Longitudinal Associations between Low Serum Bicarbonate and Linear Growth in Children with CKD

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Key Points
- Poor linear growth is common in children with CKD, and identifying modifiable risk factors is crucial to improving pediatric CKD care.
- Our study shows a negative longitudinal association between metabolic acidosis and linear growth in children with varying CKD severity.
- We found that persistent use of alkali therapy was associated with improved linear growth in children with CKD.

Abstract
Background Poor linear growth is a consequence of chronic kidney disease (CKD) that has been linked to adverse outcomes. Metabolic acidosis (MA) has been identified as a risk factor for growth failure. We investigated the longitudinal relationship between MA and linear growth in children with CKD and examined whether treatment of MA modified linear growth.

Methods To describe longitudinal associations between MA and linear growth, we used serum bicarbonate levels, height measurements, and standard deviation (z scores) of children enrolled in the prospective cohort study Chronic Kidney Disease in Children. Analyses were adjusted for covariates recognized as correlating with poor growth, including demographic characteristics, glomerular filtration rate (GFR), proteinuria, calcium, phosphate, parathyroid hormone, and CKD duration. CKD diagnoses were analyzed by disease categories, nonglomerular or glomerular.

Results The study population included 1082 children with CKD: 808 with nonglomerular etiologies and 274 with glomerular etiologies. Baseline serum bicarbonate levels ≤22 mEq/L were associated with worse height z scores in all children. Longitudinally, serum bicarbonate levels ≤18 and 19–22 mEq/L were associated with worse height z scores in children with nonglomerular CKD causes, with adjusted mean values of −0.39 (95% CI, −0.58 to −0.2) and −0.17 (95% CI, −0.28 to −0.05), respectively. Children with nonglomerular disease and more severe GFR impairment had a higher risk for worse height z score. A significant association was not found in children with glomerular diseases. We also investigated the potential effect of treatment of MA on height in children with a history of alkali therapy use, finding that only persistent users had a significant positive association between their height z score and higher serum bicarbonate levels.

Conclusions We observed a longitudinal association between MA and lower height z score. Additionally, persistent alkali therapy use was associated with better height z scores. Future clinical trials of alkali therapy need to evaluate this relationship prospectively.

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Introduction
Linear growth impairment is a consequence of CKD that has been associated with profound risk for adverse outcomes (1–3). In an early investigation from the Pediatric Growth and Development Special Study, every 1 SD decrease in height was an associated 14% increased risk for death (1). Similarly, in the North American Pediatric Renal Trials and Collaborative Studies, compared with children with heights at or above the 1st percentile, children with heights below the 1st percentile had a two-fold higher risk of death (4). Poor growth also has profound psychosocial effects. Children with CKD who suffer from short stature report lower physical functioning scores on health-related quality of life assessment tools (2,3). Higher parental scores report lower physical functioning scores on health-related quality of life assessment tools (2,3). Higher parental scores of physical and social functioning have been associated with increases in height z score (3). Given that growth failure is estimated to affect up to 35% of the pediatric CKD population (5), it is important to understand factors that contribute to short stature in order to manage these patients better.

The etiology of growth failure in pediatric CKD is complex, but numerous studies point to metabolic acidosis (MA) as a contributing factor (6–11). The theorized mechanism involves disturbances of growth hormone (GH), and its mediating hormone, IGF-1 (12–14). MA has been reported to impair GH secretion, reduce hepatic IGF-I mRNA, and alter concentration of and sensitivity to IGF-1. Baseline data from the Chronic Kidney Disease in Children (CKiD) study show that as many as one third of children with mild to moderate CKD have low serum bicarbonate levels, a proxy for MA (7,15,16). In a cross-sectional analysis of the CKiD cohort, Rodig et al. found that children with a serum bicarbonate of <18 mEq/L had a height SD score that was 0.67 lower than for those with a serum bicarbonate ≥22 mEq/L (95% confidence interval [95% CI], −1.03 to −0.31) (7). Additional support for the negative effect of MA on linear growth in pediatric CKD is the extremely high prevalence of growth failure in children with renal tubular acidosis (RTA) (9–11). However, it must be stated that these studies were small in number and largely only included children with normal eGFR. Alkali therapies (bicarbonate, citrate-containing solutions), used for the treatment of chronic MA, are widely available and well tolerated (17). Despite the reported association between MA and linear growth impairment and the availability of tolerable treatment options, treatment rates of MA remain suboptimal, with only one third of children with low serum bicarbonates in CKiD reporting treatment with alkalinizing agents (7,16). Given the prevalence of MA, low reported rates of treatment, and the profound effect of growth failure, longitudinal studies that include children with impaired kidney function are needed to inform management practices better. In this study, we described and characterized the longitudinal relationship between low serum bicarbonate, a surrogate for MA, and linear growth in children enrolled in the CKiD study. We hypothesized that low serum bicarbonate would be associated with lower height z scores and that treatment of low bicarbonate with alkali therapy would be associated with improved height.

Materials and Methods
Study Population
The CKiD study is a longitudinal observational cohort study aimed at investigating and characterizing the effect of CKD progression in children. There are more than 50 enrollment institutions across North America. Study eligibility requires that children carry a diagnosis of CKD and mild to moderately impaired kidney function defined as an eGFR of 30–90 ml/min per 1.73 m². CKiD has enrolled children from 6 months to 16 years old at study entry; our study required a minimum age of 2 years old (minimum age for standing height measurements). In the first year, participants are seen twice and then annually thereafter. At each study visit, demographic and clinical data are obtained, including growth measurements and serum samples for measurement of kidney function and related biomarkers. A full description of the CKiD study and cohort has been previously published (18). All participants and families provided informed assent or consent. All protocols were approved by the Institutional Review Board.

Primary Exposure: Serum Bicarbonate
Serum bicarbonate results were obtained and measured at local study site laboratories. Low serum bicarbonate was defined as ≤22 mEq/L, and normal was defined as >22 mEq/L (19). For both baseline and longitudinal analyses, abnormal serum bicarbonate was further clinically categorized as ≤18 mEq/L (very low) and 19–22 mEq/L (low). We also looked at height z score on serum bicarbonate as a continuous predictor in specified analyses.

Primary Outcome: Linear Growth
A wall-mounted stadiometer was used to measure height (i.e., linear growth) at study visits. Final recorded height was based on averaging two separate measurements to the nearest 0.1 cm. If the measures differed by >0.3 cm, a third measurement was made, and an average of all three measurements used. Height was converted to height z scores (i.e., standard deviations) and percentiles according to Centers for Disease Control and Prevention estimates for the normal population adjusted for age and sex (20). Longitudinal analyses included participant visits during regular study follow-up among those <20 years of age with complete data on serum bicarbonate (exposure) and height z score (primary outcome).

Stratification and Covariate Definitions
The CKD diagnoses were broadly classified into two primary disease categories: nonglomerular or glomerular (specific CKD diagnoses are described in Supplemental Table 1), and all analyses were stratified as such. In longitudinal analyses, participants were also stratified by GFR ≥45 ml/min per 1.73 m² (mild to moderate CKD) and <45 ml/min per 1.73 m² (mild to severe CKD).

Analyses were adjusted for covariates known to affect kidney disease progression—a variable recognized as correlating with poor linear growth (7,15,21). Covariates included demographic variables such as age, sex, abnormal birth history (defined as premature birth, low birth weight, or small for gestational age), and mid-parental height (defined by biologic parents’ height measured at baseline.
study visit). Clinical covariates included GFR (calculated using the CKiD U25 eGFR equation and iohexol measured, where available) (22), CKD duration (in years), proteinuria (defined categorically on the basis of urine/protein creatinine ratio, < 0.5, 0.5–<2, or ≥2 mg/mg), intact parathyroid hormone (treated as continuous), and serum calcium and phosphate levels (classified as abnormal on the basis of age-specific thresholds). In longitudinal analyses evaluating the effect of a history of alkali therapy treatment, eGFR and proteinuria were treated as a “lagged” variable such that values from the previous study visit were used. “Lagged” values were used in order to provide clinical evidence as to how historical variables could predict the subsequent year’s outcomes.

Missing covariate data were imputed using multiple imputation by chained equations methods to limit the effect of missing follow-up data. The method used Gibbs sampling to perform five imputations of missing values for the “target covariate” on the basis of values from all other covariates in the dataset. Missing values were imputed separately for those with nonglomerular and glomerular diagnoses.

Statistical Analyses

Medians, interquartile ranges, and proportions described the demographic, clinical history, growth, and kidney disease characteristics of the cohort at participants’ first available visit.

To characterize the association between serum bicarbonate and linear growth, we used repeated measures linear regression models with height z score as the outcome and bicarbonate from the previous year as a categorical exposure. Models were stratified by diagnosis and were unadjusted (i.e., no covariates), partially adjusted (specifically, age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR and proteinuria), and fully adjusted (the same covariates with the addition of calcium, phosphate, intact parathyroid hormone, and CKD duration). Generalized estimating equations (GEE) were used to account for longitudinal measurements within an individual. As a supplementary analysis, we investigated serum bicarbonate as a predictor of growth velocity z scores.

Additionally, we characterized the relationship between serum bicarbonate and height z score among participants aged ≤13 years (i.e., prepubertal age range) by longitudinal alkali therapy use. Specifically, the unit of analysis was pairs of visits. We restricted to participants who reported using alkali therapy at the first visit, and we compared those who discontinued use (i.e., used alkali therapy at the previous visit but not at the current visit) with those who were persistent users (i.e., used alkali therapy at both the previous and current visit). Children with varying alkali therapy use during yearly follow-up (i.e., discontinued user during follow-up who became a persistent user or persistent user who became a discontinued user) could contribute data to both groups. GEE were also used to account for correlated repeated measures within an individual. Estimates of differences are presented with two-sided 95% CIs. Differences were statistically significant if the interval did not contain the null value (0), which corresponds to P < 0.05. All analyses were conducted using R v4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). To address missing data, multiple imputation on the basis of predictive mean matching for all covariates was used with the mice function of the “mice” package (v3.13.0). Linear models with GEE were calculated using the geeglm function of the “geepack” package (v1.3–1).

Results

The study population comprised 1082 children: 808 with nonglomerular etiologies of their CKD and 274 with glomerular causes of their CKD. Multivariate analyses were performed to examine the association between baseline demographic, biochemical, and clinical variables with serum bicarbonate values. Descriptive characteristics of the study participants are detailed in Tables 1 and 2. In both primary disease etiology categories, there was a predominance of patients who were White and boys, and low bicarbonate was associated with lower eGFR and more significant proteinuria. Abnormal birth history was similar among all bicarbonate groups, independent of CKD etiology. In both primary disease groups, baseline serum bicarbonate ≤ 22 mEq/L was associated with lower height measurements, worse height z scores, and more patients on GH therapy. Regarding alkali therapy, in patients with nonglomerular disease, serum bicarbonate ≤ 22 mEq/L was associated with a borderline higher rate of reported alkali therapy use, whereas it trended in this direction in children with glomerular disease but was not statistically significant. For patients with nonglomerular diseases, 45% (360/808) had a baseline bicarbonate of ≤ 22 mEq/L, with 34% (122/360) of those patients reporting treatment with alkali therapy. For children with glomerular diseases, 35% (97/274) had a baseline bicarbonate of ≤ 22 mEq/L, and 16% (16/97) endorsed alkali therapy treatment. Reported GH therapy use was low in the overall analyzed cohort at 9%.

For longitudinal analyses, we grouped serum bicarbonate from the previous study visit (i.e., lagged values) by clinically relevant categories as very low (≤ 18 mEq/L), low (19–22 mEq/L), and normal (> 22 mEq/L), and we examined the distribution of height z scores across bicarbonate groups. This was done to examine the clinical utility of bicarbonate levels in predicting future height outcomes. Figure 1 demonstrates that, longitudinally, worse serum bicarbonate levels were associated with worse height z scores in all children with CKD, independent of CKD etiology. In fully adjusted models, current serum bicarbonate and growth measurements were utilized. In these analyses, we continued to find that very low and low bicarbonates were associated with significantly worse height z scores in children with nonglomerular CKD (fully adjusted mean −0.39 [95% CI, −0.58 to −0.2] and −0.17 [95% CI, −0.28 to −0.05], respectively; Table 3). When restricted to patients who had measured GFR available, we found this association continued to persist and was more pronounced (Table 4). Height z scores were overall higher in children with glomerular CKD compared with those with nonglomerular CKD (Figure 1). In examining whether lower serum bicarbonate was linked to worse height z score in children with glomerular diseases, the only significant association noted
was in unadjusted analyses of children with serum bicarbonate 19–22 mEq/L (Tables 3 and 4). In sensitivity analyses excluding the children who reported GH use, associations were unchanged for children with nonglomerular CKD. Due to the small number of children with a glomerular diagnosis, data from low bicarbonate groups were combined, and height z scores in children with serum bicarbonate ≤22 mEq/L were compared with children with normal bicarbonates, with no significant relationship observed (Supplemental Table 2).

In analyses that were stratified by GFR, both estimated (Table 5) and measured (Table 6), using ≥45 ml/min per
1.73 m² (mild to moderate CKD) and <45 ml/min per 1.73 m² (moderate to severe CKD) categories, as potential effect modifiers of the relationship. In children with nonglomerular CKD causes, across all models using eGFR, low and very low serum bicarbonate were associated with significantly worse height z score in children with an eGFR <45 ml/min per 1.73 m²; the same association was seen with measured GFR in children with serum bicarbonate 19–22 mEq/L. This association reached significance across both measured GFR groups in children with serum bicarbonate ≤18 mEq/L. For children with glomerular diseases, in fully adjusted analyses, no association between serum bicarbonate and height remained at lower and higher eGFRs, albeit with wide confidence intervals. In children with nonglomerular causes, trends toward significance with lower eGFRs and higher bicarbonates were observed. These findings suggest that serum bicarbonate level may be an important factor in the development of growth failure in children with CKD, especially those with lower eGFR levels.
bicarbonate and height z score was noted, independent of GFR type.

We also evaluated the association between MA and linear growth, treating serum bicarbonate as a continuous variable. Supplemental Table 3 depicts differences in height z score per 1 mEq/L higher serum bicarbonate in the previous year. In fully adjusted models, we observed that a 1 mEq increase in serum bicarbonate was associated with increases in height z scores in all children with CKD; however, this relationship was not significant.

In a categorical exploratory analysis of the entire cohort restricted to prepubertal aged children, low serum bicarbonate levels were linked to lower height z scores, achieving significance in the very low serum bicarbonate category when eGFR was used for fully adjusted models. When measured GFR was utilized, this relationship was significant in fully adjusted models for both very low and low serum bicarbonates (Supplemental Tables 4 and 5).

Finally, we investigated the effect of treatment of MA on height z score in children of prepubertal age (Tables 7 and 8).

### Table 3. Unadjusted, partially adjusted, and fully adjusted models of height z score on serum bicarbonate, using a categorical predictor

| Serum Bicarbonate, mEq/L | n  | Unadjusted Mean (95% Confidence Interval) | Partially Adjusted Mean* (95% Confidence Interval) | Fully Adjusted Meanb (95% Confidence Interval) |
|--------------------------|----|----------------------------------------|-------------------------------------------------|---------------------------------------------|
| Nonglomerular diagnosis  |    |                                        |                                                 |                                             |
| >22                      | 3239 | Ref.                                   | Ref.                                            | Ref.                                        |
| 19–22                    |     | −0.27 (−0.4 to −0.14)c                 | −0.17 (−0.28 to −0.05)c                         | −0.17 (−0.28 to −0.05)c                     |
| ≤18                      |     | −0.58 (−0.79 to −0.38)c                | −0.38 (−0.57 to −0.19)c                         | −0.39 (−0.58 to −0.2)c                      |
| Glomerular diagnosis     | 853 |                                        |                                                 |                                             |
| >22                      |     | Ref.                                   | Ref.                                            | Ref.                                        |
| 19–22                    |     | −0.28 (−0.52 to −0.04)c                | −0.07 (−0.25 to 0.11)                           | −0.07 (−0.25 to 0.1)                        |
| ≤18                      |     | −0.38 (−0.92 to 0.16)                 | 0.16 (−0.31 to 0.62)                           | 0.14 (−0.33 to 0.61)                       |

Missing data were imputed for covariates in the partially and fully adjusted models. UP/C, urine protein/creatinine ratio; Ref., reference.

*Adjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR and UP/C.

*Adjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR, UP/C, calcium, phosphate, intact parathyroid hormone, and CKD duration in years.

Statistical significance (P<0.05).
We examined current height z score as a function of change in serum bicarbonate in participants reporting alkali therapy use at the previous study visit. Height outcome was separated by current reported alkali therapy use (i.e., “persistent” use if still being treated with alkali therapy versus “discontinued” use for those no longer reporting use of alkali therapy). In these models that utilized bicarbonate in a “lagged” manner, persistent alkali therapy users had a significant positive association between their height z score and serum bicarbonate levels; the significance of this association was lost when measured GFR was utilized. Independent of the GFR used, there was a positive but nonsignificant relationship in discontinued users.

**Discussion**

Using annual serum bicarbonate values over a robust duration of follow-up, our data suggest a longitudinal association between MA and lower height z score. After adjusting for demographic characteristics, markers of CKD severity, and pertinent clinical variables, serum bicarbonate \( \geq 22 \) mEq/L was associated with lower height z scores, with the worst height z scores observed in the lowest bicarbonate category (\( \leq 18 \) mEq/L). This association reached significance among children with nonglomerular CKD only. Although overall height z scores were reduced in all children with CKD, children with nonglomerular diseases had greater deficits in height z score than children with glomerular diseases. Not unexpectedly, use of measured GFR data showed similar associations compared with use of eGFR except when measured GFR was dichotomized as \( > 45 \) and \( \leq 45 \) ml/min per 1.73 m\(^2\). In these analyses, in participants with nonglomerular diseases, very low serum bicarbonate was associated with worse height z score across both measured GFR groups compared with analyses that utilized eGFR where this association was only seen in children in the \( \leq 45 \) ml/min per 1.73 m\(^2\) group. This is noteworthy because although use of measured GFR is not routine clinical practice, it is more accurate than eGFR, suggesting that the association of worse height z scores with MA may be present in the milder CKD group. Finally, and of clinical relevance, our data suggest that alkali therapy use as a marker of treatment of MA was associated with improved height z score, particularly in persistent users.

We found height outcome differences between children with nonglomerular and glomerular etiologies of CKD. Observed differences in linear growth could be attributed to sample size differences between the groups, later age of CKD onset in children with glomerular disease (i.e., less time during which the sequelae of CKD can affect active linear growth), older age of the participants with glomerular disease, and previously published evidence that indicates these primary disease groups may not be similarly affected by CKD comorbidities (16,23).

Our findings are, in part, in line with previous baseline investigations of the relationship between low serum bicarbonate and growth. In a prior cross-sectional study using the CKiD cohort, Rodig et al. observed that baseline height was lower in children with a baseline serum bicarbonate of \( < 18 \) mEq/L compared with those whose serum bicarbonate was \( \geq 22 \) mEq/L (7). They did not find a link between serum bicarbonate \( \geq 18 \) to \( < 22 \) mEq/L and worse height outcomes, unlike in our study where serum bicarbonate \( 19–22 \) mEq/L was associated with greater deficits in height in children with nonglomerular CKD. Potential reasons to account for this difference may be due to the longitudinal nature of our analyses, the stratification of our data by CKD etiology (although our study did adjust for CKD diagnosis), and differences in bicarbonate categorization values. Although noting the potential benefits of alkali therapy on height outcomes, unlike in our study, differences in height on the basis of alkali therapy use were not tested. Our study is the first to incorporate robust longitudinal data in a multi-ethnic cohort to investigate this association. Our novel evaluation of height on the basis of alkali therapy uses points to the potentially positive effect of treatment of MA on height.

Although longitudinal evaluations of the relationship between MA and growth are small in number, data from a European, prospective, observational study of children...
Table 5. Unadjusted, partially adjusted, and fully adjusted models of height z score on serum bicarbonate, stratified by eGFR <45 and ≥45 ml/min per 1.73 m², using a categorical predictor

| Serum Bicarbonate, mEq/L | n   | Unadjusted Mean (95% Confidence Interval) | Partially Adjusted Meana (95% Confidence Interval) | Fully Adjusted Meanb (95% Confidence Interval) |
|-------------------------|-----|------------------------------------------|--------------------------------------------------|-----------------------------------------------|
| Nonglomerular diagnosis |     |                                          |                                                  |                                               |
| >22                    | 2014| Ref.                                     | Ref.                                             | Ref.                                          |
| 19–22                  | 970 | -0.34 (–0.5 to –0.18)                    | 0.11 (–0.29 to 0.08)                             | Ref.                                          |
| ≥18                    | 255 | -0.63 (–0.85 to –0.4)                    | -0.31 (–0.63 to 0.01)                            | Ref.                                          |
| Glomerular diagnosis   |     |                                          |                                                  |                                               |
| >22                    | 609 | Ref.                                     | Ref.                                             | Ref.                                          |
| ≤22                    | 244 | -0.12 (–0.42 to 0.18)                    | -0.29 (–0.6 to 0.02)                             | Ref.                                          |
| Missing data were imputed for covariates in the partially and fully adjusted models. UP/C, urine protein/creatinine ratio; Ref., reference. |
| aAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR and UP/C. |
| bAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR, UP/C, calcium, phosphate, intact parathyroid hormone, and CKD duration in years. |
| cStatistical significance (P<0.05). |

Table 6. Unadjusted, partially adjusted, and fully adjusted models of height z score on serum bicarbonate, stratified by measured GFR <45 and ≥45 ml/min per 1.73 m², using a categorical predictor

| Serum Bicarbonate, mEq/L | n   | Unadjusted Mean (95% Confidence Interval) | Partially Adjusted Meana (95% Confidence Interval) | Fully Adjusted Meanb (95% Confidence Interval) |
|-------------------------|-----|------------------------------------------|--------------------------------------------------|-----------------------------------------------|
| Nonglomerular diagnosis |     |                                          |                                                  |                                               |
| >22                    | 904 | Ref.                                     | Ref.                                             | Ref.                                          |
| 19–22                  | 407 | -0.35 (–0.55 to –0.14)                   | -0.17 (–0.41 to 0.07)                            | Ref.                                          |
| ≤18                    | 102 | -0.62 (–0.93 to –0.31)                   | -0.68 (–1.09 to –0.28)                          | Ref.                                          |
| Glomerular diagnosis   |     |                                          |                                                  |                                               |
| >22                    | 293 | Ref.                                     | Ref.                                             | Ref.                                          |
| ≤22                    | 110 | -0.08 (–0.46 to 0.29)                    | -0.45 (–0.96 to 0.07)                            | Ref.                                          |

Missing data were imputed for covariates in the partially and fully adjusted models. UP/C, urine protein/creatinine ratio. 

aAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of GFR and UP/C. 
bAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of GFR, UP/C, calcium, phosphate, intact parathyroid hormone, and CKD duration in years. 
cStatistical significance (P<0.05). 
dFor those with glomerular diagnoses, serum bicarbonate was dichotomized at 22 mEq/L because there were 126 and 277 person-visits for those with an eGFR of <45 and ≥45 ml/min per 1.73 m², respectively.
post kidney transplant found that MA severity predicted poor linear height in pediatric kidney transplant recipients (24). This relationship has also been investigated in the poor linear growth in pediatric kidney transplant recipients post kidney transplant found that MA severity predicted poor linear height in pediatric kidney transplant recipients.

The growth benefits of alkali therapy have mostly been shown in older, small studies of children with RTA and normal eGFR and, therefore, mild CKD (9-11,25). Alkali therapies are widely available and well tolerated in the pediatric CKD population (17). Despite the availability of tolerable treatment options, published benefits of acidosis correction in growth impaired children with RTA, and proposed benefits on overall CKD progression (16,26-31), treatment rates of MA remain suboptimal, with only approximately one third of children with low serum bicarbonates in CKiD (one of the largest cohorts of children with CKD) reporting treatment with alkalinizing agents (7,16). Data from our current investigation suggest that long-term use of alkali therapy may have beneficial effects on height in children with CKD. However, clinical trials of alkali therapy in children with varying severity of impaired kidney function are needed to inform practitioners better of the potential benefits of treatment, given that no such trial exists to date.

Although our study has several strengths, there are limitations. Nutritional data in this cohort were incomplete. So, we were unable to account fully for its effect on height. We do include data on underweight children (on the basis of body mass index; Tables 1 and 2). Only 4% of the entire cohort is underweight, reflecting the likely low occurrence of severe malnutrition. Serum bicarbonate was used as an indicator of MA in this study because serum pH data were not available; it is possible that serum bicarbonate was not equivalent to actual acid/base status. Additionally, we were not able to assess true duration of alkali therapy because exact start dates were unknown, and for those with historical use, we were unable to determine when the alkali agent was discontinued. Important to note is that we were unable to account for the previous year’s level of bicarbonate and other covariates measured one year prior.

### Table 7. Unadjusted and adjusted models of height z score on previous visits serum bicarbonate stratified by discontinued and persistent alkali therapy use on the basis of two annual study visits

| Previous Serum Bicarbonate, per 1-Unit Increase | Unadjusted Mean Difference (95% Confidence Interval) | Adjusted Mean Differencea (95% Confidence Interval) |
|-----------------------------------------------|----------------------------------------------------|--------------------------------------------------|
| Discontinued alkali therapy use over 1 year   | +0.017 (-0.03 to +0.065)                            | +0.025 (-0.011 to +0.062)                         |
| Persistent alkali therapy use over 1 year     | +0.056 (+0.023 to +0.089)b                          | +0.04 (+0.008 to +0.073)b                          |

Generalized estimating equations were used to account for repeated measures within an individual. Missing data were imputed for covariates in the partially and fully adjusted models. Analysis used estimated GFR. UP/C, urine protein/creatinine ratio.

aAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of eGFR, UP/C, calcium, phosphate, intact parathyroid hormone, and CKD duration in years.

bStatistical significance (P<0.05).

### Table 8. Unadjusted and adjusted models of height z score on previous visits serum bicarbonate stratified by discontinued and persistent alkali therapy use on the basis of two annual study visits

| Previous Serum Nicarbonate, per 1-Unit Increase | Unadjusted Mean Difference (95% Confidence Interval) | Adjusted Mean Differencea (95% Confidence Interval) |
|-----------------------------------------------|----------------------------------------------------|--------------------------------------------------|
| Discontinued alkali therapy use over 1 year   | +0.042 (-0.171 to +0.254)                            | +0.078 (-0.035 to +0.191)                         |
| Persistent alkali therapy use over 1 year     | +0.061 (-0.005 to +0.126)b                          | +0.043 (-0.013 to +0.099)b                         |

Generalized estimating equations were used to account for repeated measures within an individual. Missing data were imputed for covariates in the partially and fully adjusted models. Analysis used measured GFR. UP/C, urine protein/creatinine ratio.

aAdjusted for age, sex, abnormal birth history, mid-parental height, and previous levels of GFR, UP/C, calcium, and phosphate, intact parathyroid hormone, and CKD duration in years.

bStatistical significance (P<0.05).
It would have been preferable to account for longer duration of clinical covariates in a marginal structural model framework, but data were limited to account for longer than one year earlier. An additional limitation is the inclusion of the small number of children on GH in primary analyses; however, sensitivity analyses showed no significant changes in study conclusions when these patients were excluded. Finally, we are aware that results may be affected by confounding by indication because children with more severe acidosis and complications were more likely to be prescribed alkalai therapy.

Despite its limitations, to our knowledge, our study is the first to examine the longitudinal relationship between MA and linear growth, and the potential effect of acidosis correction, in a multi-ethnic cohort of children with varying CKD severity. Although there are safe and effective therapies to treat MA, an increased understanding of this relationship may inform treatment practices and prove crucial to improving pediatric CKD care. Although our observed associations were small in number, our findings of a negative correlation between low serum bicarbonate and linear growth in children with CKD, and the suggested height benefits of alkalai therapy are important, given the profound effect impaired growth may have in this vulnerable population. Future clinical trials of alkalai therapy need to evaluate this relationship and other important disease outcomes prospectively in children with MA and chronically impaired kidney function.

Disclosures
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Author Contributions
D.D. Brown, F.J. Kaskel, and M.L. Melmed were responsible for funding acquisition; All authors wrote the original draft of the manuscript; D.D. Brown, M. Carroll, A. Dauber, M.L. Melamed, and D.K. Ng curated the data; D.D. Brown and A. Dauber were responsible for the investigation; D.D. Brown, A. Dauber, and M.L. Melamed were responsible for supervision; D.D. Brown, S.L. Furth, M.L. Melamed, and B.A. Warady conceptualized the study; M. Carroll and D.K. Ng were responsible for validation; M. Carroll and D.K. Ng were responsible for the formal analysis and software; B.A. Warady and S.L. Furth were responsible for resources; and all authors were responsible for the methodology and reviewed and edited the manuscript.

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References
1. Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherrard DJ, Watkins SL, Stehman-Breen C. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis 36: 811–819, 2000
2. Gerson AC, Wentz A, Abraham AG, Mendelley SR, Hooper SR, Butler RW, Gipson DS, Lande MB, Shinnar S, Moxey-Mims MM, Warady BA, Furth SL: Health-related quality of life in children with mild to moderate chronic kidney disease. *Pediatrics* 125: e349–e357, 2010

3. Al-Uzri A, Matheson M, Gipson DS, Mendelley SR, Hooper SR, Yadin O, Rozansky DJ, Moxey-Mims M, Furth SL, Warady BA, Gerson AC: Chronic Kidney Disease in Children Study Group: The impact of short stature on health-related quality of life in children with chronic kidney disease. *J Pediatr* 163: 736–41.e1, 2013

4. North American Pediatric Renal Trials and Collaborative Studies: NAPRTCS 2008 Annual Report. Rockville, MD, NAPRTCS, 2008

5. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A: Chronic renal insufficiency in children: The 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 18: 796–804, 2003

6. Furth SL, Stabilein D, Fine RN, Powe NR, Fivush BA: Adverse clinical outcomes associated with short stature at dialysis initiation: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatrics* 109: 909–913, 2002

7. Rodig NM, McDermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, Furth SL, Warady BA: Growth in children with chronic kidney disease: A report from the Chronic Kidney Disease in Children study. *Pediatr Nephrol* 29: 1987–1995, 2014

8. Harambat J, Kunzmann K, Azukaitis K, Bayazit AK, Canpolat N, Doyon A, Duzzova A, Niemirsk a A, Sozeri B, Thurn-Valsassina A, Anarat A, Bessenay L, Candan C, Pec o-Antic A, Yilmaz A, Tschumi S, Testa S, Jan kauksiene A, Erdogan H, Rosales A, Alpay H, Lugani F, Arbeiter K, Mencarelli F, Kayak A, Donmez O, Drozdz M, Melk A, Querfeld U, Schafer E; 4C Study Consortium: Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. *Kidney Int* 92: 1507–1514, 2017

9. McSherry E, Morris RC Jr: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest* 61: 509–527, 1978

10. C aldas A, Broyer M, Dechaux M, Kleinknecht C: Primary distal tubular acidosis in childhood: Clinical study and long-term follow-up of 28 patients. *J Pediatr* 121: 233–241, 1992

11. Sharma AP, Singh RN, Yang C, Sharma RK, Kapoor R, Filler G: Bicarbonate therapy improves growth in children with incomplete distal tubular acidosis. *Pediatr Nephrol* 24: 1509–1516, 2009

12. Chan W, Val erie KC, Chan JC: Expression of insulin-like growth factor-I in uremic rats: Growth hormone resistance and nutritional intake. *Kidney Int* 43: 790–795, 1993

13. Challa A, Krieg RJ Jr, Thabet MA, Veldhuis JD, Chan JC: Metabolic acidosis inhibits growth hormone secretion in rats: Mechanism of growth retardation. *Am J Physiol* 265: E547–E553, 1993

14. Brungger M, Hulte RN, Krapf R: Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: New cause of growth hormone insensitivity in humans. *Kidney Int* 51: 216–221, 1997

15. Furth SL, Abraham AG, Jerry-Fluker J, Schwartz GJ, Benfield M, Kaskell F, Wong C, Mak RH, Moxey-Mims M, Warady BA: Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clin J Am Soc Nephrol* 6: 2132–2140, 2011

16. Brown DD, Roem J, Ng DK, Reidy KJ, Kumar J, Abramowitz MK, Mak RH, Furth SL, Schwartz GJ, Warady BA, Kaskell FJ, Melamed M: Low serum bicarbonate and CKD progression in children. *Clin J Am Soc Nephrol* 15: 753–763, 2020

17. Andrade OV, Ibara FQ, Troster EJ: Metabolic acidosis in childhood: Why, when and how to treat. *J Pediatr (Rio J)* 83(Suppl): S11–S21, 2007

18. Furth SL, Cole SR, Moxey-Mims M, Kaskell F, Mak RH, Schwartz G, Wong C, Munoz A, Warady BA: Design and methods of the Chronic Kidney Disease in Children (CKID) prospective cohort study. *Clin J Am Soc Nephrol* 1: 1006–1015, 2006

19. KDOQI: Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis* 46: S1–S122, 2005

20. Kuczynski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF; Johnson CL: 2000 CDC growth charts for the United States: Methods and development. *Vital Health Stat 11* 221, 1997

21. Seikaly MG, Salhab N, Gipson D, Yiu V, Stabilein D: Stature in children with chronic kidney disease: Analysis of NAPRTCS database. *Pediatr Nephrol* 21: 793–799, 2006

22. Pierce CB, Munoz A, Ng DK, Warady BA, Furth SL, Schwartz CJ: Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. *Kidney Int* 99: 948–956, 2021

23. Warady BA, Abraham AG, Schwartz GJ, Wong CS, Munoz A, Betoko A, Mitsnefes M, Kaskell F, Greenbaum LA, Mak RH, Flynn J, Moxey-Mims MM, Furth S: Predictors of rapid progression of glomerular and nonglomerular kidney disease in children and adolescents: The Chronic Kidney Disease in Children (CKID) cohort. *Am J Kidney Dis* 65: 878–888, 2015

24. Franke D, Thomas L, Steffens R, Pavičić L, Gellermann J, Fro eke E, Querfeld U, Haffner D, Živčinjak M: Patterns of growth after kidney transplantation among children with ESRD. *Clin J Am Soc Nephrol* 10: 127–134, 2015

25. Santos F, Chan JC: Renal tubular acidosis in children. *Diagnosis, treatment and prognosis. Am J Nephrol* 6: 289–295, 1986

26. Gadola L, Noboa O, Márquez MN, Rodríguez MJ, Nín N, Boggia J, Ferreiro A, García S, Ortega V, Musto ML, Ponte P, Sessèr P, Pizarroza C, R avaglio S, Vallega A: Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int* 65: 1224–1230, 2004

27. Tanner GA: Potassium citrate/citric acid intake improves renal function in rats with polycystic kidney disease. *J Am Soc Nephrol* 9: 1242–1248, 1998

28. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE: Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 78: 303–309, 2010

29. Wiegand A, Ritter A, Graf N, A rampatzis S, Siddler D, Hadaya K, Muller TF, Wagner CA, Wuthrich RP, Mohребi N: Preservation of kidney function in kidney transplant recipients by alkali therapy (Preserve-Transplant Study): Rationale and study protocol. *BMC Nephrol* 19: 177, 2018

30. Tangri N, Reaven NL, Funk SE, Ferguson TW, Collister D, Mathur V: Metabolic acidosis is associated with increased risk of adverse kidney outcomes and mortality in patients with non-dialysis dependent chronic kidney disease: An observational cohort study. *BMC Nephrol* 22: 185, 2021

31. Djamali A, Singh T, Melamed ML, Stein JH, Aziz F, Parajuli S, Mohamed M, Garg N, Mandalbrot D, Wesson DE, Aster BC: Metabolic acidosis 1 year following kidney transplantation and subsequent cardiovascular events and mortality: An observational cohort study. *Am J Kidney Dis* 73: 476–485, 2019

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See related editorial, “Impact of Acidosis on Growth in Pediatric Chronic Kidney Disease: What Is the Current Evidence?”, on pages 590–596.