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Acid Base Balance and Progression of Kidney Disease

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Abstract

A large body of work in animals and humans supports the hypothesis that metabolic acidosis has a deleterious effect on the progression of kidney disease. Alkali therapy, whether pharmacologically or through dietary intervention, appears to slow CKD progression, but an appropriately powered randomized-controlled trial with a low risk of bias is required to reach a more definitive conclusion. Recent work on urinary ammonium excretion has demonstrated that the development of prognostic tools related to acidosis is not straightforward, and that application of urine markers such as ammonium may require more nuance than would be predicted based on our understanding of the pathophysiology.

SUMMARY

A large body of work in animals and humans supports the hypothesis that metabolic acidosis has a deleterious effect on the progression of kidney disease. Alkali therapy, whether pharmacologically or through dietary intervention, appears to slow CKD progression, but a larger, randomized-controlled trial with a low risk of bias is required to reach a more definitive conclusion. Recent work on urinary ammonium excretion has demonstrated that the development of prognostic tools related to acidosis is not straightforward, and that application of urine markers such as ammonium may require more nuance than would be predicted based on our understanding of the pathophysiology.

Keywords

Renal insufficiency; chronic; acidosis; alkalosis; alkali therapy; kidney disease progression

INTRODUCTION

Metabolic acidosis is common among patients with chronic kidney disease (CKD).^{1,2} Approximately 15% of patients with CKD have some degree of metabolic acidosis.³ The

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prevalence of metabolic acidosis begins to rise when glomerular filtrate rate (GFR) falls below ~ 40 ml/min/1.73m² and increases as GFR decreases.^{3–6} Metabolic acidosis is associated with numerous deleterious effects, including bone loss, insulin resistance, muscle wasting, and CKD progression.^{7,8} In this article, we review metabolic acidosis and CKD progression, including its pathogenesis, epidemiology including the new findings on urinary ammonium excretion as well interventional trials of alkali therapy, and summarize them in Figure 1.

PATHOPHYSIOLOGY OF METABOLIC ACIDOSIS AND CKD PROGRESSION

Mechanism of Maintaining Acid-base Balance

Tight regulation of acid-base balance plays a pivotal role in normal human physiology. Substantial changes in intracellular and extracellular pH are not compatible with life. Humans have multiple mechanisms in place to protect against extracellular acidemia and alkalemia. The 3 major regulators of acid-base balance are: excretion of carbon dioxide via the lungs, intracellular and extracellular buffering systems, and renal elimination of non-volatile acid and generation of base.⁵⁶ We will focus on the discussion of the renal handling of acid-base regulation.

The kidneys primarily use 2 major mechanisms to maintain acid-base balance. The first process involves reabsorption of the filtered bicarbonate. A healthy glomerulus can filter 4,500 mEq of bicarbonate per day and as much as 80% of the filtered bicarbonate is reabsorbed in the proximal tubule.⁹ Several conditions can increase proximal tubule reabsorption of bicarbonate including metabolic acidosis, hypokalemia, hypovolemia, angiotensin II, and glucocorticoids.⁶ The second process involves the formation of new bicarbonate by ammonia generation and distal nephron acid secretion. H⁺ ions secreted into the urine are largely bound by H⁺ acceptors, as even maximally acidified urine is incapable of excreting the daily acid load in the absence of buffering. Urinary phosphate as well as other buffers fulfill this role and are often described as titratable acids. However, the production of ammonia by the kidney is the major mechanism of new bicarbonate generation in the setting of metabolic acidosis and increases several-fold more than does titratable acid excretion. In the proximal tubule, the metabolism of glutamine to glutamate and subsequently oxaloacetate produces ammonia and bicarbonate.^{6,7} Other metabolic pathways may be involved as well but to a lesser extent.¹⁰ If the ammonia produced by the kidney is returned to the systemic circulation, its metabolism in the liver consumes bicarbonate. Therefore, excretion of ammonium in the urine is required for net gain of bicarbonate and reflects the quantity of base that has been added to the bicarbonate pool.

Development of metabolic acidosis in CKD

Adults consuming a typical western diet produce approximately 1meq of net acid per kilogram of body weight.⁹ The metabolism of protein produces sulfates and non-volatile acids which increase the acid load. Fruits and vegetables contain significant amounts of alkali and help neutralize the amount of acid that the kidneys need to excrete.¹¹ When renal function is preserved, the healthy renal tubule generates a comparable amount of bicarbonate which replaces the losses from intracellular and extracellular buffers. In an individual with

normal renal function, acid-base balance is neutral in a steady state and serum bicarbonate remains unchanged.⁸

In patients with CKD, the reduction of nephron mass results in significant impairment in total renal acid excretion ultimately leading to a positive acid balance.¹² In response to nephron loss, the remaining viable nephrons filter more blood per nephron thus increasing single nephron GFR.⁶ Although there is a net decrease of renal acid excretion with progressive CKD, single nephron acid excretion, especially ammoniogenesis, is enhanced.¹³ In spite of the increase in single nephron GFR, the remaining viable nephrons are unable to produce sufficient ammonia to excrete the acid load. The inability of the kidney to generate ammonia is directly related to the inability of the proximal tubule to uptake glutamine.^{9,14} The impairment in acid excretion is especially pertinent for individuals on high animal protein and low fruit and vegetable diets since the high protein intake increases the daily acid load.¹¹ The inability of the kidneys to produce sufficient ammonia to neutralize the daily acid load contributes to the non-anion gap metabolic acidosis that develops in patients with moderate CKD.⁶

In contrast to reduced total renal ammonium production in CKD, the titratable acid excretion is relatively preserved.⁶ In spite of renal function decline, the kidney maintains the ability to excrete titratable acids until GFR falls below 15 ml/min/1.73 m².^{6,9} With CKD progression, fibroblast growth factor 23 and parathyroid hormone increase which in turn cause an increase in urinary phosphate excretion.¹⁵ It is thought that this increase in urinary phosphorous allows for the preservation of titratable acid excretion in moderate to advanced CKD.^{6,16,17}

However, as kidney disease progresses, a positive anion gap develops secondary to the accumulation of phosphate and other anions as well as the loss of renal titratable acid excretion.⁶ There is evidence to suggest that there is a tendency for slight increases in the anion gap in individuals with mild chronic kidney disease.¹⁸ These findings are suggestive of accumulation of organic solutes even in relatively mild renal impairment.⁵ Bicarbonate wasting may play a role in the development of metabolic acidosis as well.^{5,19}

Pathophysiology of acidosis contributing to CKD progression

Epidemiologic studies have demonstrated that metabolic acidosis, defined by low serum is associated with increased risk of CKD progression. These studies are Several mechanisms for progression of CKD in metabolic acidosis have been described (Figure 1). The increased amount of [H⁺] that accompanies CKD causes enhanced single nephron ammoniogenesis and generation of aldosterone and endothelin 1.^{8,20,21} The increases in these hormones enhance renal [H⁺] excretion in the urine which helps mitigate metabolic acidosis.^{8,21} However, these same hormones promote renal fibrosis and progressive kidney disease.^{22,23} Hyperaldosteronism may increase glomerular pressure leading to glomerulosclerosis and reduction in GFR.^{24–27} There is also evidence that aldosterone increases cellular proliferation altering the structure of the kidney which then leads to fibrosis.^{23,25,26} Aldosterone stimulates oxidative stress and inflammation which further contributes to renal fibrosis.^{23,28}

The increase in single nephron ammonia generation causes high levels of ammonia to accumulate in the medullary interstitium.^{29–32} The increased ammonia reacts with C3 leading to the formation of the C3 convertase and activation of the alternative complement pathway.²⁹ The activated complement cascade causes deposition of C3 and C5b9 in the renal tubules which causes tubulointerstitial injury and renal fibrosis.^{30,31} The administration of alkali in rats with metabolic acidosis causes a reduction in single nephron ammonia synthesis which reduces progression of renal disease.²⁹ The up-regulated alternative complement system can be suppressed when metabolic acidosis is treated with alkali supplementation.³³

In the setting of metabolic acidosis, increased levels of endothelin 1 also contribute to progression of CKD.^{12,20} Endothelin-1 is an isoform of endothelial cell-derived peptide. Kidneys produce endothelin-1 and contain endothelin receptors, particularly in the vasculature and the medulla.³⁴ The increased level of endothelin 1 promotes the synthesis of fibronectin and 5,35 Rats administered a dietary acid load increased endothelin-1 and pharmacological inhibition of endothelin receptor blunted distal tubule acidification.³⁵ In patients with CKD, treatment of metabolic acidosis with alkali reduced serum levels of aldosterone and endothelin 1 along with urine markers of fibrosis and CKD progression.^{5,8,12,20}

CLINICAL ACID-BASE PARAMETERS IN CKD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFKK/DOQI) Guidelines suggest to treat metabolic acidosis and maintain bicarbonate 22 mEq/L.³⁶ Using serum bicarbonate as a treatment target over-simplifies the disease process and treatment of metabolic acidosis in patients with CKD. Besides bicarbonate concentration, dietary acid load, renal acid excretion and net acid balance are also significant parameters involved in metabolic acidosis (Table 1).

Dietary acid load can be estimated from the net endogenous acid production (NEAP), where NEAP is calculated using protein and potassium intake and based on the principle that protein intake is a surrogate for acid ingestion and potassium intake is a marker for alkali intake.³⁷ If protein intake is not available, it can be estimated by from 24-hour urine urea nitrogen excretion based on the fact that urea is the principal end product of amino acid degradation.³⁸

Renal acid excretion is calculated by adding urine ammonium and titratable acid, minus urine bicarbonate. Urine ammonium is measured directly or calculated using the urine anion gap (sodium + potassium – chloride),³⁹ but a more recent study showed that urine anion gap only weakly correlated with urine ammonium unless phosphate and sulfate were also included in the calculation.⁴⁰ Titratable acid can be measured by the direct titration method or calculated from total urine phosphorous, creatinine, and urine pH.^{41,42} Urine bicarbonate concentration is considered negligible in the physiological range of urine pH.^{43,44} Net acid balance is calculated by subtracting renal acid excretion from dietary acid load.

In patients with CKD, lower serum bicarbonate is associated with higher net endogenous acid production and higher renal acid excretion.^{43,45} Net acid balance increases as GFR declines and is inversely correlated with urinary ammonium excretion, but not related to bicarbonate concentration.⁴⁶

OBSERVATIONAL STUDIES OF ACID-BASE BALANCE AND CKD PROGRESSION

Low bicarbonate concentration and CKD progression

Low bicarbonate concentrations were shown to be associated with faster CKD progression in multiple epidemiologic studies (Table 2). Overall, with every 1 mEq/L increase in bicarbonate concentration, the risk of CKD progression (defined as either end stage renal disease (ESRD) or 50% reduction in GFR) decreased by 3–8% in ~4 years.^{47–49} In a non-institutionalized CKD cohort—Chronic Renal Insufficient cohort (CRIC), participants with CKD stage 2–4 and bicarbonate ≤ 22 mEq/L were at a greater risk of CKD progression compared to those with bicarbonate >26 mEq/L (10.3 vs. 3.6 renal events per 1000 person-years).⁴⁸ After adjusting for covariates including estimated GFR (eGFR) and proteinuria, serum bicarbonate was independently associated with the development of renal outcomes (ESRD or 50% reduction in eGFR) with a hazard ratio of 0.97 (95% CI 0.94–0.99) per 1 mEq/L increase in bicarbonate level ($p=0.01$). In a hospital-based CKD cohort—NephroTest cohort, the odds of having a $>10\%$ decline in GFR per year increased by 88% (OR 1.88, 95% CI 1.17–3.03) in participants with CKD stage 1–4 with bicarbonate <24.8 mEq/L compared to those with bicarbonate between 24.8 and 27.2 mEq/L, while there was no difference in the risk of developing ESRD.⁴⁶

Non-CKD cohorts showed similar findings. Among community living elders from the Health, Aging and Body Composition study, those with bicarbonate concentrations <23 mEq/L had a faster GFR decline by 0.55 ml/min/1.73m² per year (95%CI 0.13–0.97) compared to those with bicarbonate of 23–28 mEq/L.⁵⁰ Among participants with eGFR >60 ml/min/1.73m² from the Multiethnic Study of Atherosclerosis, the odds ratio for the association of bicarbonate <21 mEq/L compared to those with 23–24 mEq/L was 1.35 (95%CI 1.05–1.73) for rapid kidney function decline, which was defined as more than 5% eGFR decline per year.⁵¹

Low urine ammonium excretion may be a better indicator of acidosis

In most epidemiologic studies,^{46–50,52,53} bicarbonate concentrations were used to assess acid-base status. While the specificity of low bicarbonate concentrations for the presence of metabolic acidosis is likely greater in people with CKD than in the general population, this approach presumes the absence of a meaningful respiratory contribution and should be interpreted cautiously.

In addition, bicarbonate concentrations are not the best index for assessing the status of acid balance in CKD as patients with CKD may have acid retention despite having a normal or stable bicarbonate concentration. In a study involving patients with CKD stages 1 and 2 with normal serum bicarbonate, oral sodium bicarbonate reduced renal net acid excretion, but the

reduction was less in those with CKD stage 2 than stage 1, suggesting the presence of acid retention in patients with CKD stage 2.²¹ In a cohort of patients with CKD stage 1–4, acid balance was positive in patients with CKD stage 4 when most of these patients still had a normal bicarbonate concentration.⁴⁶ Acid balance increased as GFR declined, but was not associated with bicarbonate concentrations.

Recent studies suggest that urine ammonium excretion may be a better and perhaps earlier acid-base indicator than serum bicarbonate, especially in patients without overt acidosis.^{42,46} In 1,044 participants from the AASK trial,⁴² the mean serum bicarbonate was 25.1 ± 3.0 mEq/L with 12% of participants having acidosis (defined as bicarbonate <22 mEq/L). The median urine ammonium excretion was 19.5 mEq per day. Serum bicarbonate was not associated with urine ammonium excretion at baseline in unadjusted and adjusted analyses. Of those without acidosis at baseline, 10% developed acidosis at 1 year. The adjusted odds of incident acidosis at 1 year was 2.56 (95%CI 1.04–6.27) for those in the lowest tertile of urine ammonium excretion compared with the highest tertile. This suggests that low urine ammonium may be an indicator of acid retention and a risk factor for acidosis.

Urine ammonium excretion and CKD progression

In patients with CKD stage 2–4 from the CRIC study, the mean renal acid excretion was ~ 30 mEq per day with the percentage of acid excreted as ammonium being $\sim 45\%$.⁴³ The total renal acid excretion and the percentage of acid excreted as ammonium were lower with lower eGFR.⁴³ In response to acid retention in CKD, ammonia production per residual nephron increases.¹² As discussed above, this augmented renal ammoniogenesis may contribute to kidney disease progression through activation of the alternative complement cascade with resultant tubulointerstitial injury and stimulatory effects of ammonia on renal growth, and this relationship was demonstrated using a remnant kidney model of rats.³⁰

Several clinical studies have examined the association between urine ammonium excretion and CKD progression (Table 3). Since ammonium-mediated tubulointerstitial fibrosis was thought to contribute to CKD progression, one might expect that higher urine ammonium excretion would predict CKD progression. In a cross-sectional study of 144 patients with CKD stage 2–4 and normal serum bicarbonate concentration,⁵⁴ 24-hour urine ammonium excretion and urine transforming growth factor $\beta 1$ (TGF- $\beta 1$) were measured. Urine TGF- $\beta 1$ was selected as a kidney profibrotic marker^{55,56} because a prior study showed that TGF- $\beta 1$ was reduced by oral alkali therapy suggesting that TGF- $\beta 1$ may be a marker of acid-mediated organ injury.⁵⁷ While there was no association between serum bicarbonate and urine TGF- $\beta 1$, urine ammonium excretion was significantly associated with urine TGF- $\beta 1$. After adjusting for covariates including eGFR and proteinuria, each standard deviation increase of urine ammonium was associated with a 1.22 fold (95%CI 1.11–1.35) higher geometric mean urine TGF- $\beta 1$ per urine creatinine. These findings suggest that urine ammonium excretion is more tightly linked with kidney fibrosis than bicarbonate concentration, supporting the effect of intrarenal ammonium on renal fibrosis.

However, other clinical studies examining the relationship between urine ammonium excretion and CKD progression showed the opposite relationship. That is, lower daily urine ammonium excretion was associated with faster CKD progression.^{42,43,46} After a median

follow-up of 4.3 years, CKD participants from the NephroTest cohort with the lowest tertile of urine ammonium excretion had a higher risk of developing ESRD (HR 1.82, 95%CI 1.06–3.13, $p=0.02$ for trend) and a higher odds of fast GFR decline ($>10\%$ decline per year) (OR, 1.84; 95% CI, 0.98 to 3.48) compared to those in the highest tertile, after adjusting for demographics, co-morbidities, GFR, renin-angiotensin-aldosterone system blockade, urine albumin and fasting urine osmolality.⁴⁶ Similar findings were observed in the CRIC study,⁴³ but the association was only significant among participants with diabetes. Participants with CKD and diabetes had overall higher renal acid excretion, lower urine pH and a lower percentage of acid excreted as ammonium compared with those without diabetes. Higher urine ammonium excretion trended toward a lower risk of CKD progression among participants with diabetes ($p=0.14$ for trend), but not among those without diabetes ($p=0.66$ for trend).⁴³

The association between low urine ammonium and CKD progression could be due to poor dietary intake, which was not adjusted for in the analyses of the NephroTest cohort.⁴⁶ Thus, Raphael et al.⁴² evaluated the association of baseline ammonium excretion with the composite outcome of death or dialysis in participants from the African American Study of Kidney Disease and Hypertension (AASK) trial, which included dietary data. In participants from the AASK trial,⁴² urine ammonium excretion was moderately associated with protein intake, but there was little or no correlation with GFR, serum bicarbonate or net endogenous acid production. After adjusting for demographics, GFR, proteinuria, body mass index, net endogenous acid production and serum potassium and bicarbonate, the hazard ratio of the composite outcome of death or dialysis was 1.46 (95%CI 1.13–1.87) for those in the lowest tertile of urine ammonium excretion compared with the highest tertile.

The clinical findings of urine ammonium excretion and CKD progression seem contradictory to the findings from animal studies, which indicated that intrarenal ammonium contributes to renal injury in CKD. However, it is important to note that daily urine ammonium excretion may not reflect the renal tissue concentration of ammonium or urine ammonium excretion per nephron. A low urine ammonium excretion is likely an indicator of acid retention and impaired tubular function to excrete acid.⁴² Thus, the results from clinical studies do not necessarily contradict the findings from the animal studies.³⁰

Urine titratable acidity, urine pH, dietary acid load and CKD progression

Similar to urine ammonium excretion, higher titratable acidity and lower urine pH were associated with lower risk of CKD progression in patients with CKD and diabetes.⁴³ The association was not significant among CKD patients without diabetes in the same cohort.⁴³ The association between dietary acid load, estimated using net endogenous acid production, and CKD progression is less robust. Among African Americans with hypertensive CKD from the AASK trial, the trend for higher net endogenous acid production with faster decline was significant, but time to event analyses for composite renal events (ESRD or doubling serum creatinine) were not.⁵⁷ Among CKD patients from the CRIC study, dietary acid load was only associated with higher risk of CKD progression among those without diabetes and if dietary acid load was estimated using net endogenous acid production calculated from urine markers.⁴³ In the general population from the 1988–1994 National Health and

Nutrition Examination Survey, higher dietary acid load (determined by 24-hour dietary recall questionnaire) was associated with increased risk of ESRD with a relative hazard of 3.04 (95% CI 1.58–5.86) for those in the highest tertile compared to those in the lowest tertile in a fully adjusted model.⁵⁸

INTERVENTIONAL STUDIES ON THE EFFECT OF ALKALI THERAPY ON CKD PROGRESSION

Several interventional studies investigated the effect of alkali therapy on CKD progression. We have identified 7 main studies and summarized the findings in Table 4.^{21,57,59–63} The findings from these studies suggest that alkali therapy using either sodium bicarbonate/citrate or fruits and vegetables has promising effects on preserving renal function. However, most of these studies were conducted in hypertensive patients with either normal to mildly low bicarbonate levels. Patients with more profound acidosis were excluded due to ethical concerns of assigning them to the placebo group as the NKF-K/DOQI guidelines recommend to treat metabolic acidosis and maintain bicarbonate ≥ 22 mEq/L (even though this guideline was made based on weak evidence).³⁶ This exclusion criterion limits the generalizability of the findings to those with more severe metabolic acidosis.

The interventions in these studies were oral sodium bicarbonate or citrate and/or fruits and vegetables. These interventions were compared to usual care, sodium chloride or placebo. Sodium bicarbonate was given either at a constant dose based on weight (0.3 to 1 mEq/kg per day) or an escalating dose to achieve a specific bicarbonate concentration. Studies using fruits and vegetables as alkali therapy were mostly conducted by Wesson et al.^{61–63} Their method of implementing dietary intervention was creative. Individuals randomized to the fruits and vegetables group received an amount of fresh fruits and vegetables free of charge to reduce their dietary acid load by 50%, using primarily fruits and vegetables that were base-inducing. Participants did not receive specific dietary instructions and were allowed to integrate the provided fruits and vegetables into their diet *ad lib*. Each household member also received the same amount of fruits and vegetables to ensure that the participant did not share the prescribed amount with their families. Clinical trials involving dietary interventions are important to conduct, but they are often difficult to execute. Understandably, these studies were unblinded with difficult to assess compliance rate.

The primary outcome for these studies ranged from urine markers of kidney injury including urine albumin, N-acetyl- β -D-glucosaminidase, transforming growth factor- β and angiotensinogen as well plasma endothelin-1 and aldosterone, to the rate of GFR decline. Sodium bicarbonate supplementation lowered urine markers of kidney injury,^{57,61–63} reduced plasma endothelin-1 and aldosterone levels,²¹ and reduced GFR decline.^{57,59–62,64} In a study involving patients with CKD stage 4 and bicarbonate between 16 and 20 mEq/L, participants were randomized to receive sodium bicarbonate to achieve bicarbonate ≥ 23 mEq/L or usual care.⁵⁹ After 2 years of intervention, creatinine clearance in the sodium bicarbonate group declined by 1.9 ml/min/1.73m², whereas the usual care group declined by 5.9 ml/min/1.73m² (p<0.001). Fruits and vegetables were comparable with sodium bicarbonate supplementation in improving metabolic acidosis and CKD progression.^{61–63}

We assessed the quality of these studies using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Supplementary Table 1).⁶⁵ Only one study was rated as good quality by the Agency for Healthcare Research and Quality (AHRQ) standards with a low risk of bias.⁶⁰ However, the study population for this study was limited to patients with relatively normal eGFR and bicarbonate concentration. The rest of the studies were at best fair quality due to their high or unclear biases in selection (i.e. random sequence generation and allocation concealment) and performance (i.e. blinding of participants and personnel). Studies that involve dietary interventions are rarely rated as good quality by the AHRQ standards because it is difficult to blind participants and personnel in these trials. In addition, there might have been a presence of publication bias as all published studies showed positive treatment effects of alkali therapy. Thus, larger randomized-controlled trials focusing on patients with more advanced CKD and more profound metabolic acidosis are warranted before we will have a definitive conclusion on the effect of alkali therapy on CKD progression.

ON-GOING STUDIES AND FUTURE DIRECTIONS

On-going clinical trials on alkali therapy and CKD progression

There are several on-going clinical trials examining the effect of sodium bicarbonate supplementation in CKD, and they have been previously described.^{5,31} Two of these trials examine CKD progression as the primary outcome. One clinical trial is based in Italy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01640119); NCT01640119) and is a multicenter, randomized controlled, open label study.⁶⁶ The investigators plan to randomize 728 patients with CKD 3b-4 to either bicarbonate groups (with administration of sodium bicarbonate or other alkalinizing agent such as sodium citrate) to keep bicarbonate above 24 mEq/L or to a usual treatment group. The primary outcome is doubling of creatinine in 3 years. The other trial is based in Austria (European Union Clinical Trials Register; EUDRACT no. 2012-001824-36).⁶⁷ Patients with CKD stage 3-4 and bicarbonate <21 mEq/L (target n=200) are randomized to either receive a high dose oral sodium bicarbonate with target bicarbonate level of 24±1 mEq/L or to receive a rescue therapy of sodium bicarbonate with a target bicarbonate of 20±1 mEq/L. The primary outcome is decline in renal function (definition not specified in the clinical trial registry), mortality and time of initiation of renal replacement therapy in 2 years.

New development in alkali therapy

In the studies examining the effect of alkali therapy on kidney disease progression, sodium bicarbonate, sodium citrate or fruits and vegetables were used as the intervention.^{57,59-63} Sodium based alkali therapy may contribute to fluid overload and hypertension in patients with CKD. Patients with poorly controlled blood pressure, edema and overt congestive heart failure were excluded in the studies of sodium based therapy.^{57,59,61} In the studies involving fruits and vegetables, participants with a baseline potassium concentration >4.6 mEq/L were excluded,^{61,62} as fruits and vegetables may contribute to hyperkalemia, especially in those with low GFR.

Recently, a novel acid binding agent was developed and is currently being studied in clinical trials. TRC101 is a sodium-free, non-absorbed hydrochloric acid binder that removes

hydrochloric acid from the gastrointestinal tract, and thus does not contribute to fluid overload or hypertension. In a randomized, double-blind, placebo-controlled, multicenter, in-unit, phase 1/2 study, 135 patients with CKD stage 3–4 and metabolic acidosis received either placebo or one of 4 TRC101 dosing regimens for 14 days.⁶⁸ All TRC101 treatment groups had a mean increase in serum bicarbonate of 3.2–3.9 mEq/L ($p < 0.001$) compared with placebo at the end of the treatment. After discontinuation of TRC101, serum bicarbonate decreased nearly to baseline levels within 2 weeks. A phase 3 study is currently ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03317444); NCT03317444). It is a multicenter, double-blind, placebo-controlled, parallel-design study and will enroll ~210 adults with eGFR of 20–40 ml/min/1.73m² and bicarbonate concentration of 12–20 mEq/L. Participants are randomized to receive either TRC101 or placebo for 12 weeks. The primary outcome is the change in bicarbonate levels from baseline. We look forward to the results of this trial and hopefully future trials investigating the effect of TRC101 on CKD progression.

The findings on urine ammonium excretion, serum bicarbonate levels, and CKD progression suggest that urine ammonium excretion may be an early indicator of metabolic acidosis, and may change future clinical practice.^{42,46} In these studies, participants with normal serum bicarbonate concentration but a low urinary ammonium excretion had a high risk of CKD progression, and thus might benefit from alkali therapy. Perhaps future studies will investigate whether urine ammonium excretion can risk-stratify individuals with CKD and normal serum bicarbonate to identify who might benefit from alkali therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Overview of acid-base balance and CKD progression.

Abbreviations: NEAP, net endogenous acid production; CKD, chronic kidney disease; ET, endothelin.

Table 1.

Clinical acid-base parameters

	Calculation/Measurement
Bicarbonate concentration	-Measured by an electrode or enzymatic procedure -calculated from blood gas using Henderson-Hasselbalch equation: $\text{pH} = \text{pK}_a + \log ([\text{A}^-]/[\text{HA}])$
Dietary acid load NEAP (mEq/d)	$-10.2 + [54.5 \times \text{protein intake (g/day)}] / [\text{potassium intake (mEq/day)}]^{37}$ Note: Based on the principle that protein intake is a surrogate for acid ingestion and potassium intake is a marker for alkali intake. Potassium intake can be estimated from 24-hour urinary potassium.
Protein intake (g/day)	$6.25 \times [\text{urine urea nitrogen} + (\text{weight} \times 0.031)]^{38}$ Note: Based on the fact that urea is the principal end product of amino acid degradation
Renal acid excretion Net acid excretion (mEq)	Urine ammonium + titratable acid – urine bicarbonate Note: Urine bicarbonate is considered negligible in the physiological range of pH ⁴³
Titratable acid (mEq)	-direct titration method -Henderson-Hasselbalch equation using pK _a of phosphate and creatinine ⁴ Note: Calculated from total urine phosphorous, creatinine and urine pH using the Henderson-Hasselbalch equation
Net acid balance	Dietary acid load – renal acid excretion

Abbreviations: NEAP, net endogenous acid production.

Table 2.

Observational studies of bicarbonate levels with CKD progression

Study	Population	Bicarbonate measurement	Definitions of kidney injury or disease progression	Findings
Shah et al. 2009 ⁵²	5,422 outpatients in the Bronx, NY; 9% had eGFR<60 ml/min/1.73m ²	Serum bicarbonate	50% decrease in eGFR or eGFR<15 ml/min/1.73m ²	HR 1.54 (95%CI 1.13–2.09); bicarbonate 22 vs. 25–26 mEq/L
Menon et al. 2010 ⁵³	1,781 participants from the MDRD study; women with Cr 1.2–7 mg/dL; men with Cr 1.4–7 mg/dL	Fasting serum bicarbonate	Need for renal replacement therapy with dialysis or transplant	HR 1.05 (95%CI 0.87–1.28); bicarbonate 11–20 vs. 26–40 mEq/L
Raphael et al. 2010 ⁴⁷	1,094 African Americans with hypertensive CKD (iothalamate GFR 20–65 ml/min/1.73m ²) from the AASK trial	Serum bicarbonate	ESRD (dialysis or kidney transplantation), GFR reduction by 50% or by 25 ml/min/1.73m ²	HR 0.93 (95%CI 0.88–0.99) per 1 mEq/L increase in bicarbonate
Dobre et al. 2013 ⁴⁸	3,939 participants with CKD stage 2–4 from the CRIC study	Serum bicarbonate	ESRD (dialysis or kidney transplantation) or 50% reduction in eGFR	HR 0.97 (95%CI 0.94–0.99) per 1 mEq/L increase in bicarbonate
Tangri et al. 2011 ⁴⁹	3,449 patients with CKD stage 3–5	Serum bicarbonate	Initiation of dialysis or kidney transplantation	HR 0.92 (95%CI n/a, p<0.05) per 1 mEq/L increase in bicarbonate
Driver et al. 2014 ⁵¹	6,380 participants with eGFR >60 ml/min/1.73m ² from the MESA	Serum bicarbonate	Rapid kidney function decline (eGFR decline >5% per year) and incident reduced eGFR (eGFR<60 ml/min/1.73m ² with a rate loss of 1 ml/min/1.73m ² per year)	OR 1.35 (95%CI 1.05–1.73) for rapid kidney function decline; OR 1.16 (95%CI 0.83–1.62) for incident reduced eGFR; bicarbonate <21 vs. 23–24 mEq/L
Goldenstein et al. 2014 ⁵⁰	1,073 community-living elders from the Health ABC study	Serum bicarbonate calculated from arterialized venous blood gas	per year) Change in eGFR over 7 years, incident eGFR<60 ml/min/1.73m ² with a rate loss of 1 ml/min/1.73m ² per year	Faster eGFR decline by 0.55 ml/min/1.73m ² per year (95%CI 0.13–0.97); OR 1.72 (95%CI 0.97–3.07, p=0.06) for incident eGFR<60 ml/min/1.73m ² ; bicarbonate <23 vs. 23–28 mEq/L
Vallet et al. 2015 ⁴⁶	1,065 patients of the NephroTest cohort with CKD stage 1–4	Plasma bicarbonate	Fast mGFR (using ⁵¹ Cr-EDTA renal clearance) decline (>10%/year); ESRD (dialysis or preemptive kidney transplantation)	OR 1.88 (95%CI 1.17–3.03); bicarbonate<24.8 vs. 24.8–27.2 mEq/L for fast GFR decline; no difference in the risk of developing ESRD
Raphael et al. 2017 ⁵⁴	144 veterans with CKD stage 2–4	Serum bicarbonate	Urine TGF-β1/creatinine	OR 1.06 (95%CI 0.97–1.16) per each SD increase in bicarbonate

Abbreviations: HR, hazard ratio; eGFR, estimated glomerular filtrate rate; CI, confidence interval; MDRD, Modification of Diet in Renal Disease; CKD, chronic kidney disease; VA, Veteran Affairs; AASK, African American Study of Kidney Disease and Hypertension; CRIC, Chronic Renal Insufficiency Cohort; ESRD, end stage renal disease; n/a, not available; MESA, Multiethnic Study of Atherosclerosis; Health ABC, Health, Aging and Body Composition; mGFR, measured glomerular filtrate rate; TGF, transforming growth factor; SD, standard deviation.

Table 3.

Observational studies of dietary acid load and renal acid excretion with CKD progression

Study	Population	Dietary acid load/renal acid excretion	Findings	Definitions of kidney injury or disease progression
Scialla et al. 2012 ⁶⁹	632 African Americans with hypertensive CKD (mean iothalamate GFR 48.6 ml/min/1.73m ²) from the AASK trial	Dietary acid load: NEAP (using urine dietary markers)	The trend for higher NEAP with faster decline in GFR was significant, but time to event analyses for composite renal events was not significant (p=0.17).	Time to ESRD (dialysis or kidney transplantation), or doubling serum creatinine
Banerjee et al. 2015 ⁵⁸	1,486 adults with eGFR<60 ml/min/1.73m ² from the NHANES III	Dietary acid load: estimated from 24-hour dietary recall	HR 3.04 (95%CI 1.58–5.86) for ESRD, high tertile vs. low tertile	Development of ESRD
Vallet et al. 2015 ⁴⁶	1,065 patients of the NephroTest cohort with CKD stage 1–4	Dietary acid load: NEAP (using urine dietary markers) Renal acid excretion: 24-h urine ammonia excretion/Cr	NEAP did not change with GFR. HR 1.82 (95%CI 1.06–3.13) for ESRD; OR 1.84 (95%CI 0.98–3.48) for fast mGFR decline; lowest fertile of urinary ammonia excretion vs. highest fertile	Fast mGFR (using ⁵¹ Cr-EDTA renal clearance) decline (>10%/year); ESRD (dialysis or preemptive kidney transplantation)
Scialla et al. 2017 ⁴³	980 participants with CKD 2–4 from the CRIC study	Dietary acid load: NEAP (using food questionnaires and urine dietary markers) Renal acid excretion: 24-h urine ammonium, titratable acid and total net acid excretion, urine pH	-NEAP calculated from food questionnaires was not associated with CKD progression. -NEAP calculated from urine markers was associated with higher risk of CKD progression among those without diabetes (p=0.02), but not among those with diabetes. -HR 0.88 per 10mEq/day higher net acid excretion, (95%CI 0.80–0.98) among those with diabetes, but not those without diabetes. -Among diabetics, higher ammonium, titratable acid and lower urine pH each trended toward a lower risk of CKD progression.	Development of ESRD or 50% reduction in eGFR
Raphael et al. 2017 ^{40,42}	1,044 African Americans with hypertensive CKD from the AASK trial	Renal acid excretion: 24-h urine ammonium, urine anion gap (sodium + potassium -chloride)	HR 1.46 (95%CI 1.13–1.87), low fertile vs. high fertile of daily urine ammonium; no association between union anion gap and composite outcome	Composite outcome of death/or dialysis
Raphael et al. 2017 ⁵⁴	144 veterans with CKD stage 2–4	Renal acid excretion: 24-h urine ammonium, titratable acid, urine pH	-OR 1.22 (95%CI 1.11–1.35) per each SD increase in urine ammonium. -OR 1.11 (95%CI 1.02–1.21) per each SD increase in urine pH -OR 1.03 (95%CI 0.92–1.14) per each SD increase in urine titratable acid	Urine TGF-β1/creatinine

Abbreviations: NHANES, National Health and Nutrition Examination Survey; NEAP, net endogenous acid production; Cr, creatinine; eGFR, estimated glomerular filtration; mGFR, measured glomerular filtration rate; AASK, African American Study of Kidney Disease and Hypertension; CRIC, Chronic Renal Insufficiency Cohort; ESRD, end stage renal disease; h, hour; TGF, transforming growth factor; SD, standard deviation.

Table 4.

Interventional studies on the effect of alkali therapy on CKD progression

Study	Population	Intervention	Measure of kidney injury or disease progression	Findings	Quality*
de Brito-Ashurst et al. 2009 ⁵⁹	134 patients with CKD stage 4 & bicarbonate 16–20 mEq/L	Sodium bicarbonate to achieve bicarbonate 23 mEq/L vs. usual care for 2 years	Rate of CrCl decline, proportion of patients with CrCl >3 ml/min/1.73m ² per year and ESRD (CrCl<10 ml/min)	Slower CrCl decline (1.9 vs. 5.9 ml/min/1.73m ² , p<0.001); RR 0.15 (95%CI 0.06 to 0.40, p<0.001) for rapid progression; RR0.13 (95%CI 0.04 to 0.40, p<0.001) for ESRD	Fair
Phisitkul et al. 2010 ⁵⁷	59 patients with hypertensive nephropathy (eGFR 20–60 ml/min) and bicarbonate <22 mEq/L on ACE-inhibition	Sodium citrate (1 mEq bicarbonate equivalent per kg body weight per day) vs. no sodium citrate for 2 years	Urine ET-1 excretion, urine NAG, eGFR decline at 30 month	Lower urine ET-1 excretion and NAG, Lower decline in cysGFR (–3.6 vs. 8.7 ml/min, p=0.008)	Poor
Mahajan et al. 2010 ⁶⁰	120 patients with hypertensive nephropathy (eGFR 60–90 ml/min) with mean bicarbonate 26 mEq/L	Sodium bicarbonate vs. sodium chloride vs. placebo for 5 years	Rate of eGFR decline	Slower cysGFR decline (–5.6 vs. 8.3 vs. 9.5 ml/min; p<0.001, p=0.01 respectively) compared to sodium chloride or placebo	Good
Wesson et al. 2011 ²¹	Patients with hypertensive CKD stage 1 (n=26) & 2 (n=120) and acid retention without metabolic acidosis	Oral daily and bolus sodium bicarbonate vs. sodium chloride vs. placebo for 30 days	Plasma ET-1 and aldosterone	Sodium bicarbonate reduced plasma ET-1 and aldosterone	Fair
Goraya et al. 2012 ⁶³	79 patients with hypertensive CKD stage 1 and 120 with hypertensive CKD stage 2	Fruits/vegetables vs. 0.5 mEq/kg bodyweight sodium bicarbonate vs. no intervention for 30 days	Urine markers of kidney injury:urine albumin, NAG and TGF-β	CKD stage 1: no change. CKD stage 2: decreased urine albumin, NAG and TGF-β comparing those received fruits/vegetables or sodium bicarbonate with control, while the change in urine markers were similar between fruits/vegetables and sodium bicarbonate group.	Fair-poor
Goraya et al. 2013 ⁶²	71 hypertensive CKD stage 4 with bicarbonate <22 mEq/L on ACE inhibition	Sodium bicarbonate at 1.0 mEq/kg per day vs. fruits/vegetables to reduce dietary acid by 50% for 1 year	cysGFR, urine albumin, NAG and TGF-β	No difference at baseline and 1 year between groups for cysGFR, urine albumin, NAG or TGF-β.	Poor
Goraya et al. 2014 ⁶¹	108 patients with hypertensive CKD stage 3 and plasma bicarbonate 22–24 mEq/L, on ACE inhibition	Sodium bicarbonate or base-producing fruits/vegetables to reduce dietary acid by 50% vs. usual care for 3 years	eGFR, cysGFR, urine albumin, NAG and ATG	Slower decline in eGFR and cysGFR with bicarbonate or fruits/vegetables compared to with usual care; urine NAG and ATG decreased with bicarbonate or fruits/vegetables, but increase with usual care. There was no difference between bicarbonate and fruits/vegetables groups in measures of kidney disease progression.	Fair-poor
Dubey et al. 2018 ⁶⁴	188 patients with CKD stage 3 & 4 and	Standard of care as per Kidney Disease: Improving Global Outcomes 2012	eGFR	A rapid decline in GFR (i.e. >3 ml/1.73m ²) was seen in 20% of patients in the	Fair

Study	Population	Intervention	Measure of kidney injury or disease progression	Findings	Quality*
	bicarbonate <22 mEq/L	guidelines (i.e. alkali therapy for serum bicarbonate <22mEq/L) plus oral sodium bicarbonate supplementation to maintain bicarbonate at 24–26 mEq/L vs. standard care alone for 6 months		intervention arm vs. 42% in the control group (p=0.001)	

Abbreviations: CrCl, creatinine clearance; ESRD, end stage renal disease; RR, relative risk; ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate (using creatinine); cysGFR, glomerular filtrate rate estimated using cystatin; ET, endothelin; NAG, N-acetyl-β-D-glucosaminidase; TGF, transforming growth factor; ATG, angiotensinogen.

* Study quality by the Agency for Healthcare Research and Quality standards. The details of the assessment are described in the Supplementary Table 1.