A basic solution for a complex problem: does treatment of metabolic acidosis slow CKD progression?

Kevin Bodker[a], *Natalie Freidin*[a] *and Nayan Arora*[b]

Purpose of this review
Metabolic acidosis is frequently encountered in patients with chronic kidney disease (CKD), with increasing prevalence as kidney function worsens. Treating electrolyte disturbances is the sine qua non of Nephrologists, and alkali therapy to normalize serum bicarbonate levels and slow progression of kidney disease has been embedded in clinical practice guidelines for decades on the basis of animal models and controversial clinical trials. This review will critically appraise the literature base for this recommendation and determine whether the available evidence supports this common practice, which is a timely endeavor considering the impending demotion of metabolic acidosis treatment from recommendation to practice point in forthcoming KDIGO guidelines.

Recent findings
Earlier, open-label, studies supporting the utility of sodium bicarbonate therapy to slow progression of chronic kidney disease have been challenged by more recent, blinded, studies failing to show benefit on CKD progression. This was further demonstrated in the absence of concomitant sodium administration with the hydrochloric acid binder veverimer, which failed to demonstrate benefit on renal death, end stage kidney disease or 40% reduction in estimated glomerular filtration rate in a large multicenter trial.

Summary
The current body of literature does not support the routine treatment of metabolic acidosis in patients with CKD and the authors agree with the forthcoming KDIGO guidelines to de-emphasize this common practice.

Keywords
chronic kidney disease, metabolic acidosis, sodium bicarbonate

INTRODUCTION

Metabolic acidosis is a common occurrence in patients with chronic kidney disease and correction of this metabolic derangement has been entrenched in guidelines for over two decades. Alkali therapy, generally with oral sodium bicarbonate, which is inexpensive and overall well tolerated, has emerged as an attractive option to mitigate the impact of metabolic acidosis, a concept that dates to Richard Bright (circa 1800) [1]. Alkali therapy is now ubiquitous in the armamentarium of nephrologists in the treatment of chronic kidney disease (CKD), irrespective of etiology. With the emergence and availability of newer therapies it is vital to appraise the evidentiary basis for historical practices. This review will focus on whether the available evidence supports ameliorating metabolic acidosis in an effort to curb CKD progression.

BACKGROUND

Metabolic acidosis, commonly defined as a serum bicarbonate (HCO_3^-) level <22 mEq/l, in the absence of a respiratory alkalosis, increases in prevalence and severity as glomerular filtration rate (GFR) falls. In normal conditions kidneys excrete the daily acid load, derived from a combination of endogenous metabolism and metabolism of dietary proteins, via ammoniagenesis and excretion of

[a]Medical University of South Carolina and [b]University of Washington, Seattle, Washington, USA

Correspondence to Nayan Arora, MD, Division of Nephrology, University of Washington, Seattle, WA 98195, USA. Tel: +1 503 803 0499; e-mail: narora@uw.edu

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KEY POINTS

- Metabolic acidosis is frequently encountered in patients with chronic kidney disease and treatment with alkali therapy is a common practice based on the 2012 KDIGO guidelines.
- Examination of the literature demonstrates discordance in outcomes between blinded and open-label studies, with blinded trials failing to show beneficial effects of metabolic acidosis treatment in regard to chronic kidney disease progression.
- In the era of novel and burgeoning therapies for chronic kidney disease correction of metabolic acidosis should be deemphasized.

titratable acids. In diseased kidneys, functioning nephrons substantially increase ammonium excretion per total GFR as an adaptive response to maintain serum bicarbonate levels in the normal range. This mechanism has been suggested to induce injurious "acid stress" and implicated as an independent risk factor for poor outcomes preceding the development of overt acidosis. As glomerular and tubular function declines the ability to excrete the daily acid load diminishes, leading to acid retention, which is initially buffered by bicarbonate, though ultimately leads to a fall in serum bicarbonate levels. Metabolic acidosis in chronic kidney disease (CKD) has been implicated in several pathologic conditions, such as bone health, nutrition status, cardiovascular health, progressive GFR loss and even mortality [3,6–12]. Although a causal link has not been established between metabolic acidosis and hastening of CKD progression, studies have suggested that retained acid promotes activation of the renin–angiotensin–aldosterone system (RAAS), increased production of endothelin-1 (ET-1) and complement activation, leading to tubulointerstitial inflammation and fibrosis [2–5].

Early evidence in support of alkali therapy to slow CKD progression was published by Brito-Ashurst *et al.* in a 2009 single center, randomized, open-label trial [13]. The authors demonstrated that treatment with oral sodium bicarbonate compared with standard of care (SOC) in 134 patients with CKD stage 4 reduced the rate of creatinine clearance (CrCl) decline (−5.93 vs. 1.88 ml/min/1.73 m^2, $P < 0.0001$) and reduced the incidence of end stage kidney disease (ESKD) by 87% over a 2-year follow-up. Participants in the study had serum bicarbonate levels of approximately 20 mmol/l and the intervention group received relatively modest amounts of supplemental sodium bicarbonate at a dose of 600 mg thrice daily to maintain serum bicarbonate levels greater than 23 mmol/l. The following year, Phisitkul *et al.* published results of their single-center, nonblinded, randomized trial of sodium citrate, a sodium bicarbonate equivalent, supplementation vs. SOC in 59 patients with hypertensive nephropathy and metabolic acidosis [14]. Average eGFR was 33 ml/min/1.73 m^2 and average serum bicarbonate was approximately 20 mmol/l. Treatment with sodium citrate was associated with reduced levels of urinary endothelin-1 and *N*-acetyl-β-D-glucosaminidase (markers of kidney injury) and slower eGFR decline.

On the basis of these small single-center studies, alkali therapy to maintain serum bicarbonate levels within the normal range in patients with CKD and metabolic acidosis were adopted by the 2012 KDIGO guidelines as a 2B recommendation [15]. In hindsight, this decision may have been influenced by the near decade long wake of failed trials following publication of both IDNT and RENAAL demonstrating efficacy of angiotensin receptor blockers (ARB) in diabetic kidney disease [16,17].

The above evidence was strengthened after publication of the Use of Bicarbonate in CKD (UBI) study in 2019, which remains the largest trial of metabolic acidosis treatment to date [18]. This randomized, open-label, pragmatic, controlled trial was conducted at 10 sites in Italy and randomized 795 participants with CKD 3–5 (mean eGFR 35 ml/min/1.73 m^2) and serum bicarbonate levels >18 but <24 mmol/l (mean 21 mmol/l) to sodium bicarbonate or SOC. Notable exclusion criteria included NYHA class III or IV heart failure, blood pressure >150/90 mmHg and history of cerebrovascular disease. Sodium bicarbonate was administered twice daily and adjusted to maintain serum bicarbonate levels between 24–28 mmol/l in the intervention group. Over a 36 month follow up period mean serum bicarbonate concentration was 22 mmol/l in the SOC group vs. 26 mmol/l in the sodium bicarbonate group. As compared with SOC, participants treated with sodium bicarbonate had less decline in CrCl (4.9 vs. 10.9 ml/min), 64% reduced risk of doubling of serum creatinine (HR 0.36, 95% CI: 0.22–0.58, $P < 0.01$), 50% lower risk of kidney replacement therapy (KRT) (HR 0.5, 95% CI: 0.31–0.81, $P < 0.005$) and a 57% reduced risk of all-cause mortality (HR 0.43, 95% CI: 0.22–0.87, $P < 0.01$). Sodium bicarbonate therapy was well tolerated with no appreciable differences in blood pressure, body weight or signs of fluid overload between groups. To put these numbers in context, these are large effect sizes than seen with paradigm changing interventions such as angiotensin receptor blockers (ARBs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Although results of the UBI study seemed to add to a compelling body of literature, it should be noted that all the aforementioned trials had open-label designs, limiting their credibility due to the possibility of bias. To determine whether the lack of safety signals justifies routine use of sodium bicarbonate for therapy of metabolic acidosis in CKD we must examine studies with more rigorous design.

In 2020, the bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB) study was published [19]. This was a pragmatic, multicenter, double blind placebo controlled, randomized trial that recruited participants from 27 nephrology and geriatric medicine departments in the United Kingdom. Ultimately 300 participants with an eGFR <30 ml/min/1.73 m^2 and serum bicarbonate levels <22 mmol/l were randomized to either oral sodium bicarbonate or placebo with a two year follow up. The primary outcome in this trial was between group differences in the Short Physical Performance Battery (SPPB) at 12 months, rather than changes in kidney function, and recruitment was challenging (380 participants were initially planned), possibly influenced by perceived lack of clinical equipoise suggesting that sodium bicarbonate therapy had become enshrined as SOC in this population. For those participants randomized to the intervention arm, sodium bicarbonate was titrated to a goal serum bicarbonate level of >22 mmol/l, however dose adjustments were prohibited beyond three months. There were no significant differences in the composite of doubling of serum creatinine, 40% reduction in eGFR or initiation of KRT (kidney replacement therapy) between groups, though more adverse events were reported in the intervention arm. Beyond the fact that this study was under-powered and kidney impact of sodium bicarbonate therapy was a secondary outcome, this study is criticized for lack of meaningful changes in serum bicarbonate. Serum bicarbonate in the intervention group was only 1.1 mmol/l higher in the treatment group as compared to the placebo group, which differs from the open-label trials above and could have impacted results.

ALKALI THERAPY FOR CHRONIC KIDNEY DISEASE PATIENTS WITHOUT METABOLIC ACIDOSIS

In contrast to the above studies in patients with more advanced stages of CKD and metabolic acidosis, it has been suggested that the adaptive responses in the kidney in reaction to acid accumulation insufficient to lower serum bicarbonate level below target range, termed eubicarbonatemic metabolic acidosis, may contribute to progression of CKD, a process which is mediated by endothelin-1 and aldosterone [3,20–23]. Hypothetically, earlier therapy may be more effective prior to the development of overt acidosis. Two studies have assessed the impact of alkali therapy on progression of CKD in patients with earlier stages of hypertensive nephropathy and the absence of clinically apparent metabolic acidosis. The first, a blinded placebo-controlled trial, randomized 120 patients with stage 2 CKD (mean eGFR 75 ml/min/1.73 m^2), mean urine albumin to creatinine ratio (UACR) of ~400 mg/g, and mean serum bicarbonate level of 26 mmol/l, to sodium bicarbonate, sodium chloride or placebo [24]. Over a five-year follow-up period, treatment with sodium bicarbonate resulted in a slower annual rate of eGFR decline, −1.5 mL/min/1.73 m^2, vs. −2.0 and −2.1 ml/min/1.73 m^2 with sodium chloride and placebo respectively. The second study randomized 199 participants with stage 1 or 2 CKD, >200 mg of albuminuria, and normal serum bicarbonate levels to alkali supplementation with either sodium bicarbonate or fruits and vegetables versus matching placebo [25]. Over a 30-day follow-up, participants randomized to alkali supplementation had lower urinary levels of *N*-acetyl-β-D-glucosaminidase and transforming growth factor β, regardless of whether they received oral sodium bicarbonate or supplementation with fruits and vegetables.

Although these studies have primarily focused on alkali therapy using sodium bicarbonate, it is possible that correction of metabolic acidosis using alternative therapies provides greater benefit.

VEVERIMER AS AN ALTERNATE TREATMENT TO SODIUM BICARBONATE

Veverimer is an oral nonabsorbed polymer that selectively binds and eliminates hydrochloric acid from the gastrointestinal tract, leading to an increase in serum bicarbonate levels. Initial exploratory studies demonstrated veverimer's efficacy in raising serum bicarbonate levels without an increase in adverse events [26,27]. This was confirmed in a longer extension trial of patients with an eGFR between 20–40 ml/min/1.73m^2 and metabolic acidosis with serum bicarbonate levels between 12 and 20 mmol/l [28]. A prespecified exploratory analysis demonstrated that veverimer was associated with improved time to the composite clinical endpoint of death, KRT, or a decline in eGFR of at least 50% in the 196 participants included in the cumulative 52 weeks treatment period. This culminated in the randomized multicenter randomized placebo-controlled VALOR-CKD trial, which recruited over 1400 patients [29▪]. Topline results were released by

Table 1. Relevant studies assessing the impact of alkali therapy on kidney disease progression

Trial	Design	Length	Population	Intervention	Control	Selected outcomes		
Nonblinded sodium bicarbonate trials in metabolic acidosis								
de Britto Ashurst 2009 (n-134)	Single center, open-label, randomized, prospective, parallel group	2y	CKD 4 & Serum HCO_3^- 16–20 mmol/l	SB 600 mg TID titrated to maintain serum $HCO_3^- \geq 23$ mmol/l	SOC	CrCl Decline (ml/min/1.73 m^2) SB: 1.88 Cont: 5.93 *P < 0.0002*	Rapid Decline in CrCl SB: 9% Cont: 45% *RR 0.15* *95% CI 0.06–0.40* *P < 0.0001*	ESRD SB: 6.5% Cont: 33% *RR 0.13* *95% CI 0.04–0.40* *P < 0.001*
DI Iorlo 2019 (n-750)	Multicenter, randomized, unblinded, pragmatic controlled	36 mo	CKD 3–5 & serum HCO_3^- >18 and <24 mmol/l	Half bicarbonate deficit starting dose, increased to serum HCO_3^- 24–28 mmol/l	SOC	Doubling of Serum Creatinine SB: 6.6% Cont: 17% *P < 0.001*	Dialysis Initiation SB: 6.9% Cont:12.3% *P = 0.016*	Death SB: 3.1% Cont: 6.8% *P = 0.004*
Phisitkul2010 (*n* = 59)	Single center, prospective, open label, nonrandomized	24 mo	Hypertensive nephropathy & metabolic acidosis average eGFR ~33 average serum HCO_3^- ~20	Sodium citrate 1 mEq/kg/day sodium bicarbonate equivalent	SOC	Yearly eGFRcr decline SC: -1.6 ± 0.13 Cont: –3.79 ± 0.3 *P < 0.0001*	NAG at 30 months (ng/g) SC: 7.72 ± 2.14 Cont: 10.37 ± 3.15 *P = 0.0004*	
Blinded, placebo controlled sodium bicarbonate trials in metabolic acidosis								
BiCARB Study Group 2020 (n-300)	Multicenter, double blind, placebo Controlled, randomized	2y	CKD 4–5 & Serum HCO_3^- <22 mmol/L	500 mg SB TID at 3 months titrated to 1000 mg TID if serum HCO_3^- <22 No additional titrations after 3 months	Placebo	Composite: doubling of serum creatinine, 40% eGFR loss or RRT initiation *HR 1.16; 95% CI 0.73–1.84; P = 0.53*	Initiation of RRT or transplant SB:22% Cont: 22% *P = 1.0*	
Raphael 2020 (n-194)	Multicenter, randomized, double-blinded, placebo controlled	28w	eGFR 20–44 ml/min/1.73m^2 or eGR4 45–59 ml/min per 1.73 m^2 with UACR ≥50 mg/g & Serum HCO_3^- 20–28 mmol/L	Higher Dose (HD) SB 0.8 meq/kg of lean body wt/d Lower-dose (LD) SB 0.5 /meq/kg of lean body wt/d	Placebo	eGFR and CrCl no significant difference among groups during follow up.	UACR trend LD: 12% higher than baseline (95% CI -12% to 42%) HD: 30% higher than baseline (95% CI 8% to 56%)	
Mahajan 2010 (n-120)	Prospective, randomized, placebo controlled, blinded	5y	CKD 2 with Ualb 200–2000 mg/g Irrespective of Serum HCO_3^-	Bicarbonate group 0.5mEq/kg lean body weight of $NaHCO_3$ Sodium Chloride group 0.5mEq/kg lean body weight of NaCl	Placebo	eGFR Loss (ml/min/year) SB: -1.47 ± 0.19 Placebo: -2.13 ± 0.19 ml/min/year *P = 0.014* and NaCl: -2.05 ± 0.19 ml/min/year *P = 0.029*		

Table 1 (*Continued*)

Trial	Design	Length	Population	Intervention	Control	Selected outcomes
CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HCO_3^-, bicarbonate; RR, relative risk; RSC, routine standard of care; SB, sodium bicarbonate; SC, sodium citrate; UACR, urinary albumin to creatinine ratio; Cont-control, NAG, *N*-acetyl-β-D-glucosaminidase.						
Alkali therapy in patients with normal serum bicarbonate						
Mahajan 2010 (N-120)	Prospective, randomized, placebo controlled, blinded	5 years	Hypertensive Nephropathy with CKD 2 & macroalbuminuria (200–2000 mg/g cr) & Normal bicarb (avg 26 mmol/l)	Sodium Bicarbonate or Sodium Chloride 0.5mEq/kg lean body weight/day	Placebo	eGFR by Cr change (ml/min/yr) SB: -1.49 ± 0.19 Vs Placebo: -2.13 ± 0.19 *P* = *0.012* & NaCl: -2.05 ± 0.19 *P* = *0.029*
Goraya 2012 (N-		30 d	CKD 1 (n-79) or 2 (n-120) & Albuminuria >200mg/g & normal serum bicarb	Sodium Bicarbonate 0.5mEq/kg/d Fruits and Vegetables	SOC	CKD I Group No difference between groups on indices of Kidney Injury CKD II Group Ualb change Cont: +9.0 ± 20mg/g (*P* = *0.0565*) SB: -14.7 ± 22.2 mg/g (*P* < *0.001*) F+V: -34.3 ± 46.9 mg/g (*P* < *0.001*) Significantly less Ualb in SB and F+V compared to control (*P* = 0.003 and *P* < *0.001*, respectively) UNAG change Cont: +0.062 ± 0.136 U/g Cr (*P* = *0.006*) SB: -0.088 ± 0.134 U/g Cr (*P* < *0.001*) F+V: -0.080 ± 0.080 U/g Cr (*P* < *001*) Significant decrease in UNAG in SB and F+V compared to control (*P* = < 0.001 and *P* < *0.001*) UTGF change Cont: +2.298 ± 6.994 ng/g Cr (*P* < *0.001*) SB: -6.888 ± 4.953 ng/g Cr (*P* < *0.001*) F+V: -6.483 ± 4.908 ng/g Cr (*P* < *0.004*) Significant decrease in UTGF in SB and F+V compared to control (*P* = < 0.001 and *P* < *0.001*)

F+V, fruits and vegetables; Ualb, urinary albumin; UNAG, urinary *N*-acetyl-β-D-glucosaminidase; UTGF, urine transforming growth factor β.

the parent company Tricida indicating that the study did not meet its primary endpoint, which was defined as time to first occurrence of any event in the composite of renal death, ESKD or greater than or equal to 40% reduction in eGFR. It is worth noting that two years prior to this trial the FDA had denied Tricida's application to fast-track Veverimer, suggesting skepticism of metabolic acidosis as a surrogate marker.

DIETARY INTERVENTIONS FOR METABOLIC ACIDOSIS – 'FOOD AS MEDICINE'

Conventional Western diets are high in animal protein with less emphasis on intake of fruits and vegetables, including in those patients with CKD, even though diets rich in fruits and vegetables are recommended as first line in patients with diabetes and hypertension, which are leading causes of CKD in the US. Fruits and vegetables have demonstrated success in reducing the daily acid load and can effectively treat metabolic acidosis without the obligate sodium load that accompanies conventional therapy with sodium bicarbonate [30]. The addition of 2–4 cups of fruit and vegetables to patients with stage 2 CKD was comparable to giving 0.5 mEq/kg/day of bicarbonate [31]. A prospective RCT comparing a ketoanalogue-supplemented vegetarian very low-protein diet to a conventional low protein diet (0.60 g/kg/day including animal proteins) conducted in 207 patients with an eGFR <30 ml/min/1.73 m^2 over a 3-month period demonstrated improvement in serum bicarbonate from as baseline of 16.7 to 22.9 mEq/l ($P < 0.01$) compared to 16.8–16.2 in the nonvegetarian arm [32]. The number needed to treat to avoid the composite primary endpoint of $>50\%$ reduction in eGFR or initiation of kidney replacement therapy was 4.4 in the intervention arm. Goraya *et al.* [33] randomized 71 patients with stage 4 CKD secondary to hypertensive nephropathy and metabolic acidosis to either one-year of therapy with oral sodium bicarbonate or fruits and vegetables, which were provided free of charge and distributed from the food bank. Both therapies resulted in improvement in serum bicarbonate levels, though oral sodium bicarbonate was more effective. There was no difference in cystatin C calculated eGFR at baseline and one year, although was associated with urinary indices of kidney injury, such as urine *N*-acetyl-beta-D-glucosaminidase (NAG) and urine transforming growth factor-beta, leading the authors to conclude that fruits and vegetables may be an effective strategy to improve metabolic acidosis and reduce kidney injury in this vulnerable population. While we cannot refute that increasing base producing fruit and vegetable intake would be expected to improve metabolic acidosis, improves cardiovascular outcomes, and may slow progression of kidney disease, it cannot be overstated that the impact of this dietary intervention on metabolic acidosis cannot be isolated from the pleiotropic effects of improved nutrition, which is more likely responsible for improvement in outcomes.

CONCLUSION

Slowing progression of chronic kidney disease and preventing ESKD is the raison d'etre of Nephrologists. Alkali therapy to correct metabolic acidosis has been a standard approach to care on the heels of biologic plausibility and flawed studies concluding with a 2B recommendation by the 2012 KDIGO guidelines. However, when existing trials are appraised critically, inconsistent results are clear. A 2021 meta-analysis concluded that sodium bicarbonate may slow CKD progression, however the authors acknowledged this was based on low certainty evidence [34]. A summary of relevant studies is displayed in Table 1. Subgroup analysis of the effects of sodium bicarbonate therapy on change in kidney function according to trial quality demonstrated attenuation of any benefit when only high-quality trials were included. Contemporary studies have failed to show benefit on CKD progression with correction of metabolic acidosis, resulting in demotion in the KDIGO guidelines to a practice point where alkali therapy may be considered to maintain serum bicarbonate levels >16 mmol/l, which has thus far been presented in draft form. The landscape of CKD treatment has advanced considerably in the past several years with the advent of SGLT2 inhibitors, Glucagon-like peptide 1 (GLP-1) agonists and nonsteroidal mineralocorticoid antagonists. When effective therapies, including RAS inhibitors, are already underutilized it begs the question why focus on an intervention of questionable efficacy? Unless large-scale randomized trials demonstrate success in the future, we agree with the proposed KDIGO guidelines to de-emphasize therapy of metabolic acidosis. In our own clinics we will be spending more time de-escalating alkali therapy rather than prescribing it.

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Conflicts of interest

Dr Arora provides consulting services for Bayer Pharmaceuticals.

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- ■■ of outstanding interest

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