Impact of Metabolic Acidosis and Alkali Therapy on Linear Growth in Children with Chronic Kidney Disease: What Is the Current Evidence?

Emma H. Ulrich and Rahul Chanchlani

KIDNEY360 3: 590–596, 2022. doi: https://doi.org/10.34067/KID.0000072022

CKD in childhood is associated with multiple comorbidities, including growth failure (1–4). Earlier detection and management of reduced growth velocity have enhanced the growth potential for children with CKD (5). Despite these advances, nearly half of prepubertal children with ESKD will have short stature in adulthood (height <3rd percentile) (1,6,7). Short stature at initiation of dialysis is associated with increased risk of death and dialysis-related complications (8), and short stature pretransplant is associated with reduced graft survival (9). Impaired growth also places significant psychosocial burdens on the child and family, including reduced quality of life and ability for social advancement (10–12). The etiology of growth impairment in CKD is multifactorial, including growth hormone (GH) resistance, salt wasting, metabolic acidosis, proteinuria, malnutrition, and anemia (3,13).

Metabolic acidosis is widely recognized as a cause of poor growth, and consensus guidelines recommend maintaining serum bicarbonate ≥22 mEq/L in children with CKD (2,14). There are several hypothesized mechanisms. Animal models suggest that acidosis activates catabolic pathways, leading to impaired muscle development (15) and protein wasting (16), and increased inflammation and cytokine release (17,18). Acidosis disrupts the somatotropic hormone axis, including reduced expression of IGF-1 and GH receptors, reduced IGF-1 levels and resistance to GH secretion, and reduced cellular proliferation at skeletal growth plates (19–22). However, few pediatric studies have examined whether metabolic acidosis is independently associated with growth failure in children with CKD (23–25).

In this issue of Kidney360, Brown et al. (26) seek to characterize better the effect of metabolic acidosis, and treatment with alkali therapy, on linear growth in a large cohort of children with CKD in a longitudinal observational cohort study. The authors analyzed data from the Chronic Kidney Disease in Children (CKiD) study—a prospective, multicenter cohort of children with mild-moderate kidney impairment (eGFR 30–90 ml/min per 1.73 m²) (27). The authors included 1082 children 2–20 years of age, stratified by CKD diagnosis: nonglomerular (n=808) and glomerular disease (n=274). Serum bicarbonate was used as a surrogate marker of metabolic acidosis, defined as normal (≥22 mEq/L), low (19–22 mEq/L), and very low (≤18 mEq/L); height z score was the primary outcome. Adjusted analyses were reported using repeated-measures linear regression models, controlling for relevant demographic variables (age, sex, abnormal birth history, mid-parental height), eGFR (measured, if available), proteinuria, abnormal calcium or phosphate, intact parathyroid hormone, and CKD duration (years).

The authors reported four principal findings: (1) low and very low serum bicarbonate levels are associated with reduced height at baseline; (2) low and very low serum bicarbonate levels are associated with worse height z scores in children with CKD due to nonglomerular disease but not in glomerular disease; (3) metabolic acidosis has a greater adverse effect on height among children with nonglomerular disease and eGFR <45 ml/min per 1.73 m²; and (4) among children ≤13 years of age (i.e., prepubertal), treatment with alkali therapy is positively associated with improved growth.

Strengths

We have summarized the results of prior studies examining the effect of metabolic acidosis and/or its treatment on growth in children since 1975 (23–25,28–37) (Table 1). Current evidence regarding metabolic acidosis and its association with growth impairment is mainly limited to populations with renal tubular acidosis (23,28–34,37) and has not been longitudinally studied in children with CKD. The study by Brown et al. (26) aims to fill this knowledge gap and reports novel findings that treatment of metabolic acidosis with alkali therapy improves growth in children with CKD.

The other strength is the uniqueness of the CKiD study, in which data are collected across 50 centers in

1Division of Pediatric Nephrology, Department of Pediatrics, University of Alberta, Edmonton, Canada
2ICES, Toronto, Canada
3Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada
4Division of Pediatric Nephrology, Department of Pediatrics, McMaster University, Hamilton, Canada

Correspondence: Dr. Rahul Chanchlani, Division of Pediatric Nephrology, Department of Pediatrics, McMaster Children’s Hospital, 1280 Main St. W, Hamilton, ON, Canada, L8N 3Z5. Email: chanchlr@mcmaster.ca
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Study Population</th>
<th>N</th>
<th>Renal Comorbidities</th>
<th>Alkali Therapy Use</th>
<th>Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McSherry, 1978 (28)</td>
<td>Longitudinal, single-center study; children (age 8 days–9.5 years) with KTA</td>
<td>10</td>
<td>NR</td>
<td>Alkali therapy to maintain normal serum bicarbonate levels on four measurements over 1–2 weeks</td>
<td>Children had impaired growth before alkali therapy, mean height percentile 1.4±4</td>
</tr>
</tbody>
</table>
| Caldas, 1992 (29)            | Longitudinal, single-center study; children (age 2 weeks–11 years) with distal KTA | 28 | - Normal serum phosphate  
- Hypercalcemia in all patients  
- Low 25-hydroxy-vitamin D and elevated iPTH: 14% (4/28)  
- Normal eGFR (creatinine clearance)  
- Nephrocalcinosis or nephrolithiasis: 50% (14/28)  
- Rickets or osteoporosis: 68% (19/28) | Alkali therapy to maintain normal serum level and urine calcium excretion <2 mg/kg per day; 93% achieved adequate metabolic control | Children had impaired growth (height SD score <−2) at diagnosis in 64% (18/28) |
| Chang, 2002 (30)             | Longitudinal, single-center study; children (age 1 month–10 years) with distal KTA | 28 | - Hypokalemia: 89% (25/28)  
- Normal serum calcium, phosphate, creatinine, and urea  
- Nephrocalcinosis: 24% (5/28)  
- No children with rickets  
- No children hypothyroidism  
- Hypokalemia: 100% (18/18)  
- No children with eGFR <50 ml/min per 1.73 m² (Schwartz formula)  
- Nephrocalcinosis: 44% (8/18)  
- Rickets or fracture: 100% (18/18) | Alkali therapy to maintain normal serum bicarbonate level | Children had impaired growth: mean height SD score −2.81, SD 1.80 |
| Bajpai, 2005 (31)            | Longitudinal, single-center study; children (age 2–13 years) with distal KTA | 18 | - Children with Fanconi syndrome were significantly older, had worse initial height SD score, and had a higher proportion of hypophosphatemia and rickets relative to children with proximal KTA  
- Rickets: 14% (3/21; all had Fanconi syndrome) | Alkali therapy to maintain serum bicarbonate 20–24 mmol/L; 89% (16/18) achieved | Children had impaired growth (height SD score <−2) at diagnosis in 100% (18/18) |
| Hsu, 2005 (32)              | Longitudinal, single-center study; children (age 1–11 years) with idiopathic Fanconi syndrome or primary proximal KTA | 21 | - Children with Fanconi syndrome and proximal KTA had impaired growth: mean height SD score −3.25, SD 0.95 and −2.13, SD 1.10, respectively; children with Fanconi syndrome had worse impaired growth (P<0.05)  
- For children with Fanconi syndrome, height SD score (P=0.79) failed to increase over follow-up (mean follow-up 7 years); for children with proximal KTA, height SD score increased at last visit (P=0.02) over follow-up (mean follow-up 5 years) | Long-term alkali therapy; normal serum bicarbonate defined as ≥20 mmol/L | - Mean height increased after sustained alkali therapy (P<0.02) over follow-up (range of follow-up 1–10 years)  
- In infants (2 weeks–24 months, n=16), mean height SD score increased (P<0.001) over follow-up (mean follow-up 13 years); in children (44–132 months, n=12), mean height SD score increased (P<0.001; mean follow-up 7 years)  
- Mean adult height SD score in seven children without rickets was −0.6, SD 0.2  
- Children had impaired growth: mean height SD score −2.81, SD 1.80 | Mean height SD score increased (P=0.02) over follow-up (follow-up 1–6 years) |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Study Population</th>
<th>N</th>
<th>Renal Comorbidities</th>
<th>Alkali Therapy Use</th>
<th>Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seikaly, 2006 (25)</td>
<td>Cross-sectional study; multicenter data from NAPRTCS chronic renal failure registry; children (age birth–21 years)</td>
<td>5615</td>
<td>- Calculated eGFR (creatinine clearance): &gt;50 ml/min per 1.73 m²: 29% (1641/5615); 25–50: 40% (2256/5615); 10–25: 26% (1487/5615); &lt;10 4% (231/5615)</td>
<td>Alkali therapy to maintain normal serum bicarbonate levels throughout follow-up period</td>
<td>- Children had impaired growth (height SD score &lt;−1.88) at baseline in 37% (2071/5615)</td>
</tr>
<tr>
<td>Sharma, 2009 (33)</td>
<td>Longitudinal, single-center study; children (age 1–10 years) with distal KTA after surgical management of PUV</td>
<td>49</td>
<td>- Normal eGFR (Schwartz formula)</td>
<td>Alkali therapy to maintain normal serum bicarbonate levels throughout follow-up period</td>
<td>- Children with distal KTA and partial distal KTA had impaired growth (mean height SD score) at baseline, relative to patients without distal KTA (P&lt;0.05)</td>
</tr>
<tr>
<td>Rodig, 2014 (24)</td>
<td>Cross-sectional study; Multicenter data from CKiD Study (27); children (median age 11 years) with CKD stages I–III</td>
<td>799</td>
<td>- Median GFR (calculated if measured result unavailable): 50 ml/min per 1.73 m²</td>
<td>NR; of children with serum bicarbonate level &lt;18 mmol/L, two thirds were not prescribed alkali therapy</td>
<td>- Children had impaired growth: median height SD score −0.55, IQR −1.35 to 0.19</td>
</tr>
<tr>
<td>Besouw, 2017 (34)</td>
<td>Longitudinal, single-center study; children (age 2 weeks–5 years) with distal KTA</td>
<td>24</td>
<td>- Hypokalemia: 58% (14/24)</td>
<td>Alkali therapy to maintain normal serum bicarbonate level</td>
<td>- Children had impaired growth (height SD score &lt;−2) at diagnosis in 50% (12/24)</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Study Population</td>
<td>N</td>
<td>Renal Comorbidities</td>
<td>Alkali Therapy Use</td>
<td>Study Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>-----</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Franke, 2017 (35)</td>
<td>Longitudinal, two-center study; children (median age 9 years) undergoing kidney transplant</td>
<td>322</td>
<td>• Mean duration of dialysis (years): 12 months</td>
<td>Mean duration of dialysis (years): 12 months</td>
<td>• Mean annual plasma pH value was a significant predictor of post-transplant growth ($P&lt;0.05$) over follow-up (mean follow-up 4.9 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Median calculated eGFR (revised Schwartz formula): 58 ml/min per 1.73 m$^2$</td>
<td>Median calculated eGFR (revised Schwartz formula): 58 ml/min per 1.73 m$^2$</td>
<td>• Authors used linear mixed-effect model accounting for other covariates, including congenital CKD, age, mid-parental height, eGFR, anemia, and steroid dosage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• SGA (&lt;10th percentile): 29% (94/322)</td>
<td>SGA (&lt;10th percentile): 29% (94/322)</td>
<td>• Children had impaired growth: mean height SD score −1.2, IQR −2.1 to −0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• GH therapy (height SD score &lt;−2 OR height velocity &lt;25th percentile) after transplant: 9%</td>
<td>GH therapy (height SD score &lt;−2 OR height velocity &lt;25th percentile) after transplant: 9%</td>
<td>• Presence of metabolic acidosis (serum bicarbonate &lt;22 mmol/L) was not significantly associated with height SD score ($P=0.18$) over follow-up (median follow-up 3.3 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Corticosteroid withdrawn: 18%</td>
<td>Corticosteroid withdrawn: 18%</td>
<td>• The estimated average prevalence of metabolic acidosis: CKD stage III 43%, IV 61%, and V (including dialysis) 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mean duration of dialysis (years): 12 months</td>
<td>Mean duration of dialysis (years): 12 months</td>
<td>• For children &lt;15 years, mean height SD score higher in patients with adequate metabolic control, relative to those without adequate metabolic control ($P&lt;0.001$)</td>
</tr>
<tr>
<td>Harambat, 2017 (36)</td>
<td>Cross-sectional study; multicenter data from 4C Study (58); children (age 6–17 years) with CKD stages III–V</td>
<td>704</td>
<td>• Median calculated eGFR (updated Schwartz formula; $n=681$): 27 ml/min per 1.73 m$^2$</td>
<td>Median calculated eGFR (updated Schwartz formula; $n=681$): 27 ml/min per 1.73 m$^2$</td>
<td>• Children had impaired growth: median height SD score −1.2, IQR −2.1 to −0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Median urine albumin-creatinine ratio ($n=674$): 349 mg/g</td>
<td>Median urine albumin-creatinine ratio ($n=674$): 349 mg/g</td>
<td>• Presence of metabolic acidosis (serum bicarbonate &lt;22 mmol/L) was not significantly associated with height SD score ($P=0.18$) over follow-up (median follow-up 3.3 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Median iPTH ($n=675$): 125 pg/mol</td>
<td>Median iPTH ($n=675$): 125 pg/mol</td>
<td>• The estimated average prevalence of metabolic acidosis: CKD stage III 43%, IV 61%, and V (including dialysis) 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• GH therapy: 9% ($60/704$)</td>
<td>GH therapy: 9% ($60/704$)</td>
<td>• For children &lt;15 years, mean height SD score higher in patients with adequate metabolic control, relative to those without adequate metabolic control ($P&lt;0.001$)</td>
</tr>
<tr>
<td>Lopez, 2019 (23)</td>
<td>Cross-sectional study; multicenter data; children and adults (age 2–60 years)</td>
<td>340</td>
<td>• Calculated eGFR (Schwartz formula) &lt;90 ml/min per 1.73 m$^2$ in children (age 2–18 years): 35%; CKD stage II (by KDIGO criteria): 32%; III: 2.5%; IV: 0.4%</td>
<td>Alkali therapy used in 55% (386/704)</td>
<td>• Children had impaired growth: median height SD score −1.2, IQR −2.1 to −0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nephrocalcinosis or nephrolithiasis: 88% ($229/261$)</td>
<td>Nephrocalcinosis or nephrolithiasis: 88% ($229/261$)</td>
<td>• Presence of metabolic acidosis (serum bicarbonate &lt;22 mmol/L) was not significantly associated with height SD score ($P=0.18$) over follow-up (median follow-up 3.3 years)</td>
</tr>
<tr>
<td>Atmis, 2020 (37)</td>
<td>Longitudinal, single-center study; children (age 1–178 months) with distal KTA</td>
<td>31</td>
<td>• Hypokalemia (at last visit): 13%</td>
<td>Alkali therapy to maintain serum bicarbonate ≥22 mmol/L and normal urine calcium-creatinine ratio; at last visit, 49% achieved adequate metabolic control</td>
<td>• Children had impaired growth (height SD score &lt;−2) at diagnosis in 45% (14/31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypokalemia (at last visit): 13%</td>
<td>Hypokalemia (at last visit): 13%</td>
<td>• Mean height SD score increased ($P=0.002$) over follow-up (median follow-up 77 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Calculated eGFR (Schwartz formula): CKD stage II (by KDIGO criteria): 16% ($5/31$); III: 10% ($3/31$)</td>
<td>Calculated eGFR (Schwartz formula): CKD stage II (by KDIGO criteria): 16% ($5/31$); III: 10% ($3/31$)</td>
<td>• Mean height SD score higher in patients with adequate metabolic control at &gt;75% of visits, relative to 50%–75% ($P=0.003$) and &lt;50% ($P=0.003$); no statistically significant difference in mean eGFR between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Microalbuminuria: two patients with CKD stage III</td>
<td>Microalbuminuria: two patients with CKD stage III</td>
<td>• Mean height SD score higher in patients with adequate metabolic control at &gt;75% of visits, relative to 50%–75% ($P=0.003$) and &lt;50% ($P=0.003$); no statistically significant difference in mean eGFR between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nephrocalcinosis: 100%</td>
<td>Nephrocalcinosis: 100%</td>
<td>• Mean height SD score higher in patients with adequate metabolic control at &gt;75% of visits, relative to 50%–75% ($P=0.003$) and &lt;50% ($P=0.003$); no statistically significant difference in mean eGFR between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypocitraturia: 78% ($18/23$)</td>
<td>Hypocitraturia: 78% ($18/23$)</td>
<td>• Mean height SD score higher in patients with adequate metabolic control at &gt;75% of visits, relative to 50%–75% ($P=0.003$) and &lt;50% ($P=0.003$); no statistically significant difference in mean eGFR between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No children with rickets</td>
<td>No children with rickets</td>
<td>• Mean height SD score higher in patients with adequate metabolic control at &gt;75% of visits, relative to 50%–75% ($P=0.003$) and &lt;50% ($P=0.003$); no statistically significant difference in mean eGFR between groups</td>
</tr>
</tbody>
</table>

CI, confidence interval; GH, growth hormone; iPTH, intact parathyroid hormone; IQR, interquartile range; KTA, kidney tubular acidosis; NAPRTCS, North American Pediatric Renal Transplant Cooperative Studies; NR, not reported; PUV, posterior urethral valves; SGA, small for gestational age.

NAPRTCS defines chronic renal failure as creatinine clearance <75 ml/min per 1.73 m$^2$ before time of registry.
North America, representing a heterogeneous, ethnically diverse population of children (27). These data increase the generalizability of the results obtained, which has been an important limitation of previous single-center studies (28–35,37).

Finally, the study findings draw particular attention to the undertreatment of metabolic acidosis in children with CKD in this cohort. Despite consensus recommendations to maintain normal serum bicarbonate levels, alkali therapy was reported in only 34% (122/360) of children with nonglomerular disease and 16% (16/97) of children with glomerular disease with low or very low serum bicarbonate levels (<22 mEq/L). Poor medication adherence has previously been reported in children with CKD and is recognized as an important modifiable factor in improving growth (38). This finding suggests that under-recognition and/or undertreatment of metabolic acidosis contributes to short stature in adults with a history of CKD in childhood.

Limitations

The main limitations reflect the challenge of studying growth in children with CKD using an observational study design. Growth impairment in children with CKD is multifactorial and highly complex. The authors performed adjusted analyses to account for relevant comorbidities but were limited by the availability of data for some variables, including measured GFR and nutrition status.

Another important limitation of the study is that time-varying effects of confounders, especially GFR, could not be accounted for in the analysis. Previous studies in children with CKD have shown that worsening GFR is associated with worsening acidosis (36,39); furthermore, acidosis has also been associated with CKD progression (36,40–42). In addition, measured GFR was missing in approximately half of the cohort. Although measuring GFR is often impractical and resource intensive, eGFR is less accurate at higher severity of CKD due to increased tubular secretion of creatinine, and measured GFR remains the gold standard (46). To address some of these limitations, the authors performed additional analyses in which GFR was analyzed as an effect modifier. In this analysis, both eGFR and measured GFR were stratified into two categories—≥45 and <45 ml/min per 1.73 m²—to examine further the association between metabolic acidosis and height within GFR groups. Results showed that in children with nonglomerular disease, low and very low serum bicarbonate levels were associated with impaired growth at GFR <45 ml/min per 1.73 m² only. However, using measured GFR, very low serum bicarbonate levels were associated with impaired growth in both GFR categories. The study findings were unchanged and remained nonsignificant in children with glomerular CKD. Although CKD duration was included as a covariate, children with glomerular diseases were older, had a shorter duration of CKD, and were generally taller, which could explain the discrepant results. These supplemental analyses suggest that the true effect of CKD in the analyses requires further study.

The authors also noted that only 10% of the children in the overall cohort were using GH during the study period. However, sensitivity analysis excluding children treated with GH did not yield different results in children with nonglomerular disease. Other important covariates were not reflected in the study. Although mid-parental height was included in adjusted analyses, the authors do not account for prenatal factors and syndromic short stature (1,35). There was also limited nutritional data in the study. Although only 4% of the cohort was underweight by body mass index, nutritional management undoubtedly serves an important role in the management of children with CKD and impaired growth (47–50). Anemia is also an important contributor to impaired growth (51,52), and anemia severity may be affected by metabolic acidosis (53). Although the authors note that there were significantly higher rates of anemia in the very low bicarbonate group, this was not accounted for in the adjusted models. Finally, although calcium, phosphate, and intact parathyroid hormone were included in the adjusted models, the authors were not able to report on vitamin D data and other hormonal disturbances (i.e., hypothyroidism), which all play a role in adequate growth in children with CKD (54).

Conclusions

Despite these limitations, this study by Brown et al. (26) presents clinically relevant evidence of the deleterious effect of metabolic acidosis on growth in children with CKD. The study also underscores the importance of alkali therapy on improved growth in this cohort. This relatively inexpensive, well-tolerated, and conservative approach to optimizing linear growth can have a profound effect on long-term morbidity and social integration in this population (14,55,56).

Larger observational studies, accounting for time-varying comorbidities, will further strengthen our understanding of the effect of metabolic acidosis in CKD. Future randomized controlled trials studying the potential dose-dependent effects of alkali therapy on linear growth are also needed.

Future studies should also assess the effect and treatment of metabolic acidosis on other CKD comorbidities. Previous evidence suggests that acidosis may contribute to CKD progression and other nutritional parameters (23,36,40,55,57); small studies have also shown that alkali therapy may improve nutritional status and quality of life (41). Furthermore, studies are needed to examine the effect of acidosis on neurodevelopmental and patient-reported outcomes, including quality of life and mental health.

Children with CKD and their families face tremendous physical and psychosocial burdens. Growth impairment is well-established in children with CKD and results in significant morbidity. Treatment of metabolic acidosis may be a particularly effective option for improving outcomes in this population.

Disclosures

All authors have nothing to disclose.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical
advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions
R. Chanchlani was responsible for methodology and supervision; and both authors wrote the original draft of the manuscript and reviewed and edited the manuscript.

References


