Metabolic Acidosis in Chronic Kidney Disease:

A Clinical Update

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Introduction

Metabolic acidosis is a common hallmark of advanced chronic kidney disease (CKD), and in this setting it is generally defined as persistently low serum bicarbonate levels of < 22 mEq/L.[1] Although most non-dialysis patients have normal serum bicarbonate levels due to compensatory renal ammonia production and bone buffering,[2,3,4] metabolic acidosis has a prevalence in CKD of approximately 15%-19% overall.[5,6,7,8,9] However, prevalence increases as kidney function declines.[7,10]

While possibly slowing kidney function decline, the timely recognition of metabolic acidosis provides an opportunity to prevent metabolic bone disease, muscle wasting, stunted growth , hormonal abnormalities, and increased risk of death.[1,14,15]

Because metabolic acidosis is considered an independent risk factor for CKD progression, there is increased interest in its management. However, managing metabolic acidosis often goes unrecognized as a treatment strategy.[16] In fact, the prevalence of alkali therapy is estimated at only 2.4% for adults and only 29% for children.[17,18] Alkali therapy and nutritional interventions have been associated with a decrease in the progression of CKD, and should therefore be considered in the CKD plan of care. Novel therapeutics may also soon be of use.

Pathophysiology

CKD as a cause of metabolic acidosis

The kidney has the primary role of maintaining acid-base balance, which is normally accomplished by the renal excretion of the daily acid load.[19]

However, as kidney function declines, net functional nephron loss results in net acid retention exceeding net acid excretion. Acid is then retained in various tissues and increases their acidity; when this acid pool reaches a critical saturation point, there is a decrease in serum bicarbonate and systemic pH.[14]

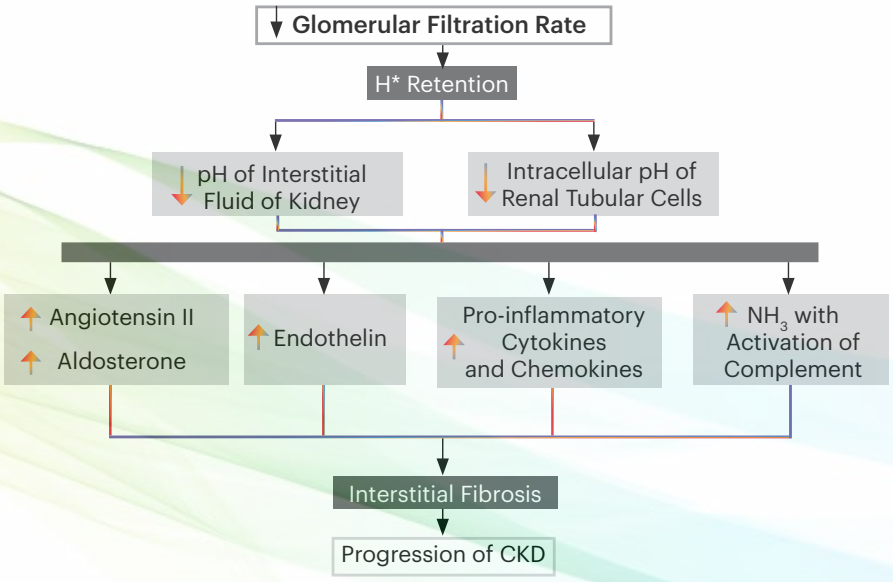
CKD progression due to metabolic acidosis

Kidney injury due to metabolic acidosis in CKD has been attributed to the loss of nephrons, leading to a compensatory hypertrophy of the remaining nephrons, as well as an increase in enzymes that generate ammonia to maintain acid-base balance.[16,20] *(Figure 1)*

Small studies[21,22,23,24] in both animals and humans indicate that metabolic acidosis is associated with progression of CKD. These findings are supported by much larger observational studies, including one with more than 5,000 subjects from a single outpatient clinic over a median follow-up of 3.4 years, that determined that a serum bicarbonate < 22 mEq/L is associated with CKD progression, defined as a decrease in estimated glomerular filtration rate (eGFR) by ≥50% of baseline or reaching eGFR < 15 mL/min/1.73 m^2.[25]

Figure 1. Proposed mechanisms for CKD progression with acid retention

Acidosis increases aldosterone, angiotensin II, and endothelin, which promote kidney injury and fibrosis. Metabolic acidosis is also associated with increased renal ammonia production, which activates complement that leads to injury and fibrosis. Finally, an acid environment stimulates pro-inflammatory cytokines, which may also cause kidney injury and fibrosis.[26]



Clinical Findings

Although hypotension and constitutional symptoms such as malaise and weakness have been reported, most CKD patients are asymptomatic. Serum bicarbonate is rarely <14 to 15 mEq/L and is often >20 mEq/L, even with severely low GFRs.[26] An early decrease in bicarbonate is compensated for by an increase in chloride and does not change the anion gap. In patients with more advanced CKD, however, bicarbonate is more greatly reduced and there is an increase in the anion gap.[27,28]

Complications

Major complications associated with metabolic acidosis in CKD include increased muscle wasting, bone disease, and, possibly cardiovascular disease and increased mortality.[26]

In children, metabolic acidosis impairs growth by inhibiting the secretion of growth hormone (GH) and decreasing its activity in peripheral tissues.[29,30]

A CKD registry at that included more than 41,000 patients revealed increased mortality associated with serum bicarbonate levels < 23 mEq/L in patients with moderate kidney disease (stage G3 CKD).[46] Randomized controlled studies are needed to determine if if correcting metabolic acidosis decreases mortality.[26]

Management

Evidence-based rationale for treatment

Studies have demonstrated that oral alkali may slow CKD progression and improve nutritional status.[24,32,33,34,35] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that serum bicarbonate concentrations <22 mEq/L be treated with oral bicarbonate to maintain serum bicarbonate within the normal range.[1] and the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines concur.[36]

Several retrospective reviews[18,25,37,38] indicate that outcomes for CKD patients with serum bicarbonate levels below normal are significantly worse than in patients with normal levels. Additionally, in four clinical trials, oral alkali increased serum bicarbonate in CKD patients with baseline levels < 22 mEq/L. The Phisitkul et al. study showed that oral alkali therapy decreased the number of CKD patients who had a ≥ 40% decline in estimated glomerular filtration rate (eGFR), a surrogate endpoint of kidney disease progression to end stage renal disease (ESRD).[33] A limitation of these studies is that subjects did not have the severe comorbidities often found in CKD, such as edema, heart failure, and poorly controlled hypertension, and sodium-based oral alkali could exacerbate these conditions.[5,39]

More recent trials with oral alkali have included patients with CKD co-morbidities. In a 2-year randomized, placebo-controlled study of 149 patients with CKD stages 3 and 4, sodium bicarbonate safely and significantly increased serum bicarbonate levels, while significantly decreasing serum potassium. No improvements in muscle function or bone mineral density occurred in both treated and untreated patients. In a 3-year randomized trial of oral sodium bicarbonate in 740 patients with CKD stages 3-5, sodium bicarbonate corrected metabolic acidosis, slowed the progression of CKD, and decreased all-cause mortality in the treatment group.[40]

Oral alkali supplementation

Due to the variation in serum bicarbonate measurements, a second measurement should be obtained before starting alkali supplementation. It is also recommended that, in most cases, venous blood gas measurement should confirm the acid-base disorder, especially if respiratory alkalosis is suspected.[41]

Clinical guidelines suggest using sodium bicarbonate with a starting dose of 650 mg twice daily (15.5 mEq/day of bicarbonate) and escalating the dose based upon the response. Recommended doses range from 0.5-1.0 mEq bicarbonate or its equivalent per kilogram body weight/day. Sodium bicarbonate is inexpensive, widely available, and generally well tolerated the most common side effects of sodium bicarbonate are bloating and burping. Sodium citrate may be used for less bloating, but citrate promotes intestinal aluminum absorption and increases the risk of aluminum toxicity for those on aluminum containing antacids.[42]

Sodium salts confer potential risks, including worsened hypertension, volume overload, and congestive heart failure. Although concern has been raised that higher doses in CKD could cause volume retention and worsen hypertension,, studies using sodium bicarbonate at much higher doses than recommended by KDIGO and KDOQI did not reveal an increase in blood pressure or edema.[43] Although these results are reassuring, patients were pre-selected and studies often excluded those with congestive heart failure and uncontrolled hypertension.[41]

Alkali therapy could cause metabolic alkalosis, and in such cases, sodium bicarbonate should be temporarily discontinued. Monitoring serum bicarbonate is important for dose titration, and to correct for over-treatment.[41] Treatment with oral alkali should target a normal serum bicarbonate level.[32,41] Table 1 includes details on commonly prescribed alkali supplements and their specific dosing considerations.

Table 1. Commonly Prescribed Alkali Supplement Doses and Considerations[10]

Agent/Dose	[HCO_3]	Considerations
$NaHCO_3$		
325-mg tablet	3.9 mEq	Inexpensive; non–potassium based; conversion of HCO_3^- to CO_2 causes upper GI symptoms
650-mg tablet	7.7 mEq	
600-mg (1/8 tsp) powder[a]	7.1 mEq	
Sodium citrate/citric acid solution		
500 mg/334 mg per 5 mL	1 mEq/mL	Fewer GI symptoms than $NaHCO_3$; non–potassium based; enhances aluminum absorption; conversion of citrate to HCO_3^- may be impaired in liver disease
490 mg/640 mg per 5 mL	1 mEq/mL	
Potassium citrate ± citric acid		
540-mg potassium citrate tablet	5 mEq	10- & 15-mEq tablets have more mEq of HCO_3^- than $NaHCO_3$ tablets; solution delivers more mEq/mL of HCO_3^- than sodium citrate solution; rare cause of GI ulceration; enhances aluminum absorption; may cause hyperkalemia; conversion of citrate to HCO_3^- may be impaired in liver disease
1,080-mg potassium citrate tablet	10 mEq	
1,620-mg potassium citrate tablet	15 mEq	
1,100 mg potassium citrate/334 mg citric acid per 5-mL solution	2 mEq/mL	
3,300 mg potassium citrate/1,002 mg citric acid packet[a]	30 mEq per packet	

Abbreviations: CO_2, carbon dioxide; GI, gastrointestinal; HCO_3^-, bicarbonate; $NaHCO_3$, sodium bicarbonate.
[a]Should be dissolved in water.

Dietary acid reduction

Diet partly contributes to the daily acid load, therefore, the typical Western diet, which is high in animal protein and limited in fruits and vegetables, increases net endogenous acid production. Conversely, a diet with a predominance of plant proteins over animal proteins, and high amounts of fruits and vegetables, may be a reasonable approach to limiting the daily acid load.[44]

In addition, because fruits and vegetables are base-inducing foods, it has been demonstrated that increasing their daily intake may also lower the dietary acid load and produce results comparable to those achieved with alkali therapy.[45,46,47] Adding 2–4 cups of fruits and vegetables to the daily diets of patients with CKD stage 2 was comparable to giving them 0.5 mEq/kg/day of sodium bicarbonate.[48] In 76 patients with CKD stage 4 and serum bicarbonate < 22 mEq/L, increased fruit and vegetable consumption increased serum bicarbonate, although less than sodium bicarbonate. After 1 year, eGFR was comparable between the 2 groups, and increased fruits and vegetables did not cause hyperkalemia in this group, all of whom had serum potassium levels ≤4.6 mEq/L when they entered the study.[46]

Based upon this evidence, adding fruits and vegetables and consuming more plant-based protein relative to animal-based protein, may be a viable approach to decreasing the acid load that exacerbates metabolic acidosis in CKD.

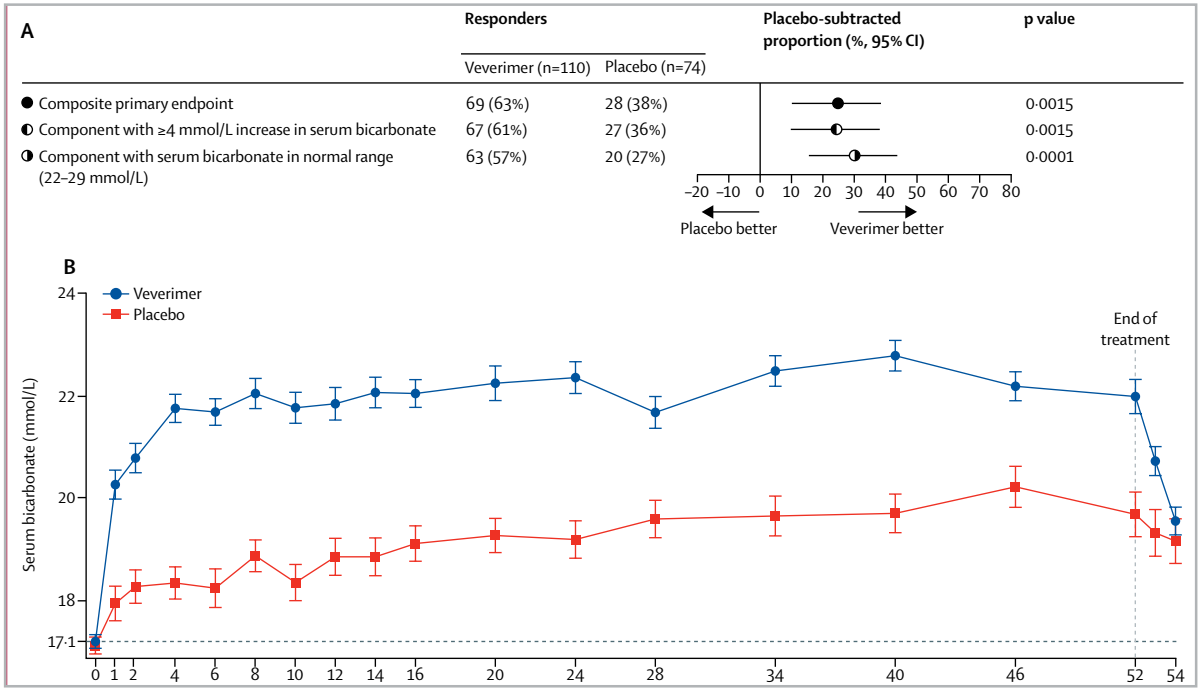
Veverimer (formerly TRC101)

Although evidence-based clinical guidelines recommend alkali therapy, there is currently no Food and Drug Administration (FDA) - approved treatment indicated for chronic metabolic acidosis in CKD. Therefore, veverimer, a sodium-free hydrochloric acid (HCl) acid binder, was developed for this purpose and is currently under FDA review. As an oral, insoluble, non-absorbed polymer, it selectively binds and removes hydrogen and chloride ions within the gastrointestinal tract. The polymer is composed of high molecular weight, crosslinked polyamine beads which bind HCl without a counterion; therefore, no mean changes occur in serum sodium, potassium, calcium, or magnesium.[49]

The TRC101 study, a multicenter, phase 1/2 randomized, double-blind, placebo-controlled trial, was the first evaluation of veverimer's efficacy and safety in 135 CKD patients. Patients treated for 14 days had a significant increase in mean serum bicarbonate that was maintained throughout the treatment period without serious adverse events.[49] A 12-week, phase 3 trial then followed, using 217 more patients with CKD; metabolic acidosis was effectively treated without serious adverse events.[50] A 40-week extension study of 196 patients from the phase 3 trial evaluated safety, efficacy, and physical functioning.[51] There were fewer serious adverse events in veverimer patients than in those on placebo, and more veverimer patients than placebo had an increase in bicarbonate at 52 weeks, and higher levels at all timepoints *(Figure 2)*. Patient responses to the Kidney Disease Quality of Life Instrument revealed subjective improvement in physical function with veverimer.

Figure 2. Change in serum bicarbonate

(A) The first secondary endpoint, durability of bicarbonate response, defined by the placebo-subtracted proportion of patients achieving a minimum of 4 mmol/L increase from baseline in serum bicarbonate or a serum bicarbonate in the normal range (22–29 mmol/L) at the end of treatment (week 52), is depicted as the top line. The two lower lines depict each component of the endpoint. The individual endpoint component analyses were prespecified but were not adjusted for multiple comparisons. p values are for the difference in proportions between veverimer and placebo groups (Fisher's exact test). (B) The baseline serum bicarbonate (treatment week 0), the mean of the screening 1, screening 2, and baseline day 1 values, was 17·2 mmol/L in the veverimer group and 17·1 mmol/L in the placebo group. Values depicted are the mean (SE).[51]



Conclusion

Chronic metabolic acidosis is a potentially modifiable risk factor associated with increased morbidity and mortality in CKD. Evidence suggests that alkali supplementation, dietary modification to reduce acid load, and HCl binding in the gastrointestinal tract can all increase serum bicarbonate levels. Controlling metabolic acidosis by increasing serum bicarbonate has been shown to slow CKD progression and improve outcomes. Long-term trials that compare all the treatments discussed with reproducible protocols and assessments, particularly in the setting of sodium-sensitive conditions such as the advanced stages of both heart failure and CKD, will help establish treatment guidelines for metabolic acidosis in CKD.

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