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Narrative Review

Metabolic Acidosis of CKD: An Update

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The kidney has the principal role in the maintenance of acid-base balance. Therefore, a decrease in renal ammonium excretion and a positive acid balance often leading to a reduction in serum bicarbonate concentration are observed in the course of chronic kidney disease (CKD). The decrease in serum bicarbonate concentration is usually absent until glomerular filtration rate decreases to <20 to 25 mL/min/1.73 m^2, although it can develop with lesser degrees of decreased kidney function. Non–anion gap acidosis, high–anion gap acidosis, or both can be found at all stages of CKD. The acidosis can be associated with muscle wasting, bone disease, hypoalbuminemia, inflammation, progression of CKD, and increased mortality. Administration of base may decrease muscle wasting, improve bone disease, and slow the progression of CKD. Base is suggested when serum bicarbonate concentration is <22 mEq/L, but the target serum bicarbonate concentration is unclear. Evidence that increments in serum bicarbonate concentration > 24 mEq/L might be associated with worsening of cardiovascular disease adds complexity to treatment decisions. Further study of the mechanisms through which metabolic acidosis contributes to the progression of CKD, as well as the pathways involved in mediating the benefits and complications of base therapy, is warranted.
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INTRODUCTION

The kidney maintains a stable serum bicarbonate concentration by reabsorbing the filtered bicarbonate and synthesizing sufficient bicarbonate to neutralize the net endogenous acid load.[1,2] Therefore, when kidney function is compromised, a primary reduction in serum bicarbonate concentration can develop. Previously termed uremic acidosis, this disorder is more appropriately called the metabolic acidosis of chronic kidney disease (CKD) because it is usually unaccompanied by signs or symptoms of uremia. In this review, we summarize current views on the mechanisms mediating the metabolic acidosis of CKD, its clinical and laboratory features, its adverse effects, and the benefits and complications of recommended therapy.

PREVALENCE

The prevalence of the metabolic acidosis of CKD depends on the definition of the entity. Defined as a serum bicarbonate concentration continually <22 mEq/L in individuals with decreased kidney function,[3-5] the metabolic acidosis of CKD has been estimated to be present in 2.3% to 13% of individuals with stage 3 CKD[4,5] and 19% to 37% of individuals with stage 4 CKD.[4,5] Recent studies suggest that positive acid balance due to decreased kidney function can be present in the absence of a subnormal serum bicarbonate concentration.[6-8] In animals with 2/3 nephrectomy and normal glomerular filtration rate (GFR), positive acid balance is observed and leads to acidification of the interstitial compartment of the kidneys and muscle despite a normal serum bicarbonate concentration.[7] Also, in humans with estimated GFRs (eGFRs) between 60 and 90 mL/min/1.73 m^2, retention of acid (as reflected by the response to bicarbonate loads) has been reported to be present despite a normal serum bicarbonate concentration (26.4 ± 0.4 mEq/L).[8] Finally, in the NephroTest Cohort study (involving >1,000 patients with CKD), positive acid balance was detected in patients with stage 4 (31% of the total) despite normobicarbonatemia in >90% of participants.[6] When examined, administration of base to animals and humans with a normal serum bicarbonate concentration has been found to slow the decline in GFR.[7,8] These findings suggest that the definition of the metabolic acidosis of CKD should be expanded to include the

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state in which acid retention is present in the absence of a decrease in serum bicarbonate concentration (subclinical metabolic acidosis).[9] Given its potential impact on clinical outcome, determination of the prevalence of the metabolic acidosis of CKD, defined in this fashion, at all stages of CKD is warranted.

PATHOPHYSIOLOGY

Normally, 1 mEq of net endogenous acid production per kilogram of body weight occurs each day in adults (the value is 2-3 mEq/kg in children).[9] Net endogenous acid production represents the sum of protons derived from the metabolism of ingested protein minus the difference between bicarbonate derived from metabolism of organic acid anions (originating predominately from ingested fruits and vegetables) and organic acid anions lost in urine (Box 1).

Thus, net endogenous acid production largely depends on the quantity and type of protein, fruits, and vegetables consumed and the quantity of organic acid anions excreted in urine. The latter depends in part on GFR, the capacity of the proximal tubule to reabsorb filtered organic acid anions, and acid-base status of the individual.[10] Diets high in protein have the largest net endogenous acid production, whereas those low in protein or rich in fruits and vegetables have the lowest.[9,11-13] In a recent study of patients with graded degrees of CKD, net endogenous acid production was not related to measured GFR.[6]

Net endogenous acid production influences steady-state serum bicarbonate concentration in individuals with normal kidney function,[14] but its impact is likely to be magnified in individuals with decreased kidney function. Thus, at entry into the Modification of Diet in Renal Disease (MDRD) Study, serum bicarbonate concentration was inversely correlated with estimated protein intake (1.0 mEq/L lower per 1-g greater protein intake per kilogram of body weight per day[11]). Furthermore, a 25% reduction in estimated protein intake in individuals with a mean GFR of 38 ± 9.2 mL/min/1.73 m^2 increased serum bicarbonate concentration by almost 1 mEq/L. This effect of estimated protein intake on serum bicarbonate concentration was confirmed by results of studies in African Americans with CKD.[9,15]

Box 1. Net Endogenous Acid Production

Net endogneous acid production (mEq/d) = Hydrogen derived from metabolism of ingested proteins − (bicarbonate derived from metabolism of ingested organic acid anions − organic acid anions lost in the urine)

Factors affecting net endogenous acid production
- Type and quantity of protein ingested
- Type and quantity of fruits and vegetables ingested
- Type and quantity of organic acid anions excreted
- Acid-base status
- Proximal tubular function

Net endogenous acid production is neutralized by body buffers. The immediate effect of its addition on acid-base balance can be estimated by applying an apparent space of distribution of 50% body weight.[16,17] Concurrently, under normal conditions, the renal tubules generate an equivalent quantity of bicarbonate (net acid excretion) to replenish body buffers while reabsorbing ~4,500 mEq of bicarbonate filtered by glomeruli each day. As a result, acid-base balance is neutral and serum bicarbonate concentration is unchanged.

With the development of CKD, the capacity of the kidney to excrete ammonium or reabsorb bicarbonate is often compromised. In general, ammonium excretion decreases when GFR corresponds to CKD stages 3b and 4. The decrease in ammonium excretion is the major cause of the acidosis[2,6,18,19] and reflects a reduction in number of functioning nephrons because ammonium excretion per nephron is substantially increased.[20] Enhanced ammonia production is due to hypertrophy of residual nephrons and increased activity of critical ammoniogenic enzymes.[19] The increased localization of the ammonium/ammonia transporters RHCG and RHBG on the apical and basolateral membranes of the renal tubules observed in experimental CKD would facilitate the entry of ammonia and ammonium into tubular fluid.[21]

The increased ammonia production activates the complement pathway and promotes kidney fibrosis and a reduction in GFR, suggesting it as a potential target for delaying CKD progression.[22] Additional factors that enhance tubular acid excretion include endothelin, aldosterone, and angiotensin II, hormones for which production is stimulated by the acidosis of CKD.[8] These hormones also promote renal fibrosis and progressive kidney disease and therefore are targets for treatment.[7,23,24]

Titratable acid excretion is usually minimally changed in CKD because its 2 major determinants, urinary phosphate and urinary pH, are not much affected.[6,25] However, restriction of dietary protein, change in type of protein to one containing less phosphorus,[26] or administration of phosphate binders[27] can reduce phosphate excretion and thus titratable acid excretion.

Bicarbonate excretion is usually minimal in CKD,[28] although in several small studies, it was reported to be as high as 24% of the filtered bicarbonate load.[25,29] Abnormalities of vitamin D and parathyroid hormone secretion have been associated with the largest degree of bicarbonaturia.[30]

The ability to acidify urine in CKD is generally intact, reflected by urine pH < 5.5 when serum bicarbonate concentration is below normal.[28,31] However, urine pH is slightly higher than that observed in individuals with intact kidney function at the same serum bicarbonate concentration.[31]

When serum bicarbonate concentration decreases, it often remains stable despite an apparent positive hydrogen balance of 12 mEq/d (a value derived in one study[32]). The stability of serum bicarbonate concentration was ascribed to buffering of protons by body buffers other than bicarbonate, predominately those within bone.[33]

However, there is disagreement as to whether individuals with CKD are in continuing positive proton balance.[1,6] Carefully performed balance studies in 20 patients with CKD and chronic metabolic acidosis showed that these individuals were in neutral acid balance.[1] By contrast, a recent study of more than 1,000 patients in the NephroTest cohort with CKD stages 1 to 4 followed up over 4.3 years revealed that patients with CKD stage 4 were in positive acid balance while most maintained a normal serum bicarbonate concentration.[6] Additional studies are required to resolve this issue.

Serum bicarbonate concentration can vary among individuals despite similar GFRs. Factors associated with lower serum bicarbonate concentrations include smoking, albuminuria, greater waist circumference, and use of converting enzyme inhibitors.[4] Other likely factors include higher dietary protein intake and lower partial pressure of carbon dioxide.[11,34] Superimposed tubular acidification defects produced by intrinsic damage to the renal tubules (as might occur with sickle cell nephropathy)[35] or hypoaldosteronism[36] will also predispose to more severe metabolic acidosis.

CLINICAL FINDINGS

Patients with the metabolic acidosis of CKD are generally asymptomatic and the acid-base disorder is usually recognized by examining blood chemistry results. Serum bicarbonate concentration is rarely <14 to 15 mEq/L and is frequently >20 mEq/L.[4,11] As an example, analysis of a cohort of more than 900 patients from a single renal clinic followed up for up to 7 years revealed that serum bicarbonate concentration was reduced only with severe declines in GFR.[37] Thus, mean serum bicarbonate concentration was within the reference range, 26.3 ± 0.3 (SD) mEq/L, when serum creatinine level was <5 mg/dL and decreased to <20 (19.5 ± 0.14) mEq/L only when serum creatinine level increased to >10 mg/dL. In the MDRD Study[11] and AASK (African American Study of Kidney Disease and Hypertension),[15] there was an inverse correlation between GFR and serum bicarbonate concentration, but mean serum bicarbonate concentration was 21.0 ± 3.9 mEq/L in the MDRD Study even when GFR was <18 mL/min. Furthermore, analysis of more than 5,000 individuals followed up at Veteran Administration hospitals with stage 5 CKD (eGFR < 15 mL/min/1.73 m^2) revealed that only 20% had a serum bicarbonate concentration < 22 mEq/L.[38] The ventilatory response is similar to that of other types of chronic metabolic acidosis: change in partial pressure of carbon dioxide is equal to 1.2 times the change in serum bicarbonate concentration.[39] Consequently, blood pH is usually ≥7.30.

However, a reduction in serum bicarbonate concentration might not be inevitable, even with severe reductions in GFRs. In one observational study from a single center examining data accumulated over 2 years in 70 patients on the verge of beginning dialysis therapy, 14 patients with a mean serum creatinine level of 9 ± 2.3 mg/dL had a mean serum bicarbonate concentration within the reference range for their laboratory (25.0 ± 3.0 mEq/L).[40] The majority of these patients had no history of vomiting or ingestion of substances that might affect acid-base balance.

At first examination, a normal serum bicarbonate concentration in CKD (in the absence of processes with the potential of increasing serum bicarbonate concentration) might suggest the absence of any significant impairment in kidney regulation of acid-base balance. However, as noted, studies in animals[7] and humans with CKD[6,8] indicate that a normal serum bicarbonate concentration can be seen even in the presence of apparent impairment in renal acid excretion and documented acid retention.

These findings emphasize the complexity of acid-base balance in CKD and the difficulty determining the reason(s) for a particular serum bicarbonate concentration in an individual patient. Similar to those with intact kidney function, potential factors that might affect serum bicarbonate concentration include dietary intake of substances metabolized to acid or base, the rate of absorption of these substances by the gastrointestinal tract, the capacity of the individual's renal tubules to excrete acid or reabsorb base, the prevailing level of partial pressure of carbon dioxide, and the administration of medications such as diuretics or phosphate binders that can themselves alter acid-base balance. Others have also speculated that the variability of bone disease could also affect body buffering capacity,[41] but this remains to be clarified.

The pattern of the metabolic acidosis of CKD remains controversial.[28,40,42,43] Using the usual formulation of serum anion gap, that is, the concentration of sodium minus the sum of chloride and bicarbonate concentrations, some investigators found that early in the course of CKD, a non–anion gap acidosis was present, which progressed into a mixed normal– and high–anion gap variety (as anions, predominately sulfate and phosphate, were retained). As GFR continued to decrease (to GFR < 10 to 15 mL/min/1.73 m^2), a dominant high–anion gap acidosis evolved.[42] However, in a single study involving

70 patients, a non–anion gap acidosis continued to dominate even immediately prior to the initiation of dialysis (mean serum creatinine, 10.0 ± 3.0 mg/dL).[40]

Others adjusting serum anion gap for the contribution of serum albumin alone (albumin adjusted: traditional anion gap − [2.5 × serum albumin in g/dL]) or for the contributions of serum albumin, phosphate, potassium, and ionized calcium (full anion gap: albumin adjusted + serum potassium in mEq/L + ionized ca in mEq/L − serum phosphate in mEq/L) found an increment in serum anion gap throughout all stages of CKD.[43]

Characterizing the type of acidosis can be important because certain abnormalities, including tubulointerstitial kidney disease and hyporenininemic hypoaldosteronism, are associated with predominately non–anion gap acidosis.[44] These disorders are also characterized by hyperkalemia out of proportion to the GFR and a more severe acidosis than found in other patients with the same GFRs. The hyperkalemia is linked to the acidosis because it suppresses ammonium production. Correction of the hyperkalemia alone increases ammonium excretion and improves the acidosis, at least in individuals with hyporeninemic hypoaldosteronism.[45] These patients can be distinguished from each other because patients with hypoaldosteronism can reduce urine pH to <6.0, whereas those with interstitial kidney disease are unable to do so.[44] Identifying these individuals can be valuable because various treatments, such as administration of potassium-exchange resins, diuretics, and alkali or alkali precursors, can ameliorate or fully correct the metabolic acidosis. Mineralocorticoid replacement in individuals with hypoaldosteronism is also successful, but is less frequently pursued because of its potential to exacerbate hypertension.

ADVERSE EFFECTS

The major adverse effects of the metabolic acidosis of CKD include increased muscle protein degradation with muscle wasting, reduced albumin synthesis and hypoalbuminemia, bone disease, progression of CKD, possible development or worsening of heart disease, stimulation of inflammation, and an increase in mortality[46] (Box 2). These adverse effects characterize any chronic metabolic acidosis irrespective of the underlying mechanism.[46] However, a possible interaction of the milieu of CKD with metabolic acidosis cannot be excluded.

In animal experiments, chronic metabolic acidosis is associated with increased muscle protein degradation without a change in muscle protein synthesis. Increased proteolysis is attributed to altered regulation of insulin growth factor 1 and increased inflammation.[47] In humans, muscle wasting and negative nitrogen balance occur.[48,49]

Box 2. Adverse Effects of the Metabolic Acidosis of Chronic Kidney Disease

- Increased degradation of muscle protein with muscle wasting and suppression of growth in children
- Dissolution of bone and bone disease
- Decreased albumin synthesis with predisposition to hypoalbuminemia
- Progression of chronic kidney disease
- Stimulation of inflammation
- Impairment of insulin secretion and responsiveness
- Stimulation of amyloid accumulation
- Increased risk for death

An increase in degradation of muscle protein might occur even in the absence of a decrease in serum bicarbonate concentration. Thus, in postmenopausal women with a normal serum bicarbonate concentration, administration of base resulted in a more positive nitrogen balance.[50] These findings suggest that even the net endogenous acid production resulting from the usual acidogenic diet promotes increased degradation of muscle protein.

Albumin synthesis by the liver is compromised by experimentally produced metabolic acidosis.[51] Analysis of NHANES III (Third National Health and Nutrition Examination Survey) data revealed that a low serum bicarbonate concentration is associated with hypoalbuminemia in patients with CKD.[5] However, not all studies revealed evidence of impaired albumin synthesis with metabolic acidosis.[52] Therefore, the frequency of this abnormality remains uncertain.

Metabolic acidosis can induce or exacerbate bone disease[46,53] and impair growth in children.[54,55] Correction of metabolic acidosis with base results in healing of bone lesions and improved growth in children.[56] Regardless of whether serum bicarbonate concentration is decreased from normal, ingestion of an acid-producing diet might impair bone growth.[57]

Carefully performed controlled albeit small studies in both animals and humans demonstrated that metabolic acidosis is associated with progression of CKD.[7,23,24,38,58] These findings were bolstered by much larger observational studies: examination of more than 5,000 individuals from a single outpatient clinic over a median follow-up of 3.4 years revealed that serum bicarbonate concentration < 22 mEq/L is associated with CKD progression (decrease in GFR by ≥50% of baseline or reaching GFR < 15 mL/min/1.73 m^2).[59] In the CRIC (Chronic Renal Insufficiency Cohort) Study of more than 3,500 participants followed up during 6 years,[60] those who maintained serum bicarbonate concentrations < 22 mEq/L had almost a 2-fold increased risk for CKD progression (halving of GFR or end-stage renal disease).[60] Also, in 2 studies involving more than 1,000 patients each,

higher serum bicarbonate concentration, albeit within the normal range, was associated with either higher GFR or lower incidence of end-stage renal disease.[61,62] In MESA (Multi-Ethnic Study of Atherosclerosis), which included patients with baseline eGFRs $>$ 60 mL/min/1.73 m^2, lower serum bicarbonate concentration was associated with more rapid decline in kidney function and incident decreased eGFR independent of baseline GFR.[63] Also, in a study of community-living elders aged 70 to 79 years at inception with baseline eGFRs of 84 mL/min/1.73 m^2, participants with serum bicarbonate concentrations $<$ 23 mEq/L had nearly 2-fold greater odds of incident eGFR $<$ 60 mL/min/1.73 m^2 independent of baseline eGFR.[64] Finally, in the NephroTest Cohort study involving more than 1,000 patients, lower serum total carbon dioxide level was associated with more rapid decline in GFR.[6]

As noted, this exacerbation of CKD appears to be related at least in part to retention of protons in the interstitial compartment of the kidney and is present even when serum bicarbonate concentration is within the normal range.[7,8] To date, studies to determine whether the severity of metabolic acidosis affects the rapidity of progression of CKD have not been carried out. However, this is an important issue that has relevance to recommendations for treatment.

Potential mechanisms leading to acceleration of CKD progression in patients with metabolic acidosis are shown in Fig 1. Increases in tissue aldosterone,[7] endothelin,[7,65] and angiotensin II[66] levels have been documented in association with metabolic acidosis.

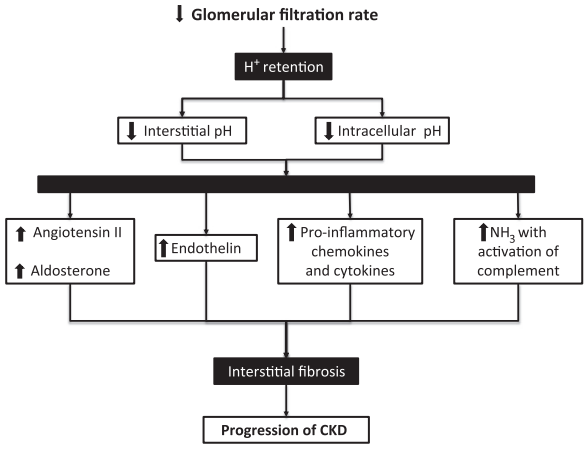

Figure 1. Putative factors induced by metabolic acidosis producing kidney injury and accelerating the progression of chronic kidney disease (CKD). Acidosis increases the production of aldosterone, endothelin, and angiotensin II, factors involved in promoting kidney injury and fibrosis. Metabolic acidosis is associated with increased renal ammonia production. This process activates complement, leading to injury and fibrosis. Finally, exposure to an acidic environment stimulates various proinflammatory cytokines, which also could lead to kidney injury and fibrosis.

These increases in hormone levels appear to contribute to the decline in GFR because correction of the acidosis leads to both a decrease in levels of these hormones and slowing of the decline in GFR in both humans and animals.[23,24,66-68]

The increased ammonia production in CKD is associated with activation of complement and an inflammatory cascade followed by renal fibrosis.[22] It is theoretically possible that progression would be more rapid in patients who have the highest level of ammonia production per residual nephron. An acidic milieu appears to stimulate kidney production of proinflammatory cytokines and chemokines,[69] providing additional mechanisms leading to kidney injury.

Glucose tolerance might be impaired and caused in part by resistance to insulin, reflecting its decreased binding to cognate receptors.[70] However, ambient insulin levels are increased because of reduced metabolism by the diseased kidney. The ultimate affect on glucose metabolism depends on the relative strengths of these competing forces.

A potential link between metabolic acidosis and abnormalities in cardiovascular function is increased production of β_2-microglobulin in patients with CKD with acidosis.[71] In patients with excess β_2-microglobulin, there is greater deposition of amyloid in various tissues, including the heart. Metabolic acidosis could indirectly be linked to cardiac disease through its effect on the prevalence of hypertension.[72] Among nonobese adult women, higher serum bicarbonate concentration was found to be associated with lower prevalence of hypertension after adjusting for matching factors.[72] Also, in children, hypertension was determined to positively correlate with increased dietary acid load.[73] These data are consistent with increased tissue acidity being a contributory factor for the development of hypertension.

Mortality is increased in the presence of chronic metabolic acidosis in patients with CKD.[74] Examination of a CKD registry at the Cleveland Clinic involving more than 41,000 patients revealed increased mortality in association with serum bicarbonate concentration $<$ 23 mEq/L, specifically in patients with moderately decreased kidney function (stage 3 CKD).[75] Furthermore, analysis of the MDRD Study[74] and NHANES III[76] databases showed that serum bicarbonate concentration $<$ 22 mEq/L in patients with CKD (GFR $<$ 60 mL/min/1.73 m^2) was associated with increased mortality. In the latter study, there was a 2.6-fold increased hazard of death.[76] The precise mechanism(s) underlying this effect has not been established, although an impact on the presence or severity of cardiac disease is an attractive possibility, which should be explored further. Because the findings were obtained from observational studies,

there remains no proof of causation. Also, randomized controlled studies have not been performed to show that correction of metabolic acidosis decreases mortality.

TREATMENT

Preventing or reversing the adverse effects associated with the metabolic acidosis of CKD is the major goal of treatment. The effect of base administration on some of the adverse effects of metabolic acidosis, including the development or exacerbation of bone disease, increased degradation of muscle protein with muscle wasting, and acceleration of the decline in GFR, have been subject to examination in animals and humans with and without CKD. Bicarbonate administration augments growth in children with renal tubular acidosis.[56] Similarly, base leads to healing of bone disease in animals and humans with metabolic acidosis and CKD.[3,77] Base administered to rats with metabolic acidosis reduces protein degradation[78] and, in some studies, improves lean body mass. It also increases the strength of major lower body muscles in patients with CKD and metabolic acidosis,[79] consistent with a decrease in muscle wasting.

The effect of correcting acidosis on CKD progression was examined in small single-center studies and the observed benefits, as promising as they are, require confirmation in large multicenter trials. Administration of sodium bicarbonate,[67] sodium citrate,[80] or an increased amount of fruits and vegetables[66] results in slowing of the decline in GFR in animals or humans with CKD and metabolic acidosis. Of great potential importance, this slowing of the progression of CKD is also observed in animals or humans who manifest acid retention, but no decrease in serum bicarbonate concentration.[7,8,67] These findings are consistent with previous observations about the beneficial effects of base administration to postmenopausal women who do not have acid-base abnormalities. Table 1 summarizes the published studies and those in progress or planned regarding the effect of base administration on CKD progression.

Given that studies have shown that base administration results in improvement in cellular function, including slowing or healing of bone disease, improved growth in children, retarding the progression of CKD, and reducing muscle wasting, at this time it seems reasonable to provide base to individuals with CKD and a depressed serum bicarbonate concentration. To this end, several major kidney organizations have provided guidelines on the issue. All recommendations are based on expert

Table 1. Published, Ongoing, or Planned Studies of the Effect of Base Administration on the Progression of CKD

Study	ClinicalTrials.gov identifier	Patients	Status	Outcome	Comments
de Brito-Ashurst et al[58]	NA	134 with GFRs 15-30	Published	Decrease in slope of decline in GFR with base	Oral sodium bicarbonate to maintain bicarbonate concentration > 23 mEq/L
Phisitkul et al[68]	NA	59 with GFRs of 20-60	Published	Less GFR decline with base	Sodium citrate given as base; urine endothelin levels measured
Mahajan et al[67]	NA	120 with GFRs of 75 ± 6	Published	Less GFR decline with base	Oral sodium bicarbonate
Melamed et al	NCT01452412	150 with GFRs of 15-45	Recruiting	NA	Oral sodium bicarbonate, 0.4 mEq/kg/d
Di Iorio et al[90]	NCT01640119	728 with stages 3-4 CKD	Ongoing	NA	Placebo controlled; oral sodium bicarbonate to maintain bicarbonate concentration > 24 mEq/L
Gaggl et al[91]	NA	200 with stages 3-4 CKD	Proposed	NA	Oral sodium bicarbonate to maintain bicarbonate concentration > 24 mEq/L vs rescue base therapy to maintain bicarbonate concentration > 20 mEq/L
Raphael & Beddhu	NCT01640119	With diabetes and stages 2-4 CKD	Ongoing	NA	Sodium bicarbonate vs placebo; effects on TGF-β1 over 3-6 mo
Little et al	NCT01894594	With adult sickle-cell anemia and GFRs < 90	Ongoing	NA	Effect of sodium bicarbonate on serum bicarbonate and potassium concentrations during 8 wk of treatment

Abbreviations and definitions: CKD, chronic kidney disease; GFR, glomerular filtration rate (in mL/min/1.73 m^2); NA, not available; TGF, transforming growth factor.

opinion derived from review of the limited studies available. The GRADE (Grading of Recommendations Assessment Development and Evaluation) system was used to rate the quality of evidence and strength of recommendations. For the KDIGO (Kidney Disease: Improving Global Outcomes) and NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines, recommendations were listed as 2B. NKF-KDOQI recommends that base be given when serum bicarbonate concentration is <22 mEq/L to maintain serum bicarbonate concentration at ≥22 mEq/L.[81] A more specific target is not provided. The Renal Association of Great Britain also recommends base administration to maintain serum bicarbonate concentration at ≥22 mEq/L,[82] as does CARI (Care of Australians With Renal Impairment).[83] Again, no specific target for serum bicarbonate concentration is provided. However, the 2013 KDIGO guideline recommends maintaining serum bicarbonate concentration within the reference range for the clinical laboratory (23-29 mEq/L).[84] On the basis of an appraisal of the literature, we have also recommended increasing serum bicarbonate concentration into the reference range.[46]

The initial report of the CRIC Study showed that participants with CKD and serum bicarbonate concentrations > 24 mEq/L (no matter the cause) had a higher prevalence of congestive heart failure, although there was no association with mortality or atherosclerotic events.[85] Mortality was not found to be increased in individuals with serum bicarbonate concentrations of 22 to 30 mEq/L in one study,[76] although it was higher when serum bicarbonate concentration was >32 mEq/L.[75] Furthermore, in a reanalysis of the CRIC Study,[60] sustained serum bicarbonate concentration > 26 mEq/L was associated with increased risk for heart failure and death when accounting for markers of inflammation, medication use, and kidney function. These studies suggest that the optimal serum bicarbonate concentration might be between 22 and 26 mEq/L. Overshooting the target for serum bicarbonate concentration could have an effect on clinical outcome. Further large-scale studies to determine the optimal serum bicarbonate concentration are needed.[34]

One other potential complication is a predisposition to tissue calcification resulting from an alkaline environment produced by base administration.[86] At present, no evidence for this possibility has been advanced. Also, alkali administration could exacerbate hypertension or volume retention in susceptible patients. However, both short- and long-term studies revealed no significant effect of base administration on systolic or diastolic blood pressure, weight gain, or the development of congestive heart failure.[79,87] These results are consistent with studies that show that sodium retention is less when it is given with bicarbonate or other organic anions rather than chloride.[88]

Table 2 depicts the various methods available to treat the metabolic acidosis of CKD. Because acid production largely arises from ingested protein, restriction of protein will lower acid and phosphate loads. Oral sodium bicarbonate is inexpensive and easy to administer. Tablets of 300 to 650 mg are

Table 2. Different Forms of Base Available for Treatment of the Metabolic Acidosis of CKD

Treatment	Formulation	Comments
Restriction of protein and or change in type of protein given		Plant-based protein has less acid production than animal protein
Sodium bicarbonate tablets	300-650 mg/tablet 3.7-8 mEq/tablet	Inexpensive and easy to administer; results in generation of gas in stomach; might be uncomfortable for patient
Enteric coated bicarbonate tablets	Alkalife Bicarbonate-Balance tablets contain potassium bicarbonate (200 mg) and sodium bicarbonate (73 mg) or enteric coated tablet or soft coated capsule containing 1 g or 0.5 g sodium bicarbonate, respectively	Enteric coating protects tablet against acidity allowing more base to reach intestine; use cautiously in patients with severe CKD; enteric coated tablet or capsule available in Europe
Shohl's solution	Each 1 mL of solution contains 1 mEq of base equivalent (sodium citrate)	Can increase aluminum absorption; easy to use
Fruits and vegetables	Quantity designed to provide 50% of acid load	Effective in controlled studies; provides calories and potentially significant potassium load
Phosphate binders	Calcium acetate; calcium citrate; sevelamer hydrogen chloride; sevelamer carbonate	Acetate and citrate provide base that will affect quantity of exogenous base required; both acidic and basic forms of sevelamer are available; the acidic formulation with hydrogen chloride tends to lower serum bicarbonate concentration, whereas the basic form with carbonate tends to increase it

Abbreviation: CKD, chronic kidney disease.

available. Bicarbonate reacts with protons in the stomach to produce carbonic acid, which dissociates into carbon dioxide and water, with carbon dioxide causing a sensation of fullness. Enteric-coated tablets and soft capsules containing sodium bicarbonate,[89] as well as formulations containing both sodium bicarbonate and potassium bicarbonate, are available (the former in Europe). These formulations protect the enclosed base from exposure to acid as it transits the stomach, allowing it to reach the small intestine, where it is absorbed. Because titration of bicarbonate in the stomach is essentially prevented, carbon dioxide production should be minimal and the proportion of bicarbonate available should be greater.[89] Shohl's solution (consisting of sodium citrate and citric acid) provides citrate that is metabolized in the liver to bicarbonate. Each 1 mL of the solution contains 1 mEq of base equivalent. Citrate enhances the absorption of aluminum and thus one should be aware of the patient's exposure to aluminum before prescribing it.

Because base can have adverse effects should it increase serum bicarbonate concentration excessively, we recommend estimating the bicarbonate requirement using an apparent space of distribution of the administered bicarbonate of 50% body weight (in kilograms). Thus, bicarbonate requirement is equal to desired serum bicarbonate minus the actual serum bicarbonate concentration, with the result being multiplied by 50% body weight measured in kg. When the bicarbonate requirement has been calculated, the quantity of base can be given over 3 to 4 days because it rarely is urgent to treat the metabolic acidosis. When serum bicarbonate concentration reaches the desired level (~24 mEq/L), the daily base quantity should be titrated to maintain that target.

Dietary management of hypobicarbonatemia has also been tried with some success. In one study, patients with stages 3 and 4 CKD who were not receiving converting enzyme inhibitors were given a quantity of fruits and vegetables (which contain organic anions that are metabolized to bicarbonate) postulated to generate sufficient base to neutralize 50% of the endogenous net acid load.[12] This dietary regimen increased serum bicarbonate concentrations to a mean of 24.5 mEq/L without producing hyperkalemia (serum potassium remained <5 mEq/L). These data are compelling and suggest that this regimen can be successful while avoiding the prescription of base therapy. However, the enrolled patients were very motivated and carefully followed up by a dietician. It is not obvious that a similar program would be effective in the general population, who might not adhere to dietary change. Nonetheless, it appears that this method of providing base might be appropriate for a select group of highly motivated patients. Our recommendations for base therapy in patients with CKD are shown in Box 3.

Box 3. Recommendations for Treatment of the Metabolic Acidosis of Chronic Kidney Disease

Recommendations

- Calculate bicarbonate requirement: (desired serum bicarbonate concentration − actual serum bicarbonate concentration) × 50% body weight (in kg)
- Administer sufficient base to increase serum bicarbonate concentration close to mean reference value of 24 mEq/L
- Administer dose over 3-4 days while monitoring serum bicarbonate concentration
- When serum bicarbonate concentration reaches target (~24 mEq/L), reduce dose of base with goal of maintaining serum bicarbonate concentration at ≤24 mEq/L
- Consider more aggressive base replacement in chronic kidney disease patients with disorders associated with base loss, such as profuse diarrhea, or generation of large acid loads, such as ketoacidosis

Example calculation

Consider a 70-kg patient with mild metabolic acidosis: serum bicarbonate concentration, 20 mEq/L. The apparent space of distribution of bicarbonate is 35 L (50% × 70 kg). To increase serum bicarbonate concentration to 24 mEq/L would require 4 mEq/L × 35 L or 140 mEq of base equivalents. To provide this amount as Shohl's solution would require a total of 140 mL (each 1 mL contains 1 mEq of base equivalent). This could be given as 2 tablespoons (30 mL) a day for 4 days. The dose could then be reduced to 1 tablespoon a day to approximate daily acid production minus acid excretion. Further adjustments can be made empirically based on changes in serum bicarbonate concentration.

CONCLUSIONS AND FUTURE DIRECTIONS

Retention of acid in the course of CKD can lead to an increase in acidity of the interstitial and intracellular compartments and the systemic circulation. The former presumably mediates the adverse consequences on several tissues. Particularly in view of the frequent progression of CKD despite contemporary treatments, there is an urgent need to better describe the characteristics of individuals with subclinical metabolic acidosis and, on the basis of randomized controlled studies, determine both the benefits of alkali therapy in slowing progression of CKD and the complications of such therapy. In addition, in both these individuals and those with overt metabolic acidosis, it is essential to determine the serum bicarbonate concentration that should be targeted. This information should provide the foundation for evidence-based recommendations for treatment of patients with metabolic acidosis of CKD.

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