Kidney Medicine

Metabolic Acidosis in CKD: A Review of Recent Findings

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Metabolic acidosis is fairly common in patients with chronic kidney disease (CKD). The prevalence of metabolic acidosis increases with worsening kidney function and is observed in ~40% of those with stage 4 CKD. For the past 2 decades, clinical practice guidelines have suggested treatment of metabolic acidosis to counterbalance adverse effects of metabolic acidosis on bone and muscle. Studies in animal models of CKD also demonstrated that metabolic acidosis causes kidney fibrosis. During the past decade, results from observational studies identified associations between metabolic acidosis and adverse kidney outcomes, and results from interventional studies support the hypothesis that treating metabolic acidosis with sodium bicarbonate preserves kidney function. However, convincing data from large-scale, double-blinded, placebo-controlled, randomized trials have been lacking. This review discusses findings from recent interventional trials of alkali therapy in CKD and new findings linking metabolic acidosis with cardiovascular disease in adults and CKD progression in children. Finally, a novel agent that treats metabolic acidosis in patients with CKD by binding hydrochloric acid in the gastrointestinal tract is discussed.

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Kidney regulation of systemic pH principally involves the excretion of protons as ammonium and dihydrogen phosphate. Proton elimination facilitates bicarbonate reclamation and generation to restore bicarbonate ions consumed to buffer endogenously produced acid. Metabolic acidosis is characterized by proton accumulation resulting from insufficient kidney acid excretion relative to the nonvolatile acid burden. In chronic kidney disease (CKD), the clinical diagnosis of metabolic acidosis is typically made when serum bicarbonate level decreases to <22 mEq/L. However, proton accumulation is present before serum bicarbonate level decreases, a state referred to as eubicarbonatemic acidosis, normobicarbonatemic acidosis, or subclinical acidosis (Fig 1[1]).

Continued proton accumulation and impaired bicarbonate production eventually lead to low serum bicarbonate levels, but a low serum bicarbonate level is not always accompanied by low systemic pH in patients with CKD.[2] Hence, there is a spectrum of metabolic acidosis in CKD extending from eubicarbonatemic metabolic acidosis to an acid state characterized by low bicarbonate level and acidemia (Fig 1). There is a theoretical direct association between the severity of the acid state and risk for poor clinical outcomes.[1] Studying this relationship is challenging because identifying eubicarbonatemic acidosis is not straightforward and systemic pH is not routinely measured in clinical practice or research protocols. Consequently, most research studies define metabolic acidosis as serum bicarbonate level <22 mEq/L in individuals with CKD, which is how the term is used here.

OVERVIEW

A number of excellent review articles have discussed the pathogenesis of and risk factors for metabolic acidosis, mechanisms of acid-mediated organ injury, evidence that treating metabolic acidosis in CKD preserves kidney function, and the role of diet as a strategy to treat metabolic acidosis in CKD.[3-7] This review discusses new findings in the field, including observational studies linking metabolic acidosis with CKD progression in children and with cardiovascular events (CVEs) in adults. A novel pharmacologic agent, veverimer, that treats metabolic acidosis by binding hydrochloric acid in the gastrointestinal tract, is also discussed. A brief discussion of metabolic acidosis in end-stage kidney disease (ESKD) and considerations regarding when to initiate alkali therapy and the target bicarbonate concentration are presented. First, the article reviews several recently published interventional trials (Table 1[8-13]), including the largest metabolic acidosis treatment trial conducted to date.

INTERVENTIONAL TRIALS

Background

Adverse effects on bone and muscle were some of the first identified complications of chronic metabolic acidosis in CKD.[14-16] Evidence that metabolic acidosis caused loss of bone architecture and muscle catabolism prompted the National Kidney Foundation to suggest treating metabolic acidosis with oral alkali in patients with CKD in the early 2000s.[17,18] However, convincing evidence that treating metabolic acidosis with alkali improved bone and/or muscle health was lacking.

In the past decade, associations between metabolic acidosis and CKD progression and death were uncovered, corroborating findings in animal studies.[19-26] Results from early-phase clinical trials also suggested that treatment of metabolic acidosis with either nutritional or pharmacologic alkali preserves kidney function.[27-32] In 2009, de Brito-Ashurst et al[27] reported results from a randomized, unblinded, non–placebo-controlled trial testing whether

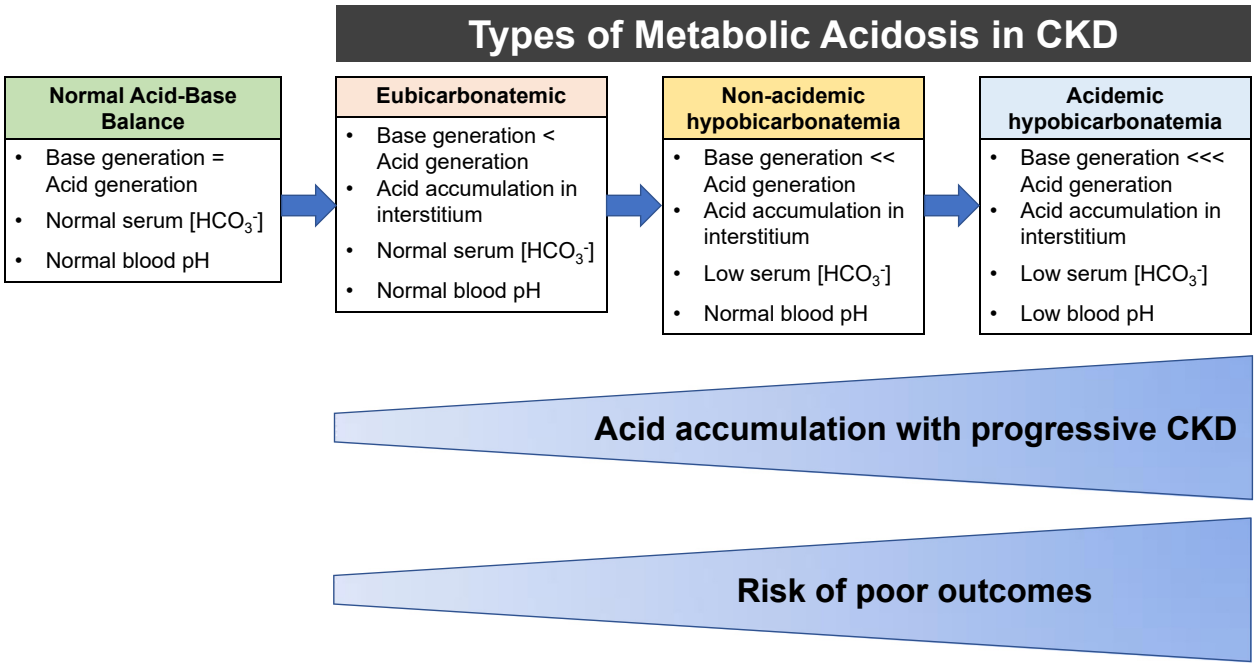

Figure 1. Spectrum of metabolic acidosis in chronic kidney disease (CKD). Acid accumulation progresses as kidney function declines. In early CKD, acid accumulation is subtle and may not be accompanied by changes in serum bicarbonate or blood pH values, a state often referred to as eubicarbonatemic metabolic acidosis or subclinical metabolic acidosis. As acid accumulates, the serum bicarbonate level decreases and may (acidemic hypobicarbonatemia) or may not (nonacidemic hypobicarbonatemia) be accompanied by a reduction in blood pH, depending on the degree of respiratory compensation. It is hypothesized that the risk for acid-mediated organ injury (eg, CKD progression, death, bone demineralization, and muscle catabolism) is directly related to the severity of acid accumulation. Reproduced from Raphael and Kraut[1] with permission of the copyright holder (Elsevier).

treatment of metabolic acidosis preserved kidney function in 134 individuals with CKD. They found that treatment with sodium bicarbonate reduced the rate of creatinine clearance decline (5.9 vs 1.9 mL/min/1.73 m^2), lowered the risk for ESKD by 87%, and improved several nutritional parameters, including midarm muscle circumference.[27] Shortly thereafter, Phisitkul et al[28] reported that hypertensive patients with CKD with metabolic acidosis treated with sodium citrate (n = 30) had an improvement in kidney injury marker levels (such as urinary endothelin-1 and N-acetyl-β-D-glucosaminidase) and better preserved kidney function over 2 years than similar individuals who were not treated with alkali (n = 29). Based on the totality of these findings, treatment of metabolic acidosis with alkali has been suggested by clinical practice guidelines.[17,18,33]

Findings from other early-phase studies challenged the notion that alkali should be reserved for those with metabolic acidosis. Mahajan et al[32] reported in 2010 that treatment with sodium bicarbonate (n = 40), irrespective of baseline serum bicarbonate concentration, better preserved estimated glomerular filtration rate (eGFR) than treatment with either placebo (n = 40) or equimolar sodium chloride (n = 40) in patients with stage 2 CKD over 5 years. Goraya et al[31] later reported that treatment with fruits and vegetables (n = 36) or sodium bicarbonate (n = 36) preserved kidney function better and similarly over 3 years compared with a control group (n = 36) in patients with stage 3 CKD and serum bicarbonate levels of 22 to 24 mEq/L. These findings raised the possibility that patients with normal serum bicarbonate levels might also benefit from alkali by mitigating compensatory responses that facilitate kidney acid excretion, but detrimentally promote kidney damage, to maintain serum bicarbonate levels.

The Use of Bicarbonate in CKD Study

Although these findings suggested that alkali preserved kidney function and improved nutritional parameters, the studies were single center with limited sample size, and most only enrolled individuals with CKD attributed to hypertension. Nevertheless, the findings led to the design and execution of other trials testing the effect of alkali therapy on kidney parameters in patients with broad causes of CKD and serum bicarbonate concentrations. The Use of Bicarbonate in CKD (UBI) Study, conducted at 10 sites in Italy, randomly assigned 795 individuals with CKD stages 3-5 and serum bicarbonate levels >18 but <24 mEq/L to receive sodium bicarbonate or usual care for 36 months. In the experimental group, the dose of sodium bicarbonate was adjusted to target a serum bicarbonate concentration of 24 to 28 mEq/L. Key exclusion criteria were New York

Table 1. Summary of Recent Interventional Trials

Trial	Population	Serum Bicarbonate, mEq/L	Total Sample Size	Duration	Intervention	Major Findings
UBI[8]	CKD stage 3, 4, or 5	>18 but <24	795	36 mo	$NaHCO_3$ to target bicarbonate 24-28 mEq/L	• Lower risk for serum creatinine doubling, RRT, and death
BiCARB[9]	Age > 60 y, eGFR < 30 mL/min/1.73 m^2	<22	300	24 mo	$NaHCO_3$ up to 3,000 mg/d	• No significant effect on Short Physical Performance Battery after 12 mo • Shorter 6-min walk distance and reduction in hand-grip strength in treatment group • More adverse events with treatment
Alkali Therapy in CKD[10]	CKD stage 3 or 4	20-26	149	24 mo	$NaHCO_3$, 0.4 mEq/kg of body weight/d	• No significant effect on bone mineral density, sit-to-stand time, other physical function assessments, or eGFR
VA BiCARB[11]	Diabetes CKD 2, 3, or 4 ACR > 30 mg/g	22-28	74	6 mo	0.5 mEq/kg of lean body weight/d	• No statistically significant effect on urinary markers of kidney injury
BASE Pilot Trial[12]	CKD stage 3b or 4 or CKD 3a with ACR ≥ 50 mg/g	20-28	192	28 wk	0.5 or 0.8 mEq/kg lean body weight/d	• No significant effect on blood pressure or weight • Dose-dependent increase in serum bicarbonate • Dose-dependent increase in urinary ACR
Veverimer (40-wk extension study)[13]	eGFR 20-40 mL/min/1.73 m^2	12-20	196	52 wk	Veverimer 6 g/d then titrated to target bicarbonate 22-29 mEq/L	• 3% in veverimer vs 10% in placebo discontinued treatment • Treatment with veverimer improved physical function • Fewer treated with veverimer died or progressed to ESKD

Abbreviations: ACR, albumin-creatinine ratio; BASE, Bicarbonate Administration to Stabilize eGFR; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; RRT, renal replacement therapy; UBI, Use of Bicarbonate in CKD.

Heart Association class III or IV heart failure symptoms and blood pressure > 150/90 mm Hg. During the follow-up period, serum bicarbonate concentration was ~26 mEq/L in the active treatment group versus 22 mEq/L in the usual care group. In the usual care group, 17% experienced a doubling of serum creatinine level (primary end point) as compared with 6% in the active treatment group ($P < 0.0001$; Fig 2[8]). Further, treatment with sodium bicarbonate was associated with 50% lower hazard of initiating renal replacement therapy, lower hospitalization rate, and lower mortality rate (6.8% vs 3.1%; $P = 0.016$), providing the first evidence in trials in humans that treatment of metabolic acidosis may improve survival. There was no appreciable effect on blood pressure or body weight.[8] Although the study was open label and not placebo controlled, the UBI Study is the largest metabolic acidosis treatment trial to date, and its results suggest that alkali therapy in patients with serum bicarbonate levels <24 mEq/L improves kidney and patient survival in CKD.

BiCARB Trial

While the primary outcome in UBI was doubling of serum creatinine level, the BiCARB Trial tested the effect of treating metabolic acidosis on physical function.[9] Although there is strong evidence that acidosis adversely affects bone and muscle health, whether treating acidosis improves physical function is unclear. Several observational studies have identified links between lower serum bicarbonate levels and poorer physical function.[34–36] As far as the interventional evidence, some studies have found that treating metabolic acidosis in CKD increases midarm muscle circumference[27] and improves sit-stand-sit time, although the latter was observed in a single-arm study.[37]

The BiCARB Trial was multicenter, double blinded, and placebo controlled.[9] Key entry criteria were eGFR < 30 mL/min/1.73 m^2, age older than 60 years, and serum bicarbonate level < 22 mEq/L. Participants were randomly assigned to receive sodium bicarbonate or placebo for up to 2 years. However the primary outcome was change in Short Physical Performance Battery (SPPB) score at month 12. Importantly, the starting dose of sodium bicarbonate was 1.5 g/d and was increased to 3.0 g/d at month 3 if serum bicarbonate level was <22 mEq/L. Dose increases after month 3 were not allowed even if serum bicarbonate level remained at <22 mEq/L. Recruitment was challenging and was eventually stopped when 300 individuals were enrolled, instead of the 380 that were planned.

In general, the study found that treatment of metabolic acidosis was unfavorable. At 1 year, treatment did not improve physical function, assessed by SPPB score. Those in the experimental arm had slightly, but not statistically significantly, lower SPPB scores at month 12 (−0.4 point; 95% CI, −0.9 to 0.1), indicating worse physical function. Along these lines, 6-minute walk distance (mean, 33 m) and grip strength (mean, 1.5 kg) were statistically significantly lower in the experimental arm. No significant treatment effect on various bone and cardiovascular markers was observed. However, more adverse events were reported in the treatment arm. Based on these findings and the results of a cost-effectiveness analysis, the authors concluded that treatment of metabolic acidosis in patients with stage 4 or 5 CKD was unfavorable, potentially harmful, and not cost-effective.

While these findings are concerning, the study had 2 major weaknesses. First, recruitment was challenging, which the authors partly attributed to a lack of equipoise.

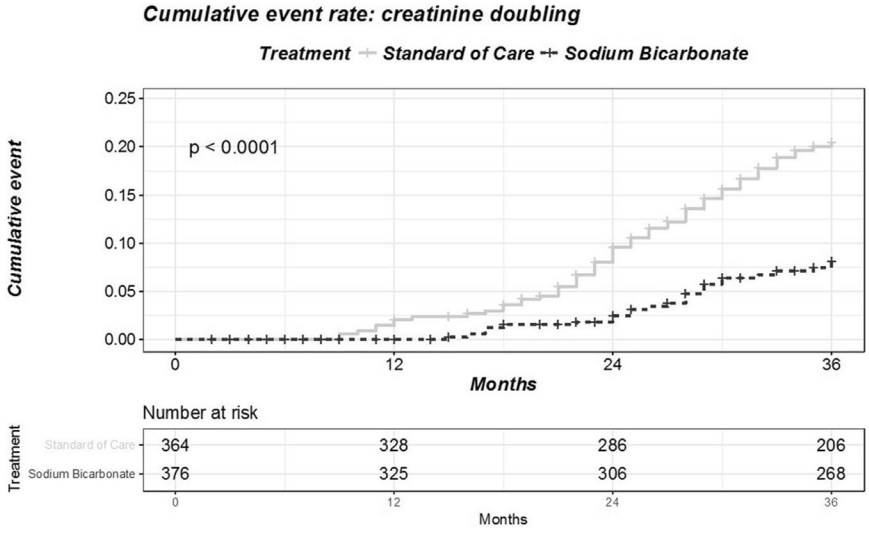

Figure 2. Time to doubling of serum creatinine level in the Use of Bicarbonate in CKD Study. In the usual care group, 17% experienced a doubling of serum creatinine level. In the sodium bicarbonate group, 6% experienced a doubling of serum creatinine level ($P < 0.0001$). Reproduced from Di Iorio et al.[8]

This led to a smaller sample size than anticipated. There was 87% power to detect a 1-point difference in SPPB score with 300 randomly assigned participants. However, data for the primary outcome (SPPB score at month 12) were available in only 274 participants at baseline and 187 at month 12. Hence, missing data was considerable. A second limitation is that metabolic acidosis was insufficiently treated during the trial. Serum bicarbonate level was 1.1 mEq/L higher in the treatment group during the course of the study; however, the mean baseline bicarbonate level was 20.6 mEq/L, indicating that a substantial proportion in the treatment group still had metabolic acidosis during the study. Hence, the overall conclusion that sodium bicarbonate was potentially harmful should be interpreted with these limitations in mind.

Alkali Therapy in CKD Trial

Like the BiCARB Trial, the primary outcome in the Alkali Therapy in CKD Trial was not kidney related. Instead, the coprimary outcomes were change in bone mineral density at the femoral neck and sit-to-stand time.[10] One hundred forty-nine individuals with CKD stage 3 or 4 and serum bicarbonate levels of 20 to 26 mEq/L at 3 United States medical centers were randomly assigned to treatment with sodium bicarbonate, 0.4 mEq/kg of ideal body weight per day or matching placebo. Mean serum bicarbonate levels increased to 26.4 (SD, 2.2) mEq/L in the sodium bicarbonate group at 2 months compared to 23.6 (SD, 2.5) mEq/L in the placebo group ($P < 0.001$). However, over time, the separation between the groups was not sustained. Bone mineral density and sit-to-stand time decreased in both groups during the 2-year follow-up period, and the differences between the groups were not significant. There was also no significant effect on hand grip strength or other measures of physical function. There was a significant decrease in serum potassium levels in the sodium bicarbonate group by ~0.1 mEq/L that persisted during the 24 months of the study.

In terms of safety, there were no significant between-group differences with respect to worsening of congestive heart failure, edema, or increase in diuretic therapy. There were fewer episodes of hyperkalemia, defined as potassium level ≥ 5.0 mEq/L, in the sodium bicarbonate group (19%) compared with the placebo group (40%).[10] The authors concluded that bicarbonate supplementation was safe in patients with CKD stages 3 and 4 but that potentially higher doses may be required to improve bone mineral content and skeletal muscle strength.

Sodium Bicarbonate in Veterans With Nonacidotic Diabetic CKD

The hypothesis that alkali therapy might benefit patients with CKD with normal bicarbonate levels had not been tested in individuals with diabetes. To investigate the kidney effects of sodium bicarbonate in this setting, a randomized, double-blinded, placebo-controlled trial in 74 US veterans with diabetes and stages 2-4 CKD was conducted. Other key entry criteria included urinary albumin-creatinine ratio ≥ 30 mg/g, serum bicarbonate level of 22 to 28 mEq/L, and blood pressure < 140/90 mm Hg. The dose of sodium bicarbonate tested was 0.5 mEq/kg of lean body weight per day. After 6 months of treatment, there was no difference in urinary transforming growth factor β1 level, the primary outcome, between the experimental and control groups over 6 months. There was also no significant difference in urinary kidney injury molecule 1 to creatinine ratio, fibronectin to creatinine ratio, or neutrophil gelatinase-associated lipocalin to creatinine ratio between the groups, or any significant differences in terms of side effects.[11]

Bicarbonate Administration to Stabilize eGFR Pilot Trial

There were 2 major goals of the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial.[12] The first was to determine whether it was feasible to conduct a phase 3 trial testing the effect of sodium bicarbonate treatment on slowing CKD progression. The second was to determine the dose of sodium bicarbonate to administer in such a trial. Building on early findings that alkali therapy might benefit individuals with low and normal serum bicarbonate levels, the study targeted individuals with levels of 20 to 28 mEq/L. At the time, the published and ongoing trials involving individuals with normal serum bicarbonate levels were principally using daily sodium bicarbonate doses in the range of 0.5 mEq/kg of lean or ideal body weight.[10,11,32] However, the ideal dose to use in this setting was not entirely clear.

BASE was consequently designed as a randomized, double-blinded, placebo-controlled trial to test the safety, tolerability, compliance, and pharmacodynamic effects of 2 doses of sodium bicarbonate (0.5 and 0.8 mEq/kg of lean body weight per day) against a placebo-treated group over 28 weeks. Key inclusion criteria were eGFR of 20 to <45 mL/min/1.73 m^2 or eGFR of 45 to <60 mL/min/1.73 m^2 with urinary albumin-creatinine ratio ≥ 50 mg/g and serum bicarbonate level of 20 to 28 mEq/L. Key exclusion criteria were blood pressure > 160/100 mm Hg and class III or IV New York Heart Association symptoms. A dose was considered feasible for a phase 3 trial if at least 67% completed the study on the full per-protocol dose and at least 80% were prescribed at least 25% of the per-protocol dose at the end of the study. In effect, the dose prescribed at the end of the trial would reflect whether the dose had to be reduced or stopped due to side effects while also factoring participant attrition. The effects of the 2 doses on urinary ammonium, urinary pH, and serum bicarbonate levels were evaluated, as well as a pharmacodynamics assessment.

One hundred ninety-four individuals were randomly assigned across 10 clinical sites in the United States; 90 to the higher sodium bicarbonate dose and 52 each to the

lower dose and placebo groups. The mean daily sodium bicarbonate dose was 4.1 g in the higher-dose group and 2.5 g in the lower-dose group. Adherence by pill count was ≥88% in each group. Both doses were considered feasible for use in a phase 3 trial because 87% in the higher-dose group and 96% in the lower-dose group completed the study on the full per-protocol dose. The proportion in the placebo group that completed the study on full dose was similar to the proportion in the higher-dose group (87%) but lower than that in the lower-dose group.

In terms of safety, neither dose of sodium bicarbonate had an appreciable effect on blood pressure or weight (Fig 3[12]) or serum potassium concentration or hospitalization rate. There was also no significant difference in the proportion requiring an increase in diuretic or antihypertensive therapy or gastrointestinal symptoms. In terms of pharmacodynamics, serum bicarbonate level was 1.3 mEq/L higher and urinary ammonium excretion was 25% lower in the higher-dose group as compared with the lower-dose group.

However, mean urinary albumin-creatinine ratio increased by 30% in the higher-dose group and 12% in the lower-dose group. This finding was unexpected because increases in urinary albumin or total protein excretion had not been reported in other sodium bicarbonate trials in CKD. Reasons for the modest increase in urinary albumin excretion observed in the BASE Pilot Trial but not others are unclear and perhaps idiosyncratic. There was no difference in eGFRs during the study between the groups, which was not unexpected given the short duration of the trial. Nevertheless, results of the study suggested that both doses were safe and tolerable. Importantly, neither dose meaningfully affected blood pressure or weight, which are commonly cited concerns regarding the use of sodium-based alkali in the treatment of metabolic acidosis. Finally, the findings suggest that the higher sodium bicarbonate dose may be a better option to study in future trials than the lower dose given the larger increase in serum bicarbonate levels observed.[12]

METABOLIC ACIDOSIS AND CARDIOVASCULAR DISEASE

Several observational studies have identified associations between metabolic acidosis and mortality.[19,21-23] The reasons for the increased mortality risk were not clear but it was logical to suspect that cardiovascular disease (CVD) was a major contributor given the established link between CKD and CVD.[38] However, data from the Chronic Renal Insufficiency Cohort (CRIC) Study did not show a link between metabolic acidosis and CVD. Higher bicarbonate concentrations (>26 mEq/L) were associated with heart failure in CRIC, providing some uncertainty regarding a link between bicarbonate levels and CVD.[39,40]

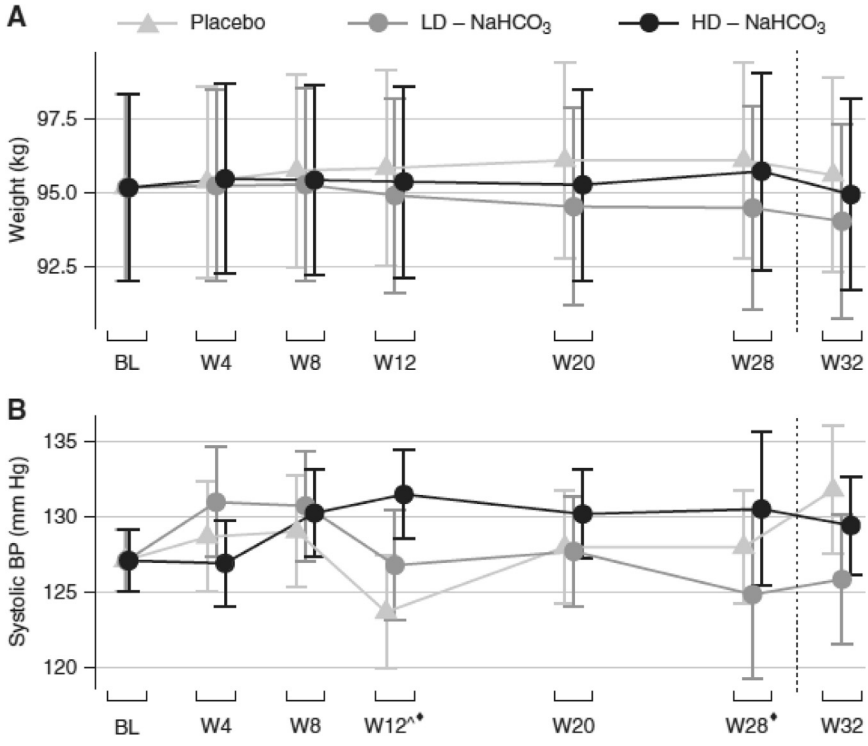

Figure 3. Changes in total body weight and systolic blood pressure in the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial. The 2 doses of sodium bicarbonate used in the trial did not have an appreciable effect on: (A) total body weight or (B) systolic blood pressure. Abbreviations: BP, blood pressure; HD, high dose; LD, low dose; W, week. Reproduced from Raphael et al[12] with permission from the copyright holder (American Society of Nephrology).

Recent studies in other populations have identified associations between lower bicarbonate concentration and CVD. For example, in the Systolic Blood Pressure Reduction Intervention Trial (SPRINT), serum bicarbonate level <22 mEq/L was associated with 54% higher risk for the primary outcome in the trial (composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, and CVD death) as compared with those with bicarbonate levels of 22 to 26 mEq/L (Fig 4).[41] Because SPRINT included individuals with and without CKD, this finding suggests that low bicarbonate level is associated with CVD in individuals without CKD as well. Djamali et al[42] also reported that serum bicarbonate level < 20 mEq/L was associated with 2-fold higher risk for CVEs, principally ischemic events, compared with those with serum bicarbonate levels of 24 to 26 mEq/L, among kidney transplant recipients. However, high, but not low, serum bicarbonate concentration (>26 mEq/L) was associated with cardiovascular death among participants in the National Health and Nutrition Examination Survey (1999-2020).[43] An interesting finding from this study that is worth further exploration was that low bicarbonate concentration was associated with increased risk for cancer-related mortality.[43] Nevertheless, serum bicarbonate concentration might be considered a nontraditional CVD risk factor.

The mechanisms linking metabolic acidosis with risk for adverse CVEs are unclear but important to delineate because many more patients die of CVD than progress to ESKD. In a recent study of more than 2,000 patients with CKD in South Korea, metabolic acidosis was associated with greater arterial stiffness assessed using pulse wave velocity.[44] Kendrick et al[45] reported that treatment of metabolic acidosis modestly improved flow-mediated dilation in the brachial artery in a crossover study of 18 individuals with CKD. Another noteworthy finding was that serum calcification propensity, assessed by calciprotein particle maturation time, was not increased with treatment, a finding that was also reported in the ongoing SoBic Study.[46] These findings are important because in animal models of CKD, treatment of metabolic acidosis was found to increase vascular calcification, raising some concern that treating acidosis may be harmful in humans.[47,48] The effect of treating metabolic acidosis on CVD, such as vascular calcification, left ventricular mass, heart failure, and myocardial infarction, is unclear.

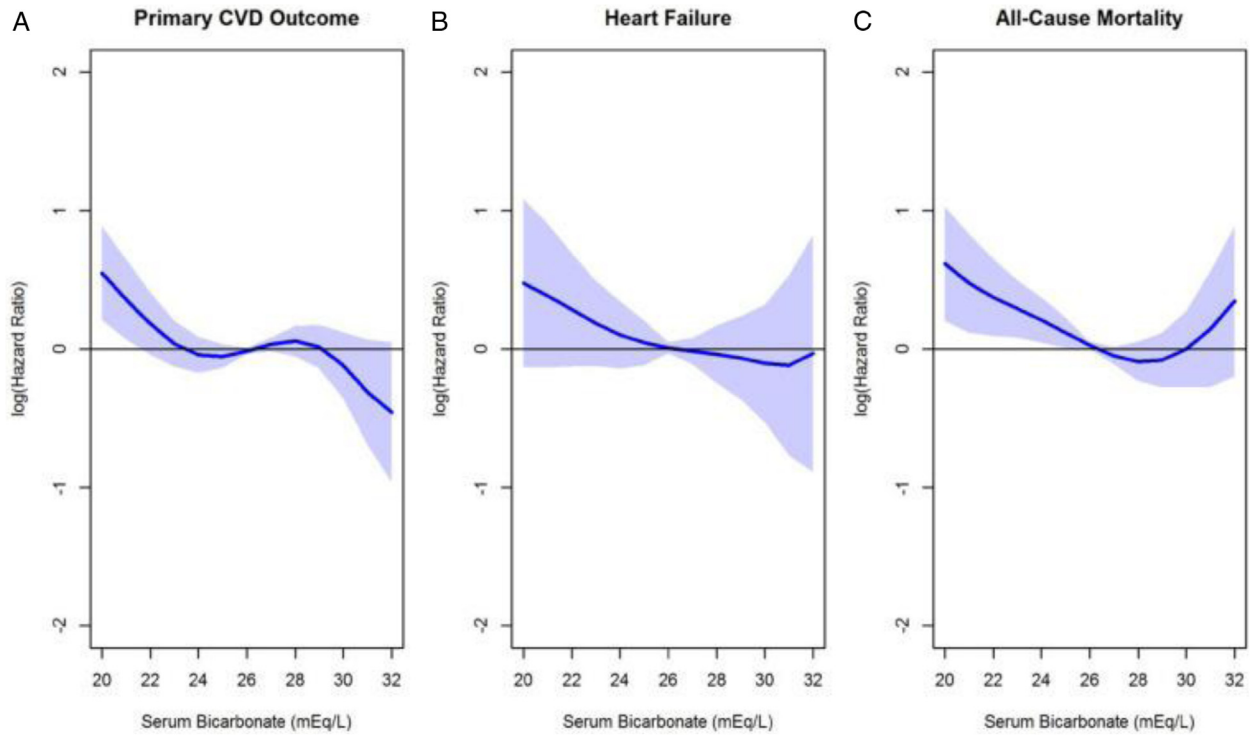

Figure 4. Association between baseline (BL) serum bicarbonate concentration and clinical events in the Systolic Blood Pressure Reduction Intervention Trial (SPRINT). Lower serum bicarbonate levels were associated with significantly higher risks for: (A) the primary composite outcome and (C) all-cause mortality in SPRINT. (B) There was a suggestion that lower bicarbonate levels were also associated with higher risk for heart failure. Abbreviation: CVD, cardiovascular disease. Reproduced from Dobre et al[41] with permission from the copyright holder (Oxford University Press).

METABOLIC ACIDOSIS AND CKD PROGRESSION IN PEDIATRIC POPULATIONS

Fewer data about the relationship between metabolic acidosis and clinical outcomes in children are available than in adults. Data for pediatric kidney disease include only observational studies with no randomized clinical trials. Earlier pre-post studies suggest that treatment with alkali therapy may improve growth in children with renal tubular acidosis.[49,50] However, associations of serum bicarbonate levels and progression of pediatric CKD have only recently been published. In the European Cardiovascular Comorbidity in Children With CKD Study (4C), an analysis of 704 children followed up for a median of 3.3 years showed that participants with serum bicarbonate levels < 18 mEq/L had higher risk for CKD progression (defined as ESKD or 50% decline in eGFR) compared with participants with serum bicarbonate levels >22 mEq/L (hazard ratio, 2.44; (95% CI, 1.43-4.15).[51]

In an analysis of the Chronic Kidney Disease in Children (CKiD) Study, data for 858 children with both glomerular and nonglomerular causes of kidney disease showed that only ~30% of patients with serum bicarbonate levels <22 mEq/L were treated with alkali therapy.[52] This was especially true in patients with glomerular disease, for which only 18% of the patients with bicarbonate levels ≤ 22 mEq/L were treated with alkali.[52]

The authors evaluated the associations of longitudinally assessed serum bicarbonate levels with a composite outcome of 50% decrease in eGFR or kidney replacement therapy over 3 years. They found that participants with glomerular disease with serum bicarbonate levels < 18 mEq/L had much higher risk for CKD progression (hazard ratio, 2.16; 95% CI, 1.05-4.44) compared with participants with bicarbonate levels >22 mEq/L.[52] Similar hazard ratios were found in participants with underlying nonglomerular disease, but the associations were not statistically significant. Interestingly, participants who had lower serum bicarbonate levels that then resolved experienced less CKD progression than those who had consistently low serum bicarbonate levels.

Thus, metabolic acidosis is associated with progression of kidney disease in children, as it is in adults. Metabolic acidosis seems to be undertreated in children despite suggestive evidence that it improves growth. Clinical trials should be conducted to determine the impact of treatment of metabolic acidosis on progression of CKD and growth in children.

VEVERIMER

Base administration has been the mainstay treatment of metabolic acidosis in CKD. Veverimer is a novel nonabsorbed polymer that selectively binds and eliminates hydrochloric acid from the gastrointestinal tract. In a phase 1/2 trial of 135 patients with a mean eGFR of 35 mL/min/1.73 m^2 and serum bicarbonate level of 17.7 mEq/L who were kept on a standard diet, a range of veverimer doses increased serum bicarbonate levels by ~3 mEq/L during the 14-day study period.[53] Based on these findings, the effect of veverimer on serum bicarbonate levels was investigated in a 12-week trial[54] and then in a 40-week extension study of the 12-week trial.[13] In the longer-term follow-up study, 63% versus 38% experienced an increase in serum bicarbonate level by ≥4 mEq/L (Fig 5[13]), and veverimer was found to be safe (3% in veverimer vs 10% in placebo discontinued treatment prematurely). In secondary analyses, fewer participants treated with veverimer progressed to ESKD or died, and self-reported and objective measurements of physical function improved in the active treatment group.[13]

Based on these promising findings, a large-scale, randomized, placebo-controlled clinical trial (VALOR-CKD) testing the effect of veverimer on kidney and patient survival is ongoing (NCT03710291). If approved for clinical use, veverimer would treat metabolic acidosis by binding and eliminating protons from the intestinal tract instead of by administering base as with bicarbonate or citrate formulations. At this time, it is unclear whether binding hydrochloric acid in the gut is superior to base administration. Head-to-head trials comparing the safety and efficacy of this novel agent against base therapy will help clinicians decide which, if any, should be preferred.

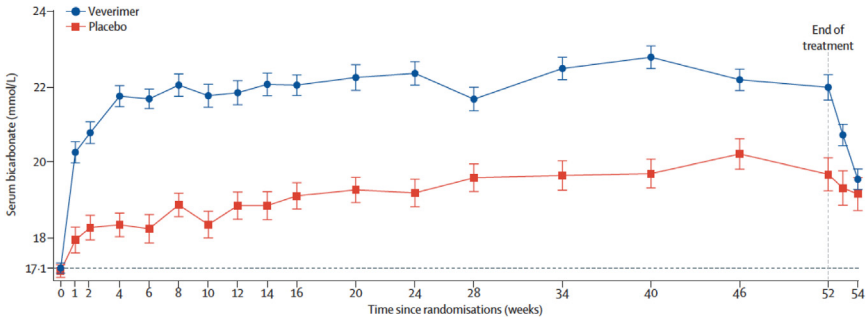

Figure 5. Effect of veverimer on serum bicarbonate concentration in individuals with metabolic acidosis and chronic kidney disease. At week 52, mean serum bicarbonate level was 2.0 (SD, 0.5) mEq/L higher than in the placebo group. Serum bicarbonate levels decreased after stopping active treatment. Adapted from Wesson et al[13] with permission from the copyright holder (Elsevier).

END-STAGE KIDNEY DISEASE

A comprehensive discussion of metabolic acidosis in ESKD is beyond the scope of this review. Several excellent reviews are available.[55-57] The optimal predialysis serum bicarbonate concentration in hemodialysis (HD) patients is unclear. In the Dialysis Outcomes and Practice Patterns Study, both low (≤17 mEq/L) and high bicarbonate levels (>27 mEq/L) were associated with increased mortality in persons receiving HD.[58] In a separate study, bicarbonate level > 22 mEq/L was associated with lower risk for death in HD after multivariate adjustment.[59] Complicating matters is that pre-HD serum bicarbonate concentration is an imperfect indicator of the severity of acidemia for individuals receiving HD. In a sample of 25 US veterans receiving in-center HD, 9 experienced at least 1 instance in which serum total carbon dioxide measured by the clinical laboratory was <22 mEq/L but the corresponding pH was not low. In these instances, median postdialysis pH was 7.51 (interquartile range, 7.48-7.52).[60] Increasing bicarbonate dialysate concentration in response to a low bicarbonate level may provoke or worsen alkalemia in some patients, and higher dialysate bicarbonate concentrations have been associated with increased risk for death as well.[61] There is a clear need to improve understanding of the interplay between pre- and post-HD acid-base status, dialysate bicarbonate concentrations, and their effect on clinical outcomes. In peritoneal dialysis, bicarbonate level < 24 mEq/L has been associated with 2.6-fold higher risk for loss of residual renal function [62] and results from small studies suggest that treatment with sodium bicarbonate may maintain residual kidney function and improve nutritional status.[63,64]

WHEN TO TREAT AND WHAT TO TARGET

Clinical practice guidelines have suggested maintaining serum bicarbonate levels at ≥22 mEq/L in CKD, suggesting that treatment should be initiated below this range. Serum bicarbonate levels can vary depending on dietary factors, volume status, kidney function, and others. Hence, an important question to consider is when to start treatment. It is likely that longer exposure to an acidic environment increases the possibility of adverse acidosis-related effects. Nevertheless, it is reasonable to verify that a low bicarbonate level persists on more than 1 blood draw before initiating therapy. The UBI Study enrolled individuals with serum bicarbonate levels < 24 mEq/L, challenging the current paradigm to wait until bicarbonate level is <22 mEq/L before starting treatment. UBI Study participants were treated with sodium bicarbonate targeting bicarbonate levels of 24 to 28 mEq/L, also challenging the current paradigm's target level. Based on the available interventional and observational data, we propose that an ideal target bicarbonate level is in the range of 24 to 26 mEq/L (Fig 6[65]).

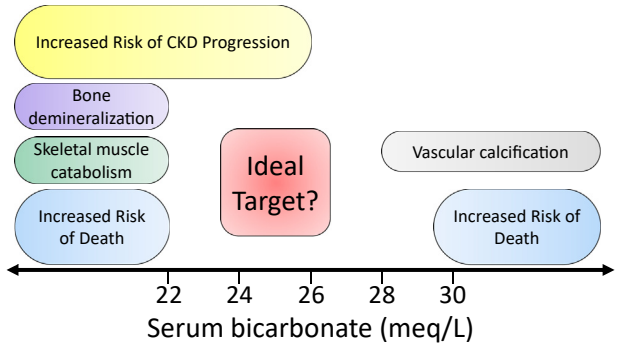

Figure 6. Summary of major associations between serum bicarbonate levels and adverse outcomes in chronic kidney disease (CKD). Bicarbonate levels < 22 mEq/L and >28 mEq/L are associated with increased risks for adverse events. Results from observational studies and a few interventional studies suggest that the ideal serum bicarbonate concentration may be in the 24- to 26-mEq/L range. Using alkali therapy to target bicarbonate levels in this range is reasonable. Adapted from Raphael[65] with permission from the copyright holder (Elsevier).

FUTURE DIRECTIONS

With mounting evidence that metabolic acidosis is associated with adverse clinical outcomes and the positive findings from interventional trials such as the UBI Study and others, it seems that treatment of metabolic acidosis in CKD is warranted. Ideally, the results of these studies should be confirmed in a large, well-designed, appropriately powered trial with sufficient follow-up to assess both efficacy and safety. In the meantime, results of the large-scale veverimer trial on kidney and patient survival in acidotic patients with CKD are eagerly anticipated. Trials investigating the long-term effect of preventing metabolic acidosis (ie, in those with normal bicarbonate levels) should continue to be pursued. Studies testing the effect of alkali on CKD progression and other clinically meaningfully end points in children are warranted.

ARTICLE INFORMATION

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