements standardized for age, gender, and height. At baseline, 124 children were normotensive, 211 had elevated BP, and 243 had controlled hypertension. Linear mixed-effects models accounting for informative dropout determined factors associated with BP changes over time and relative sub-hazards (RSH) identified factors associated with the achievement of controlled BP in children with baseline elevated BP. Younger age, black children, higher body mass index, and higher proteinuria at baseline were associated with higher standardized BP levels. Overall average BP decreased during follow-up, but nephrotic-range proteinuria and increased proteinuria and body mass index were risk factors for increasing BP over time. Only 46% of hypertensive patients achieved controlled BP during follow-up; least likely were those with nephrotic-range proteinuria (RSH 0.19), black children (RSH 0.42), and children with baseline glomerular filtration rate under 40 ml/min per 1.73 m<sup>2</sup> (RSH 0.58). Thus, of many coexisting factors, nephrotic-range proteinuria was most strongly associated with poor BP control and worsening BP over time. Future research should focus on strategies to reduce proteinuria, as this may improve BP control and slow the progression of CKD.

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Hypertension (HTN) is common in patients with chronic kidney disease (CKD). Previously, we demonstrated that 54% of children in the Chronic Kidney Disease in Children (CKiD) observational cohort study had evidence of HTN, and 36% of those on antihypertensive medications had uncontrolled blood pressure (BP) at the time of study entry.<sup>1</sup> Risk factors for elevated BP included black race, shorter duration of CKD, and the absence of therapy with an antihypertensive medication. The high prevalence of HTN in this vulnerable population is of concern, as lower BP slows the progression of CKD.<sup>2,3</sup>

Despite the importance of BP control in CKD, few longitudinal data on BP trends exist in either pediatric or adult CKD patients. We do not know whether HTN remains stable or worsens over time, and we do not understand the long-term contributions of specific clinical factors to changes in BP. This gap in our knowledge limits our ability to predict which patients will remain hypertensive and which children's HTN will be more easily controlled, thereby limiting our management strategies. Given its longitudinal design, the CKiD study offers a unique opportunity to characterize longitudinal BP patterns in children with mild-to-moderate CKD.

In this study, we examined longitudinal casual BP data available from the CKiD cohort. Our specific aims were to: (1) determine clinical and demographic factors associated with longitudinal BP changes in children with CKD and (2) identify factors associated with the achievement of controlled HTN in children with previously elevated BP.

## RESULTS

### Cohort characteristics

Between January 2005 and December 2010, 586 children enrolled in CKiD. Of these, 581 had at least one casual systolic BP (SBP)/diastolic BP (DBP) measurement that could be standardized for age, sex, and height (SBPz and DBPz). Three children without self-reported history of HTN data could not be classified by their baseline BP status and were excluded, leaving 578 children available for analysis.

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**Table 1 | Baseline characteristics, overall and by baseline BP status**

| Characteristic <sup>a</sup>             | Overall (N = 578) | Baseline BP status     |                      |                    | P <sup>b</sup>    |
|-----------------------------------------|-------------------|------------------------|----------------------|--------------------|-------------------|
|                                         |                   | Normotensive (N = 124) | Controlled (N = 243) | Elevated (N = 211) |                   |
| Age, years                              | 11 (7, 14)        | 9 (5, 13)              | 12 (9, 15)           | 10 (6, 15)         | <0.001            |
| Male, %                                 | 62 (359)          | 65 (80)                | 54 (132)             | 70 (147)           | 0.003             |
| Black race, %                           | 23 (134)          | 20 (25)                | 21 (50)              | 28 (59)            | 0.13              |
| Hispanic ethnicity, %                   | 14 (82)           | 12 (15)                | 14 (34)              | 16 (33)            | 0.67              |
| Glomerular CKD, %                       | 22 (127)          | 5 (6)                  | 28 (68)              | 25 (53)            | <0.001            |
| GFR, ml/min per 1.73 m <sup>2</sup>     | 44 (33, 57)       | 48 (39, 62)            | 41 (32, 54)          | 45 (32, 58)        | <0.001            |
| <i>Duration of CKD, years</i>           |                   |                        |                      |                    |                   |
| Non-glomerular                          | 7 (4, 11)         | 6 (3, 9)               | 9 (5, 12)            | 6 (3, 10)          | <0.001            |
| Glomerular                              | 4 (2, 7)          | 5 (1, 8)               | 4 (2, 8)             | 3 (2, 6)           | 0.64              |
| Urine protein/creatinine                | 0.46 (0.16, 1.20) | 0.32 (0.12, 0.77)      | 0.51 (0.19, 1.17)    | 0.57 (0.20, 1.50)  | 0.001             |
| 0.2–2.0                                 | 57% (321)         | 52% (62)               | 60% (141)            | 58% (118)          |                   |
| > 2.0                                   | 14% (78)          | 8% (10)                | 13% (31)             | 18% (37)           |                   |
| BMI percentile                          | 65 (35, 89)       | 52 (29, 83)            | 66 (37, 90)          | 69 (39, 92)        | 0.006             |
| (85–95)                                 | 14% (82)          | 15% (18)               | 14% (33)             | 15% (31)           |                   |
| > 95                                    | 17% (94)          | 8% (10)                | 18% (44)             | 20% (40)           |                   |
| Antihypertensive use, %                 | 63 (362)          | 0% (0)                 | 95% (232)            | 62% (130)          | n/a               |
| ACE/ARB, %                              | 54 (314)          | 0% (0)                 | 88% (213)            | 48% (101)          | n/a               |
| Calcineurin inhibitor, %                | 2 (10)            | 0% (0)                 | 2% (4)               | 3% (6)             | 0.17              |
| Corticosteroid, %                       | 7 (38)            | < 1% (1)               | 8% (20)              | 8% (17)            | 0.005             |
| Total follow-up, years                  | 4.1 (2.1, 5.4)    | 4.9 (3.1, 5.5)         | 4.1 (1.7, 5.3)       | 3.9 (2.0, 5.8)     | 0.023             |
| Number of BP measures over follow-up    |                   |                        |                      |                    | 0.02 <sup>c</sup> |
| 1–2                                     | 13% (75)          | 7% (9)                 | 14% (35)             | 15% (31)           |                   |
| 3–4                                     | 22% (126)         | 14% (17)               | 25% (60)             | 23% (49)           |                   |
| 5–6                                     | 31% (180)         | 40% (50)               | 27% (66)             | 30% (64)           |                   |
| 7+                                      | 34% (197)         | 39% (48)               | 34% (82)             | 32% (67)           |                   |
| Observed progression to RRT or death, % | 29% (168)         | 17% (21)               | 30% (74)             | 35% (73)           | 0.002             |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; RRT, renal replacement therapy.

Missing data: uP/C, *n* = 19; BMI percentile, *n* = 10; Hispanic ethnicity, *n* = 8; years of CKD, *n* = 10.

<sup>a</sup>At baseline, unless otherwise indicated. Median (interquartile range) for continuous variables; percent (frequency) for categorical variables.

<sup>b</sup>For comparison of the three baseline BP status groups. Based on Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables, unless otherwise indicated.

<sup>c</sup>Based on  $\chi^2$ -test for independence.

Subjects' baseline characteristics are summarized in Table 1. Subjects had a median age of 11 years, 62% were male, 23% were of black race, and 14% were of Hispanic ethnicity. Twenty-two percent of children were diagnosed with glomerular CKD, and the median glomerular filtration rate (GFR) was 44 ml/min per 1.73 m<sup>2</sup>. The use of antihypertensive medications was common (63%).

Of the 578 subjects, 124 (21%) were normotensive, 211 (37%) had elevated BP, and 243 (42%) had controlled HTN. As a group, normotensive children were slightly younger, less likely to have glomerular CKD, and had higher baseline GFRs, lower urine protein-to-creatinine ratio (uP/C; mg/dl:mg/dl), and lower body mass index (BMI) percentiles than those with elevated or controlled BP. Children with elevated BP were disproportionately male, and had the highest average uP/C levels and BMI percentiles of the three groups. Baseline normotensive patients were the least likely to progress to renal replacement therapy (RRT).

#### Longitudinal patterns of standardized SBP and DBP

Overall, a significant decrease over time in SBPz and DBPz was observed in the cohort. In univariate analysis, overall mean SBPz at baseline was 0.385 standard deviation scores (SDs; 95% confidence interval (CI): 0.296, 0.473) with an

average decrease of 0.038 SDs/year (95% CI: –0.060, –0.015; *P* = 0.001). Factors associated with higher SBPz level included younger age, black race, use of a non-ACE/ARB (angiotensin-converting enzyme/angiotensin receptor blocker) antihypertensive therapy at baseline, and higher baseline BMI z-score (BMIz) and uP/C.

In addition, baseline GFR and age significantly modified change in SBPz over follow-up. Specifically, children with baseline GFR  $\geq 40$  ml/min per 1.73 m<sup>2</sup> had an average SBPz decline of 0.052 SDs/year (95% CI: –0.079, –0.025), whereas children with baseline GFR  $< 40$  ml/min per 1.73 m<sup>2</sup> had little change in their SBPz over time (–0.006 SDs/year, 95% CI: –0.044, 0.032; *P* = 0.04 for difference between GFR  $\geq 40$  vs.  $< 40$  ml/min per 1.73 m<sup>2</sup>). Similarly, children with baseline age  $< 11$  years had an average SBPz decline of 0.067 SDs/year (95% CI: –0.096, –0.038), whereas children with baseline age  $\geq 11$  years had no change in their SBPz over time (–0.003 SDs/year, 95% CI: –0.037, 0. –0.031; *P* = 0.004 for difference between baseline age  $\geq 11$  vs.  $< 11$ ). Other baseline factors that presented as possible (although non-significant) modifiers of SBPz change over time were uP/C  $\geq 2$  (*P* = 0.12) and male sex (*P* = 0.06).

Overall, mean DBPz at baseline was 0.529 SDs (95% CI: 0.460, 0.599) and decreased on average 0.051 SDs/year

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