CHAPTER 8.4 Metabolic acidosis

Agnieszka Prytuła

Department of Pediatric Nephrology and Rheumatology, Ghent University Hospital, Ghent, Belgium

ORCID:
https://orcid.org/0000-0001-9551-8758

1 Definition and types of metabolic acidosis

Metabolic acidosis is defined as plasma bicarbonate (HCO_3^-) level ≤ 22 mmol/L. It is often subdivided into low HCO_3^- levels (18.1 to 21.9 mmol/L), corresponding to mild to moderate metabolic acidosis, and very low HCO_3^- levels (≤ 18 mmol/L), corresponding to severe metabolic acidosis. The reported prevalence of mild to moderate and severe metabolic acidosis ranged from 20% to 39% and from 3% to 7%, respectively, over time in a cohort of 1911 paediatric kidney transplant recipients with up to 10 years of follow-up [1].

Post-transplant metabolic acidosis with *normal anion gap* can be classified as follows: (i) type I (distal, classic), (ii) type IVa, aldosterone resistance with low blood pressure due to hypovolaemia and hyperkalemia and (iii) type IVb, also known as pseudohypoaldosteronism type 2, with elevated blood pressure and hyperkalemia.

Experimental data suggest that calcineurin inhibitors impair mineralocorticoid transcriptional activity in the distal tubular cells and may cause aldosterone resistance, hyperkalemia, and type IV metabolic acidosis [2]. In addition, there is a strong clinical and experimental evidence that calcineurin inhibitors induce activation of salt reabsorption in the distal convoluted tubule with consequent impaired delivery of sodium to the collecting duct, thereby inducing hypervolaemia and hypertension [3, 4]. Distinguishing between different types of metabolic acidosis may be useful in tailoring and personalising treatment. In contrast to type I metabolic acidosis, type IV metabolic acidosis may respond to treatment with fludrocortisone (type IVa) or thiazide (type IVb) rather than to alkaline supplementation. In a cohort of 576 adult kidney transplant recipients with stable allograft function, 28% of patients developed type IV metabolic acidosis [5]. Paediatric data on the prevalence of different types of metabolic

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acidosis are not available, but persistently low HCO_3^- levels have been reported in 42% of paediatric kidney transplant recipients on alkaline therapy [1].

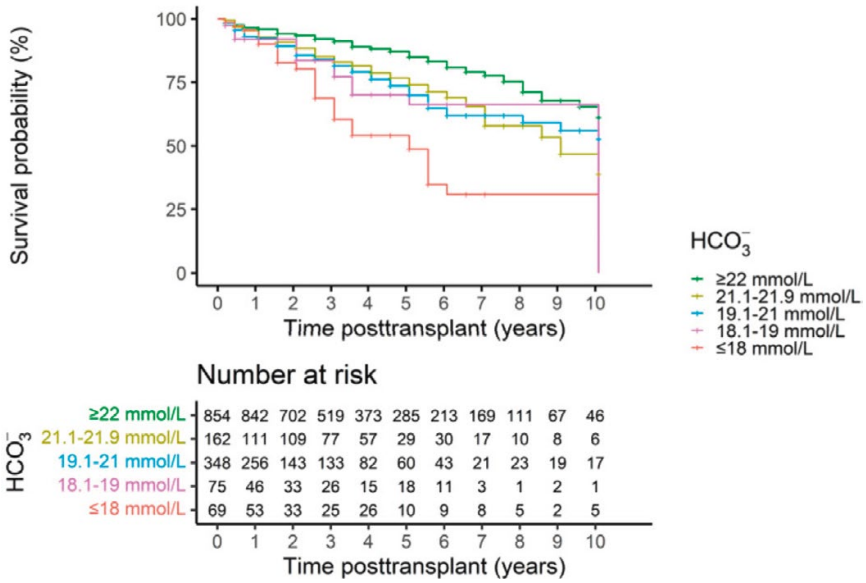
2 Factors associated with metabolic acidosis in paediatric kidney transplant recipients [1, 6]

- *Mild to moderate metabolic acidosis:* younger recipient age, female sex, deceased donor, tubulointerstitial kidney disease
- *Severe metabolic acidosis:* higher tacrolimus pre-dose concentration, younger recipient age, female sex, low systolic blood pressure, low estimated glomerular filtration rate (eGFR)

3 Metabolic acidosis and allograft outcome

In patients with chronic kidney disease (CKD), metabolic acidosis is associated with accelerated loss of kidney function [7, 8], and a large observational study of adult kidney transplant recipients reported an association between metabolic acidosis, graft failure and mortality [9]. These findings were not confirmed in a randomised trial analysing the effect of sodium bicarbonate supplementation on the rate of eGFR decline in 240 adult kidney transplant recipients with a mean HCO_3^- level of 21 mmol/L (placebo group) to 21.3 mmol/L (treatment group), which is mild metabolic acidosis [10]. There was no difference in eGFR decline after 2 years of follow-up, and the authors concluded that treatment with sodium bicarbonate should not be generally recommended in adult kidney transplant recipients with metabolic acidosis to preserve allograft function [10]. Given the differences in age, comorbidities, comedication, diet and distinct risk factors for metabolic acidosis such as young patient age in paediatric patients, these findings should not be directly extrapolated to a paediatric population. In a recent report including 1911 paediatric patients, there was a stepwise increase in the rate of allograft dysfunction with the severity of time-varying metabolic acidosis, as shown in Figure 1 [1].

Figure 1 Association between the degree of time-varying metabolic acidosis and time to composite endpoint defined as either graft failure or estimated glomerular filtration rate (eGFR) ≤ 30 mL/min per 1.73 m^2 or ≥ 50% decline in eGFR from eGFR at month 3 post-transplant (source: Kidney International Reports, 2024 [1]).



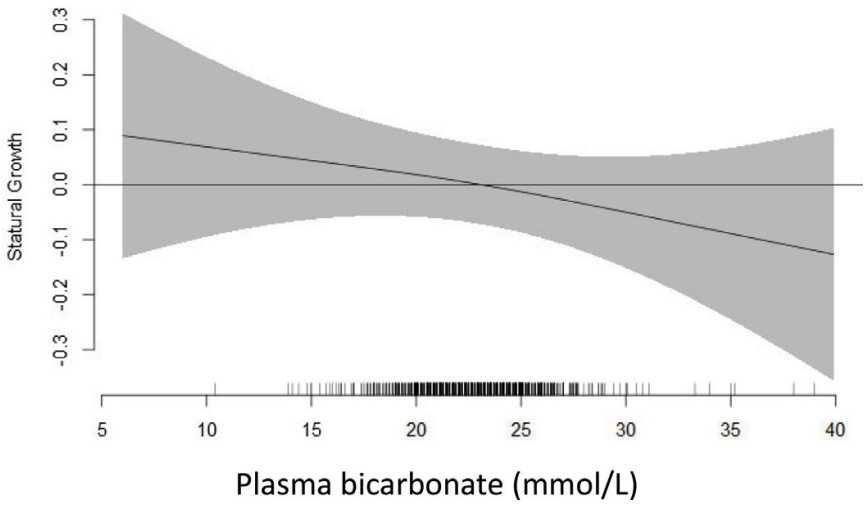
Reference: HCO_3^- ≥ 22 mmol/L
HCO_3^- 21.1 – 21.9 mmol/L; HR, 1.90, 95% CI, 1.27 to 2.85, p = 0.002
HCO_3^- 19.1 – 21 mmol/L; HR, 1.94, 95% CI, 1.40 to 2.67, p < 0.0001
HCO_3^- 18.1 – 19 mmol/L; HR, 2.57, 95% CI, 1.42 to 4.67, p = 0.002
HCO_3^- ≤ 18 mmol/L; HR, 4.09, 95% CI, 2.58 to 6.51, p < 0.0001

4 Metabolic acidosis and statural growth

Metabolic acidosis has been implicated as a risk factor for poor growth in paediatric CKD by causing disturbances in the growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis [11]. In animal models, metabolic acidosis inhibits GH secretion and activates catabolic pathways, leading to impaired muscle development, protein wasting and increased inflammation [12, 13]. It also inhibits osteoblast activity while stimulating osteoclasts, resulting in a defect in bone mineralisation [14]. In humans, metabolic acidosis causes a decreased IGF-1

response to circulating GH, resulting in a state of GH resistance [15]. Although treatment of metabolic acidosis has been postulated as one of the strategies to improve growth in paediatric kidney transplant recipients, there is a paucity of literature on the clinically relevant relationship between metabolic acidosis and growth failure. In a German study of 389 patients, metabolic acidosis was present in 30% of patients and showed an inverse association with body height, leg length, and sitting height [16]. More recently, in an analysis of 2,147 primary kidney transplant recipients, no statistically significant association was found between statural growth and HCO_3^- levels, and the shape of the estimated association showed a decreasing estimated growth with increasing HCO_3^-, as shown in Figure 2 [17].

Figure 2 Lack of association between plasma bicarbonate levels and statural growth expressed as Δ height relative to time between 2 consecutive visits in 2,147 primary KTx recipients analysed using Generalised Additive Mixed Models adjusted for covariates. The shape of the estimated association showed a decreasing estimated statural growth with increasing plasma bicarbonate levels.



Although these findings do not support alkaline treatment in paediatric kidney transplant recipients with metabolic acidosis to attenuate growth failure, they should be confirmed in a prospective study to analyse whether mild to moderate metabolic acidosis requires treatment.

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