

## Metabolic Acidosis in CKD: Core Curriculum 2019

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Maintenance of normal acid-base homeostasis is one of the most important kidney functions. In chronic kidney disease, the capacity of the kidneys to excrete the daily acid load as ammonium and titratable acid is impaired, resulting in acid retention and metabolic acidosis. The prevalence of metabolic acidosis increases with declining glomerular filtration rate. Metabolic acidosis is associated with several clinically important complications, including chronic kidney disease progression, bone demineralization, skeletal muscle catabolism, and mortality. To mitigate these adverse consequences, clinical practice guidelines suggest treating metabolic acidosis with oral alkali in patients with chronic kidney disease. However, large clinical trials to determine the efficacy and safety of correcting metabolic acidosis with oral alkali in patients with chronic kidney disease have yet to be conducted. In this Core Curriculum article, established and emerging concepts regarding kidney acid-base regulation and the pathogenesis, risk factors, diagnosis, and management of metabolic acidosis in chronic kidney disease are discussed.

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Am J Kidney Dis. XX(XX): 1-13. Published online Month X, XXXX.

doi: 10.1053/j.ajkd.2019.01.036

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### Introduction

**Case:** A 45-year-old woman with chronic kidney disease (CKD) stage 3, type 2 diabetes mellitus, and hypertension is seen in the clinic for routine follow-up. During the past year, estimated glomerular filtration rate (eGFR) has been 38 to 43 mL/min/1.73 m<sup>2</sup>. She takes lisinopril, 20 mg, and chlorthalidone, 12.5 mg, daily. Serum total carbon dioxide (tCO<sub>2</sub>) concentrations at the last 2 visits were 19 and 21 mEq/L; the most recent serum potassium concentration was 5.2 mEq/L.

**Question 1: What is the most appropriate next step regarding the low tCO<sub>2</sub>?**

- Increase the dose of chlorthalidone
- Measure urine pH
- Obtain an arterial or venous blood gas
- Start oral sodium bicarbonate treatment
- Stop lisinopril treatment

For the answer, see the following text.

Metabolic acidosis was one of the earliest recognized complications of decreased kidney function. Landmark studies demonstrated that impaired kidney acid elimination in CKD leads to metabolic acidosis, which in turn adversely affects bone mineral content and promotes skeletal muscle catabolism. More recently, observational studies have identified metabolic acidosis as a risk factor for CKD progression and mortality. During the past decade, several small-scale studies, primarily in hypertensive CKD, have found that correcting metabolic acidosis with alkali therapy preserves GFR. However, convincing evidence from large

clinical trials that treatment of metabolic acidosis preserves bone, muscle, and kidney health is lacking. There is emerging evidence that alkali therapy may also preserve GFR in patients with CKD who have normal serum tCO<sub>2</sub> concentrations by mitigating adaptive kidney responses that maintain normal tCO<sub>2</sub> concentrations but at the same time promote kidney damage. If true, this would lead to a significant paradigm shift in how alkali is prescribed in CKD.

This Core Curriculum article reviews established and emerging concepts regarding kidney acid-base regulation and the pathogenesis, risk factors, diagnosis, and management of metabolic acidosis in CKD.

Considering Question 1, clinical practice guidelines suggest treating metabolic acidosis in CKD with alkali therapy for serum tCO<sub>2</sub> concentrations < 22 mEq/L. Given the persistent low tCO<sub>2</sub> concentrations and mild hyperkalemia, treatment of metabolic acidosis is appropriate. Because the patient has CKD, it is reasonable to assume that the low tCO<sub>2</sub> concentration represents metabolic acidosis, and therefore an arterial or venous blood gas is not necessary. Urine pH is not a reliable indicator of whether metabolic acidosis or respiratory alkalosis is present in the setting of a low tCO<sub>2</sub> concentration. Although lisinopril may be contributing to the mild hyperkalemia and low tCO<sub>2</sub> concentrations, treatment of metabolic acidosis with alkali therapy may reduce serum potassium concentration and permit continued use of the angiotensin-converting enzyme inhibitor. Diuretics should not be used solely for the purpose of

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increasing serum  $t\text{CO}_2$  concentrations. Thus, the correct response is (d).

### Additional Readings

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1-150.
- National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003;42(4)(suppl 3):S1-S201.

## Overview of Acid-Base Regulation

**Question 2: What is the primary mechanism by which the kidneys increase acid excretion in response to an acid load?**

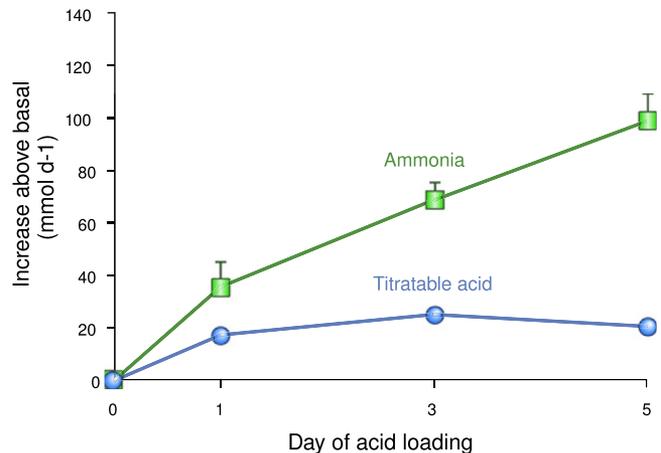
- Increasing free hydrogen ion ( $\text{H}^+$ ) excretion
- Increasing reabsorption of filtered bicarbonate
- Increasing urinary ammonium excretion
- Increasing urinary titratable acid excretion

For the answer, see the following text.

Maintaining normal pH is a vital and tightly regulated physiologic process. In the steady state, each day the lungs eliminate  $\sim 15$  mol of  $\text{CO}_2$  produced from cell respiration. In contrast, the kidneys eliminate 50 to 100 mEq/d of  $\text{H}^+$  ( $\sim 1$  mEq/kg/d). These nonvolatile acids, also referred to as fixed acids, are derived mainly from the diet and to a lesser extent endogenously produced organic acids and are eliminated in urine as ammonium ion ( $\text{NH}_4^+$ ) and titratable acid. The net effect of these highly coordinated processes between the lungs and kidneys is to maintain an arterial pH near 7.40 in the steady state and when acid or alkali excess is encountered. Although a comprehensive discussion of acid-base regulation is beyond the scope of this article, a few key points regarding kidney acid excretion deserve mention.

### Ammonium

The major adaptive kidney response to an acid load is to increase urinary  $\text{NH}_4^+$  excretion (Fig 1). The systemic circulation is not the source of urinary  $\text{NH}_4^+$ ; rather, it is produced primarily in proximal tubule cells from systemically derived glutamine. Proximal cell metabolism to glutamate, then  $\alpha$ -ketoglutarate, produces 2  $\text{NH}_4^+$  and 2 bicarbonate ( $\text{HCO}_3^-$ ) ions; the latter are subsequently delivered to the systemic circulation. The  $\text{NH}_4^+$  must be excreted from the body; otherwise, it would be metabolized in the liver to urea, consuming 2 bicarbonate ions.  $\text{NH}_4^+$  produced in proximal cells enters the urinary space by being transported in place of  $\text{H}^+$  by the apical sodium ( $\text{Na}^+$ )/ $\text{H}^+$  exchanger (NHE3) or through parallel transport of  $\text{H}^+$  (through the apical adenosine triphosphatase proton pump [ $\text{H}^+$ -ATPase])



**Figure 1.** Acid loading in healthy individuals increases urinary ammonia and titratable acid excretion; however, the increase in ammonia excretion is greater. Reproduced from Weiner et al (*Clin J Am Soc Nephrol.* 2015;10(8):1444-1458) with permission of the American Society of Nephrology (ASN); original image ©2015 ASN.

and ammonia ( $\text{NH}_3$ ). In the thick ascending limb of the loop of Henle,  $\text{NH}_4^+$  enters the cell primarily by substituting for potassium ion ( $\text{K}^+$ ) in transport by the apical sodium/potassium/chloride ( $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ ) cotransporter NKCC2.  $\text{NH}_4^+$  enters the interstitium mainly by substituting for  $\text{H}^+$  in transport by the basolateral  $\text{Na}^+/\text{H}^+$  exchanger NHE4.  $\text{NH}_4^+$  binds reversibly to highly anionic sulfatides in the interstitium, and graded expression of sulfatides, with higher levels in the inner medulla and lower levels in the cortex, generates the interstitial  $\text{NH}_4^+$  concentration gradient. In the collecting duct,  $\text{NH}_3$  and  $\text{H}^+$  are secreted in parallel into the urinary space and recombine to form  $\text{NH}_4^+$ . Transport of  $\text{NH}_3$  into the urinary space in this segment was thought to occur primarily through simple diffusion. Although true to some extent, the Rhesus glycoproteins Rhbg and Rhcg have been identified as  $\text{NH}_3$ -specific transport proteins in intercalated cells and are the major means of  $\text{NH}_3$  transport across the collecting duct.

The acid dissociation constant (pKa, 9.2) of the  $\text{NH}_3$  buffer system is much higher than the urine pH, which on the surface suggests that  $\text{NH}_3$  should not be a particularly useful urinary buffer. However, as opposed to the systemic circulation, in which maintaining constant pH is critical, the purpose of the  $\text{NH}_3$  buffer system is to eliminate  $\text{H}^+$  while maintaining a low free  $[\text{H}^+]$  ( $\text{H}^+$  concentration), not to maintain steady urine pH. The high pKa of the  $\text{NH}_3$  buffer system achieves these goals by ensuring that the vast majority of  $\text{NH}_3$  is protonated. For example, the ratio of  $\text{NH}_4^+$  to  $\text{NH}_3$  at urine pH 6.2 is 1,000:1. The net effect is that  $\text{H}^+$  is bound for excretion and the free  $[\text{H}^+]$  is low, permitting continued secretion of  $\text{H}^+$  to bind to other urinary buffers.

### Titratable Acid

Unlike  $\text{NH}_4^+$ , urinary titratable buffers are mainly derived from the systemic circulation through glomerular filtration and to a lesser extent through tubular secretion and are consequently less adaptable than  $\text{NH}_4^+$  to an acid load (Fig 1). Effective titratable buffers have pKa near the physiologic range of urine pH and bind to secreted  $\text{H}^+$  as they travel along the nephron. The principal titratable buffer hydrogen phosphate ( $\text{HPO}_4^{2-}$ ) accounts for 90% of titratable acid excretion (as dihydrogen phosphate [ $\text{H}_2\text{PO}_4^-$ ]). The  $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$  pKa is 6.8, which is about the pH of tubular fluid in the proximal tubule. Thus, half the filtered phosphate is dihydrogen phosphate as it leaves the proximal tubule. At lower urine pH (ie,  $\leq 5.5$ ), essentially all phosphate is protonated and other buffers with lower pKa, such as uric acid (pKa, 5.4) and creatinine (pKa, 5.0), contribute to titratable acid excretion.

### Net Acid Excretion

The sum of urinary  $\text{NH}_4^+$  and titratable acid excretion is the total acid excretion. In the steady state,  $\text{NH}_4^+$  accounts for  $\sim 60\%$  of total acid excretion. Net acid excretion (NAE) factors in any bicarbonate excretion that may occur ( $\text{NAE} = \text{NH}_4^+ + \text{titratable acid} - \text{HCO}_3^-$ , all units in mEq/d). The proximal tubule reclaims 85% of filtered bicarbonate and virtually all of the rest is reabsorbed in subsequent nephron segments. At urine pH  $< 6.5$ , the bicarbonate concentration in urine is negligible. Thus, if urine pH is  $< 6.5$ , urinary bicarbonate can be excluded from the NAE formula. Also, the free  $[\text{H}^+]$  is miniscule even at low pH (10  $\mu\text{mol/L}$  at pH 5.0) in comparison to the millimole quantities of  $\text{NH}_4^+$  and titratable acids in urine. Therefore, free  $\text{H}^+$  contributes very little to kidney acid excretion and is not included in the NAE formula.

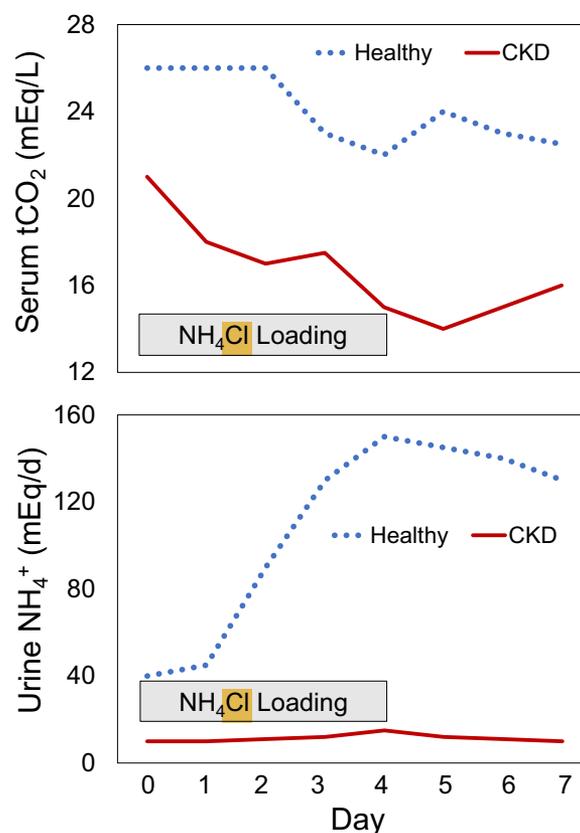
Considering Question 2, although titratable acid excretion increases to some extent in response to an acid load, urinary ammonium excretion increases substantially more. Excretion of free  $\text{H}^+$  may increase somewhat, but the concentration of free  $\text{H}^+$  in urine is minute compared to the quantity of  $\text{H}^+$  excreted as ammonium and titratable acid. In the steady state, most filtered bicarbonate is reabsorbed. Hence, increasing reabsorption of filtered bicarbonate is not a major kidney adaptation to an acid load, although an acid load increases ammoniogenesis in the proximal tubule and thus intracellular bicarbonate generation. Consequently, there is increased transport of intracellularly generated bicarbonate across the basolateral membrane of the proximal tubule. Thus, the correct response is (c).

### Additional Readings

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### Pathogenesis of Metabolic Acidosis in CKD

The development of metabolic acidosis depends on 2 key factors: kidney acid excretory capacity and daily endogenous and exogenous acid load. In CKD, metabolic acidosis develops when the kidneys are unable to excrete the acid load, leading to a positive  $\text{H}^+$  balance and low  $\text{tCO}_2$  concentration (Fig 2). Under normal circumstances, the daily acid load is largely determined by the metabolism of dietary constituents to  $\text{H}^+$  and base.  $\text{H}^+$  is produced from the sulfur-containing amino acids methionine and cysteine, which are abundant in animal sources of protein, and other amino acids (lysine, arginine, and histidine). Base is produced from the metabolism of other amino acids (glutamate and aspartate) and organic anions such as citrate, which is abundant in fruits and vegetables. Most diets are net acid producing owing to low consumption of fruits and vegetables. Inter- and intraindividual differences in dietary intake result in substantial variability, but in general, the daily nonvolatile acid load is typically on the order of 50 to 100 mEq/d, and reducing the dietary acid load,



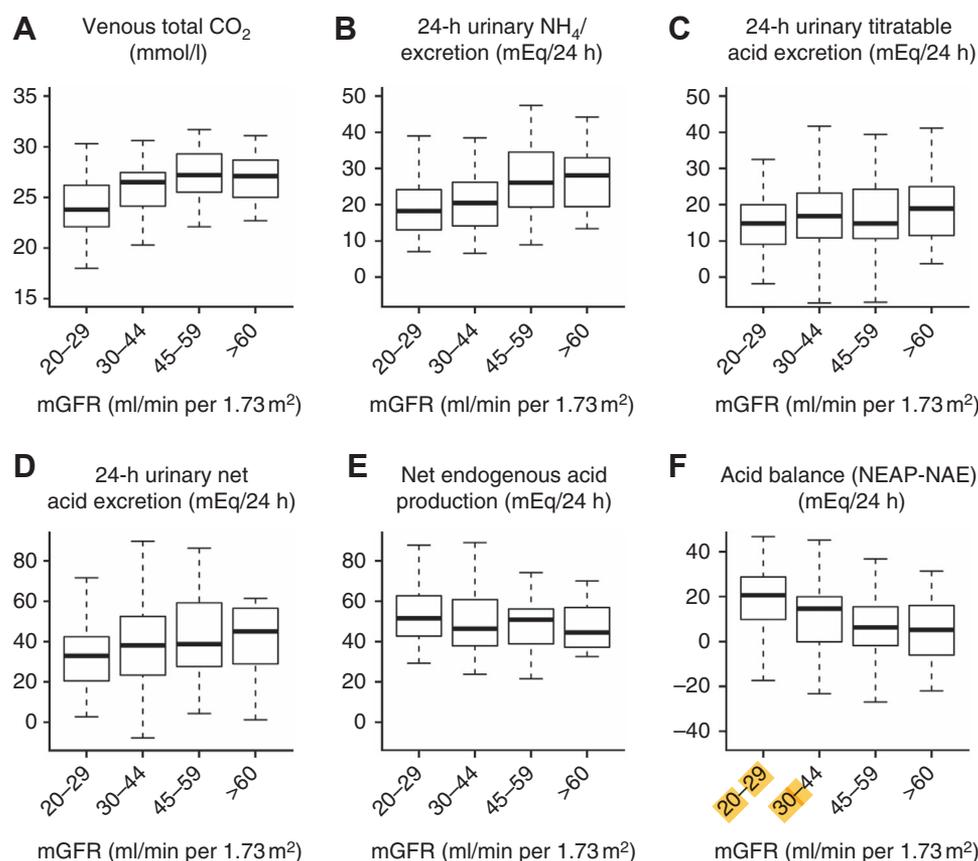
**Figure 2.** Acid loading with ammonium chloride ( $\text{NH}_4\text{Cl}$ ) over 4 days increases urinary ammonium ( $\text{NH}_4^+$ ) excretion in healthy individuals, which maintains serum total carbon dioxide ( $\text{tCO}_2$ ) level in the normal range. In chronic kidney disease (CKD), ammonium excretion fails to increase, resulting in metabolic acidosis. Adapted from Welbourne et al (*J Clin Invest*. 1972;51(7):1852-1860) with permission of the American Society for Clinical Investigation.

by reducing dietary protein or increasing fruits and vegetables consumption, increases  $t\text{CO}_2$  levels in patients with CKD.

The **second key component** in the development of metabolic acidosis in CKD is **kidney acid excretory capacity**. Although metabolic acidosis can be observed across all stages of CKD, the **risk for metabolic acidosis increases as eGFR decreases to  $<40 \text{ mL/min/1.73 m}^2$** . This is because in earlier stages of CKD, **ammonia production by residual nephrons increases to compensate for nephron loss**. This compensatory increase in per-nephron ammonium excretion is sufficient to excrete the fixed acid load and maintain normal acid-base balance in early CKD. As kidney function **deteriorates** and tubulointerstitial disease progresses, this **compensatory response is insufficient**, leading to positive acid balance and metabolic acidosis.

Figure 3 illustrates the interplay between daily acid load and kidney acid excretion in a cohort of patients with CKD and  $\text{eGFRs} \geq 20 \text{ mL/min/1.73 m}^2$ . With lower eGFRs, NAE decreases, yet the daily acid load, represented here as net endogenous acid production, is consistent across the range of eGFRs. This leads to a positive  $\text{H}^+$  balance and a progressively **lower serum  $t\text{CO}_2$**  concentration (Fig 3). It should be noted that NAE decreases primarily because of a

reduction in ammonium excretion, and lower urinary ammonium excretion is associated with higher risk for incident metabolic acidosis even after controlling for eGFR, dietary acid load, and other potential confounders. However, titratable acid excretion is not significantly altered until eGFR is severely reduced (ie,  $<15 \text{ mL/min/1.73 m}^2$ ). Preservation of titratable acid excretion appears to be due to a number of factors involving urinary phosphate handling, which is the primary titratable buffer. These include higher urinary phosphate levels owing to higher serum concentrations in more advanced CKD, a higher per-nephron phosphate load, diminished reabsorption of urinary phosphate due to higher levels of fibroblast growth factor 23 (FGF-23), and reduced proximal phosphate reabsorption induced by metabolic acidosis. Consequently, urinary phosphate delivery to the collecting duct is maintained at that which it can buffer  $\text{H}^+$  secreted by intercalated cells. The reduction in ammonium excretion observed in CKD is multifactorial. These include reduced nephron number, impaired glutamine uptake by proximal tubule cells, diminished  $\text{NH}_3$  concentration gradient in the kidney interstitium, and impaired  $\text{NH}_3$  secretion across the collecting duct. Distal  $\text{H}^+$  secretion does not appear to be impaired in CKD; therefore, impaired  $\text{NH}_3$  trapping does



**Figure 3.** Urinary (B) ammonium, (C) titratable acid, and consequently (D) net acid excretion (NAE) are lower with lower measured glomerular filtration rates (mGFRs). However, (E) net endogenous acid production (NEAP) is largely unchanged. (F) The positive acid balance with lower GFR leads to (A) reduced serum total carbon dioxide ( $t\text{CO}_2$ ) concentration. Reproduced from Vallet et al (*Kidney Int.* 2015;88(1):137-145) with permission of the International Society of Nephrology (ISN); original image ©2015 ISN.

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not seem to explain the reduction in ammonium excretion.

Along these lines, most patients with CKD have preserved distal  $H^+$  secretion and consequently have pH of  $\sim 5.5$ . Bicarbonate reabsorption along the nephron seems to be altered in CKD. In animal models of CKD, fractional reabsorption of bicarbonate is reduced at the proximal tubule, leading to greater delivery of bicarbonate to distal segments. Reduced bicarbonate reabsorption at the proximal tubule is thought to be due to an increased per-nephron bicarbonate load that exceeds reabsorptive capacity in this segment. Although there is increased distal bicarbonate delivery, these segments are capable of reabsorbing the remaining bicarbonate so bicarbonate does not appear in urine.

## Additional Readings

- ▶ Nagami GT, Hamm LL. Regulation of acid-base balance in chronic kidney disease. *Adv Chronic Kidney Dis*. 2017;24(5):274-279. ★ **ESSENTIAL READING**
- ▶ Vallet M, Metzger M, Haymann JP, et al. Urinary ammonia and long-term outcomes in chronic kidney disease. *Kidney Int*. 2015;88(1):137-145.

## Diagnosis of Metabolic Acidosis in CKD

Metabolic acidosis is usually diagnosed in patients with CKD when serum  $tCO_2$  concentration, which is a surrogate assessment of the bicarbonate concentration, is consistently  $< 22$  mEq/L. Low serum  $tCO_2$  concentration is also a feature of respiratory alkalosis, and distinguishing this acid-base disorder from metabolic acidosis requires measuring systemic pH and  $P_{CO_2}$ , preferably from an arterial sample. Blood gases are rarely performed in patients with CKD with low  $tCO_2$  concentrations, are not readily available in the outpatient setting, and are unnecessary in most cases. Given the importance of kidney nonvolatile acid excretion, a presumptive diagnosis of metabolic acidosis can be made without a blood gas in a patient with CKD and low  $tCO_2$  concentration. A blood gas may be helpful in patients with risk factors for chronic respiratory alkalosis, such as liver or cardiopulmonary disease or residence at high altitude, or if serum  $tCO_2$  concentration fails to normalize with alkali therapy. Urine pH is often not helpful because free  $[H^+]$  is influenced by the presence of urinary buffers. Most patients with CKD with metabolic acidosis have a normal serum anion gap; increased anion gap is usually not present unless eGFR is very low (ie,  $< 15$  mL/min/1.73 m<sup>2</sup>) owing to accumulation of phosphate, sulfate, and other anions. Nevertheless, it is important to consider the effect of hypoalbuminemia on the anion gap to avoid missing otherwise subtle increases in anion gap.

Importantly, the normal  $tCO_2$  concentration range reported by clinical laboratories is highly variable. In a survey of 66 clinical laboratories in the United States, the lower  $tCO_2$  limit ranged from 18 to 25 mEq/L, whereas

the upper limit ranged from 26 to 35 mEq/L. The reasons for the wide variability in normal ranges across clinical laboratories is unclear and many of these normal ranges are significantly outside the expected normal range of 23 to 30 mEq/L. Thus, the threshold of 22 mEq/L should be used to diagnose metabolic acidosis in CKD and not the lower limit of the clinical laboratory. A lower threshold may be considered for individuals residing at high altitude.

## Additional Readings

- ▶ Kraut JA, Madias NE. Re-evaluation of the normal range of serum total  $CO_2$  concentration. *Clin J Am Soc Nephrol*. 2018;13(2):343-347. ★ **ESSENTIAL READING**

## Prevalence and Risk Factors for Metabolic Acidosis in CKD

**Question 3: Which of the following is the strongest risk factor for metabolic acidosis in the patient presented earlier?**

- a) Diabetes
- b) Hyperkalemia
- c) Reduced eGFR
- d) Use of chlorthalidone
- e) Use of lisinopril

For the answer, see the following text.

Most non-dialysis-dependent patients with CKD do not have metabolic acidosis because of compensatory kidney  $NH_3$  production and bone buffering. Nevertheless, 15% of patients with CKD have metabolic acidosis, and the prevalence increases with advancing CKD. For example, in Chronic Renal Insufficiency Cohort (CRIC) participants, the prevalence of metabolic acidosis was 7% in stage 2, 13% in stage 3, and 37% in stage 4 CKD.

Reduced eGFR is the most important risk factor for metabolic acidosis (Box 1), particularly when eGFR decreases to  $< 40$  mL/min/1.73 m<sup>2</sup>. For example, those with stage 4 CKD have 7-fold higher and those with stage 3 CKD have 2-fold higher odds of metabolic acidosis than those with stage 2 CKD. Although eGFR and ammonium excretion are tightly linked, in African American Study of Kidney Disease and Hypertension (AASK) participants, the risk for incident metabolic acidosis was 2.5-fold higher if ammonium excretion was  $< 15$  mEq/d, even after controlling for eGFR and other potential confounders. Thus, quantifying ammonium excretion in patients with normal  $tCO_2$  concentrations may help identify individuals at high risk for developing metabolic acidosis. Diets high in acid-producing or low in base-producing foods contribute to metabolic acidosis risk as well. Renin-angiotensin-aldosterone-system (RAAS) inhibitors lower serum  $tCO_2$  concentration by attenuating aldosterone-mediated acid secretion. Hyperkalemia, independent of RAAS inhibition,

**Box 1. Risk Factors for Metabolic Acidosis in CKD**

Reduced GFR

Hyperkalemia

Reduced urinary acid excretion

Albuminuria

Smoking

Anemia

Higher serum albumin concentration

Nonuse of a diuretic

ACE inhibitor/ARB use

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate.

lowers serum  $t\text{CO}_2$  concentration by reducing kidney  $\text{NH}_3$  production.

Considering Question 3, the severity of CKD, and thus eGFR, is the most important risk factor for metabolic acidosis in CKD. Some, but not all, studies have found higher risks for metabolic acidosis among those with diabetes. Hyperkalemia and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are risk factors for metabolic acidosis, but eGFR is a stronger risk factor than each of these. Diuretics tend to increase serum  $t\text{CO}_2$  concentrations and are associated with a lower likelihood of metabolic acidosis. Thus, the correct response is (c).

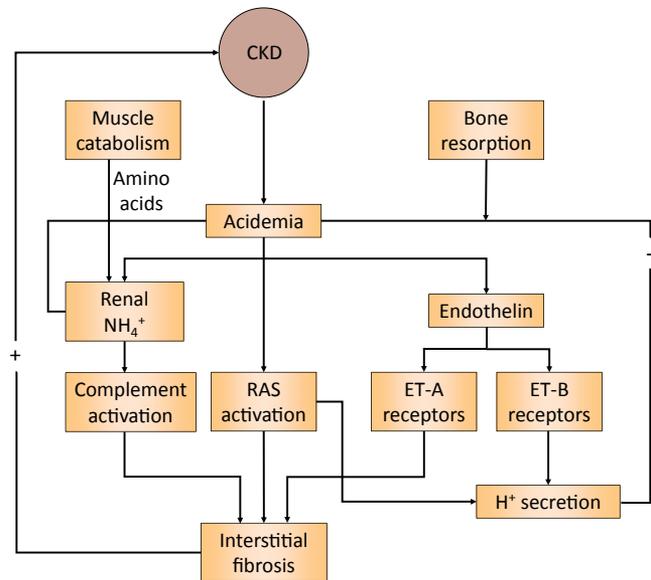
**Additional Readings**

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- ▶ Raphael KL, Carroll DJ, Murray J, Greene T, Beddhu S. Urine ammonium predicts clinical outcomes in hypertensive kidney disease. *J Am Soc Nephrol*. 2017;28(8):2483-2490.
- ▶ Raphael KL, Zhang Y, Ying J, Greene T. Prevalence of and risk factors for reduced serum bicarbonate in chronic kidney disease. *Nephrology (Carlton)*. 2014;19(10):648-654.

**Effects of Metabolic Acidosis on the Kidney**

Multiple lines of evidence support the notion that kidney adaptations that facilitate acid excretion to maintain normal acid-base balance can themselves cause kidney injury (Fig 4). One of these adaptations is an increase in per-nephron  $\text{NH}_3$  production to maintain kidney acid excretion in the setting of nephron loss. High tissue concentrations of  $\text{NH}_3$  promote cleavage of the internal thioester bond of the complement protein C3, leading to activation of the alternative pathway of complement within the kidney and tubulointerstitial fibrosis. Similarly, intrarenal complement-mediated tubulointerstitial fibrosis is observed in animals with normal renal mass and hypokalemia, which stimulates kidney ammoniogenesis.

Another adaptation that assists in maintaining normal  $t\text{CO}_2$  concentrations and pH at the cost of promoting kidney injury is upregulation of systemic and kidney endothelin 1 (ET-1) levels. ET-1 boosts acid excretion by



**Figure 4.** Mechanisms of acid-mediated tubulointerstitial fibrosis in chronic kidney disease (CKD). Abbreviations: ET-A, endothelin-A; ET-B, endothelin-B;  $\text{NH}_4^+$ , ammonium ion; RAS, renin-angiotensin system. Reproduced from Loniewski and Wesson (*Kidney Int*. 2014;85(3):529-535) with permission of the International Society of Nephrology (ISN); original image ©2013 ISN.

stimulating proximal and distal  $\text{Na}^+/\text{H}^+$  exchange, lowering distal bicarbonate secretion through nitric oxide, and triggering adrenal aldosterone release to facilitate  $\text{H}^+$ -ATPase activity. However, ET-1 is a potent systemic and intrarenal vasoconstrictor and induces inflammation, oxidative stress, and extracellular matrix accumulation in the kidney. Thus, adaptive increases in ET-1 levels to facilitate acid elimination contribute to tubulointerstitial fibrosis.

Angiotensin II, a potent vasoconstrictor that promotes tubulointerstitial fibrosis, also appears to contribute to acid-mediated kidney injury. For example, angiotensin II levels were increased in subtotal nephrectomy animals with normal  $t\text{CO}_2$  concentrations but interstitial acid accumulation, and treatment of these animals with alkali was found to reduce angiotensin II levels and preserve GFR. Interstitial acid accumulation may also contribute to kidney injury by stimulating intrarenal inflammation, insulin resistance, and oxidative stress.

In this way, compensatory upregulation of kidney  $\text{NH}_3$  production and ET-1 and RAAS activity to preserve systemic  $t\text{CO}_2$  and pH cause further kidney injury. Along these lines, several, but not all, longitudinal observational studies have found associations between metabolic acidosis and higher risks for eGFR decline and end-stage renal disease. Because these adaptive responses help maintain normal serum  $t\text{CO}_2$  concentrations in the setting of reduced eGFRs, it is likely that these mechanisms of kidney injury are occurring in a subset of patients with CKD with normal serum  $t\text{CO}_2$  concentrations. In other words, acid-mediated kidney

damage may be occurring in many patients with CKD with normal systemic acid-base balance, and some observational studies have reported that serum bicarbonate concentrations of about 26 to 28 mEq/L are associated with the lowest risk for CKD progression.

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### Effects of Metabolic Acidosis on Bone and Muscle in CKD

Bone buffering is an important response to acid excess, whether in the setting of overt metabolic acidosis or high dietary acid intake. Bone buffering leads to hypercalciuria, negative calcium balance, and loss of bone mineral content. In vivo studies demonstrated that extracellular acidification increases osteoclast activity and inhibits osteoblast activity. These effects contribute to reduced bone mineral density in patients with and without kidney disease.

For example, in a prospective observational cohort study of more than 1,000 white women older than 65 years, those in the highest quintile of animal to vegetable protein intake ratio had a higher rate of bone loss at the femoral neck and nearly 4-fold greater risk for hip fracture than those in the lowest quintile. In more than 2,200 Health, Aging, and Body Composition (Health ABC) Study participants, serum bicarbonate concentration, calculated from arterialized venous blood gas measurements, was inversely associated with the rate of bone loss at the total hip (bone loss = 0.2% higher per year for each 1-mEq/L lower bicarbonate). In CKD, serum tCO<sub>2</sub> concentration is directly associated with bone mineral density; however, a link between tCO<sub>2</sub> concentration and risk for fracture has not been established in CKD or end-stage renal disease.

Landmark animal studies demonstrated that metabolic acidosis stimulates skeletal muscle proteolysis through acidification-dependent activation of ubiquitin protein ligases, and in humans, serum tCO<sub>2</sub> concentration is associated with reduced strength, cardiorespiratory fitness, and physical function. In 1,544 Health ABC Study participants, those with bicarbonate concentrations < 23 mEq/L had 58% higher risk for incident functional limitation (defined as self-reported difficulty walking 0.25 mile or up 10 stairs

on 2 consecutive reports 6 months apart). In 2,675 National Health and Administration Examination Survey (NHANES; 1999-2002) participants, those with serum tCO<sub>2</sub> concentrations < 23 mEq/L had 43% higher odds of low gait speed and 36% higher odds of low quadriceps muscle strength (for each outcome, low was defined as being in the lowest sex-specific quartile). In 2,714 NHANES (1999-2004) participants aged 20 to 49 years, those with serum tCO<sub>2</sub> concentrations < 24 mEq/L were more likely to have low cardiorespiratory fitness (defined as being below the 20th percentile based on age- and sex-specific cutpoints). Thus, acid excess associated with overt metabolic acidosis or from a high dietary acid load has detrimental effects on musculoskeletal health.

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### Association Between Metabolic Acidosis and Mortality in CKD

Results from large cohort studies have found that metabolic acidosis is also associated with increased all-cause mortality in CKD. In US veterans with CKD, those with metabolic acidosis had 43% higher all-cause mortality than those with normal serum tCO<sub>2</sub> concentrations. Among patients with CKD at Cleveland Clinic Foundation, all-cause mortality was 23% higher for those with metabolic acidosis compared with their counterparts with normal tCO<sub>2</sub> concentrations, and in CRIC, metabolic acidosis was associated with a nominally higher risk for death (26%), though this result was not statistically significant. The reasons for the increased risk for death are unclear. Because low tCO<sub>2</sub> concentrations are more common in individuals with lower eGFRs, and lower eGFRs are linked with cardiovascular disease, it is reasonable to suspect that metabolic acidosis increases cardiovascular disease risk. However, an association between metabolic acidosis and increased cardiovascular disease risk independent of eGFR has not been clearly identified. Metabolic acidosis is also associated with malnutrition, inflammation, and oxidative stress, which are associated with mortality.

It is also important to mention that several studies have observed a U-shaped relationship between tCO<sub>2</sub> levels and mortality in CKD. In general, risk for death is lowest at tCO<sub>2</sub> levels around 26 to 28 mEq/L, and results from observational studies suggest that levels ≥ 30 mEq/L are associated with higher mortality in CKD. Mechanisms underlying the increased risk for death with higher tCO<sub>2</sub> concentrations in CKD are unclear because it is uncertain

whether these individuals have metabolic alkalosis or a primary respiratory acidosis with a compensatory increase in  $t\text{CO}_2$  concentration. Nevertheless, serum  $t\text{CO}_2$  levels  $\geq 27$  mEq/L have been associated with 66% higher risk for incident heart failure in CRIC participants, potentially indicating an adverse effect of acid-base state on the cardiovascular system in CKD. Nevertheless, these results suggest that targeting excessively high  $t\text{CO}_2$  levels with alkali therapy may be harmful.

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### Other Complications of Metabolic Acidosis in CKD

Metabolic acidosis and hyperkalemia are commonly observed contemporaneously in CKD. This is because each can worsen the other. In response to metabolic acidosis,  $\text{K}^+$  shifts from the intracellular to the extracellular compartment in exchange for  $\text{H}^+$  increasing the serum  $\text{K}^+$  concentration. In addition,  $\text{H}^+$  secretion by type A intercalated cells to facilitate acid excretion is counterbalanced by  $\text{K}^+$  reabsorption through the  $\text{H}^+/\text{K}^+$  exchanger. Hyperkalemia itself promotes metabolic acidosis by reducing kidney  $\text{NH}_3$  production and consequently acid excretion.

In large-scale observational studies, low  $t\text{CO}_2$  concentration has also been associated with cognitive impairment in hypertensive individuals with and without CKD. The mechanisms explaining this relationship are unclear. Nevertheless, this suggests that metabolic acidosis is a modifiable risk factor for poor cognition in CKD. Metabolic acidosis has also been implicated as a mediator of protein-energy wasting, which is a risk factor for mortality. Metabolic acidosis may stimulate protein-energy wasting through acidification-dependent activation of ubiquitin protein ligases, stimulation of proinflammatory cytokines, and induction of insulin resistance, and insulin resistance appears to be ameliorated when metabolic acidosis is treated with oral alkali.

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### Potential Benefits of Treating Metabolic Acidosis

#### Effects on the Kidney

Results from single-center interventional studies suggest that correcting metabolic acidosis with alkali improves kidney outcomes in CKD (Box 2). In a randomized study of 134 participants with stage 4 or 5 CKD and serum  $t\text{CO}_2$  concentrations of 17 to 19 mEq/L, de Brito-Ashurst et al found that those treated with sodium bicarbonate had a lower creatinine clearance decline and remarkably lower relative risk for end-stage renal disease (relative risk, 0.13; 95% confidence interval, 0.04-0.40) than a control group after 2 years of follow-up. In another study of patients with hypertensive stage 3 or 4 CKD and metabolic acidosis, Phistikul et al found that those treated with sodium citrate for 2 years had higher cystatin C-based eGFRs ( $27.8 \pm 7.4$  vs  $23.0 \pm 6.1$  mL/min/1.73 m<sup>2</sup>) and lower albuminuria at study completion compared with controls despite having similar values of each at baseline. Similar findings were observed in a study of 80 patients with CKD stage 4 or 5 and metabolic acidosis. In that study, the reduction in eGFR over 12 months was less in those treated with sodium bicarbonate versus controls ( $-2.03 \pm 3.39$  vs  $-4.84 \pm 5.15$  mL/min/1.73 m<sup>2</sup>).

Alkali therapy may also preserve kidney function in patients with CKD with normal serum  $t\text{CO}_2$  concentrations by attenuating the compensatory responses that maintain normal  $t\text{CO}_2$  concentrations but detrimentally promote tubulointerstitial fibrosis. In a study of hypertensive patients with stage 2 CKD with mean serum  $t\text{CO}_2$  concentrations of  $\sim 26$  mEq/L, those treated with sodium bicarbonate had higher eGFRs than those treated with placebo after 5 years. Similarly, treatment with either

#### Box 2. Major Potential Benefits and Risks of Correcting Metabolic Acidosis in CKD

##### Potential Benefits

- Reduce risk for CKD progression
- Increase skeletal muscle mass and strength
- Reduce bone buffering and preserve bone mineral
- Reduce serum potassium if hyperkalemic

##### Potential Risks

- Fluid retention, increased blood pressure, pulmonary and peripheral edema with sodium-based formulations
- Hypokalemia if bicarbonaturia is excessive
- Hyperkalemia with potassium-based formulations or nutritional therapies
- Vascular calcification
- Kidney calcification
- Calcium phosphate nephrolithiasis

Abbreviation: CKD, chronic kidney disease.

## Core Curriculum

sodium bicarbonate or fruits and vegetables better preserved the eGFR than usual care in hypertensive patients with stage 3 CKD with serum tCO<sub>2</sub> concentrations of 22 to 24 mEq/L over 3 years.

Although these results support the hypothesis that alkali therapy preserves kidney function in patients with CKD, evidence from large-scale clinical trials is necessary before definitive conclusions can be made. Several other trials evaluating the effect of alkali supplementation in patients with metabolic acidosis and CKD on kidney function are ongoing and their results are eagerly anticipated.

## Effects on Bone and Muscle

Although there is good evidence that metabolic acidosis has adverse consequences on bone and muscle health, convincing evidence that treatment of metabolic acidosis improves musculoskeletal health is lacking. The observation that oral bicarbonate treatment ameliorates impaired growth in children with renal tubular acidosis is perhaps the best evidence that treatment of metabolic acidosis improves skeletal health. In a study of adults with CKD, treatment of metabolic acidosis for 3 months mildly attenuated increases in parathyroid hormone levels. In a crossover study by Kendrick et al, treatment of metabolic acidosis with sodium bicarbonate had no effect on levels of parathyroid hormone or bone turnover markers but increased serum phosphate and FGF-23 levels. The increase in phosphate and FGF-23 levels is potentially concerning because higher levels of each are associated with increased cardiovascular risk in CKD.

In studies of persons without CKD, primarily conducted in postmenopausal women, alkali therapy was found to reduce urinary calcium excretion by mitigating dietary acid-mediated bone resorption. With respect to skeletal muscle, sodium bicarbonate treatment improved sit-stand time, but not hand grip strength, in a single-arm study of 20 patients with CKD with serum tCO<sub>2</sub> concentrations of 20 to 24 mEq/L. In de Brito-Ashurst et al, midarm muscle circumference was higher, suggesting increased muscle mass, among individuals with treated metabolic acidosis as compared with controls over 2 years. These findings suggest that treatment of metabolic acidosis improves musculoskeletal health in CKD; however, better evidence is required.

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## Management of Metabolic Acidosis in CKD

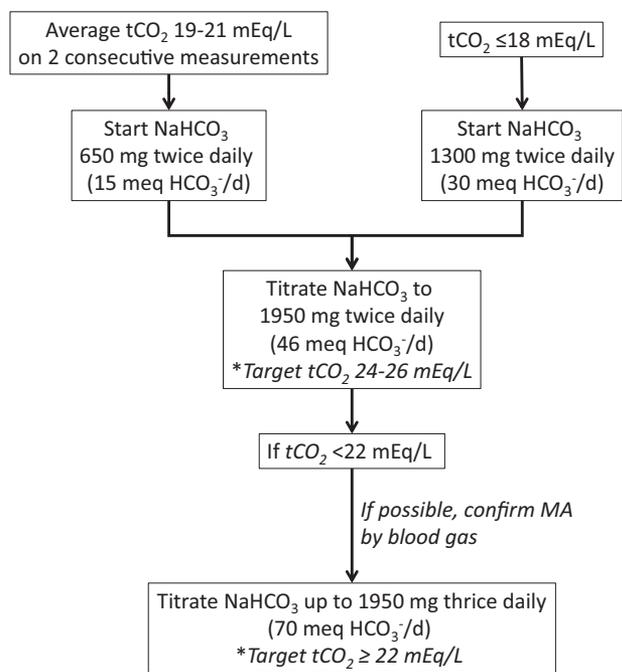
## When to Initiate Alkali Therapy in CKD

Nutritional alkali therapy with fruits and vegetables is probably warranted in most individuals with CKD, even those without metabolic acidosis, as long as serum potassium concentration allows and is monitored. In studies by Goraya et al, the dose of fruits and vegetables was calculated to offset each individual's dietary acid load by 50%. Although precise calculations are impractical in the clinic, this dose increased fruit and vegetable consumption by approximately 2 to 4 cups per day.

In terms of pharmacologic therapy, this should only be considered for patients with metabolic acidosis. As mentioned, sodium bicarbonate may preserve kidney function in patients with normal tCO<sub>2</sub> concentrations, raising the possibility that this intervention may be more broadly applied for the purpose of preserving eGFR. However, pharmacologic alkali therapy should not be offered to patients with CKD and normal tCO<sub>2</sub> concentrations at this time because large multicenter trials testing the efficacy and safety of this novel approach have yet to be conducted.

Nevertheless, a practical question is whether to start pharmacologic treatment based on a single low tCO<sub>2</sub> value because the concentration can fluctuate due to changes in eGFR, intercurrent illness, and diet. Therefore, initiating alkali therapy with a single low tCO<sub>2</sub> value may be premature in some instances. The decision to initiate pharmacologic treatment should consider these factors: severity of metabolic acidosis, blood pressure, and volume status. Hyperkalemia along with metabolic acidosis is probably the most important reason to initiate pharmacologic treatment because this maneuver can help reduce serum potassium concentration, lowering risk for arrhythmias and allowing continued RAAS blockade. Otherwise, it is reasonable to confirm a low tCO<sub>2</sub> concentration after a period of weeks to months before initiating alkali treatment. Based on the severity of metabolic acidosis (eg, ≤ 18 mEq/L), it is also reasonable to initiate pharmacologic therapy in the absence of confirmation, assuming there is not a reversible cause such as acute diarrhea or acute kidney injury.

Figure 5 presents the author's approach to the management of metabolic acidosis in CKD. If tCO<sub>2</sub> concentration is 19 to 21 mEq/L, the value is rechecked within 3 months, and if it remains low, alkali therapy can be started. For those with tCO<sub>2</sub> concentrations ≤ 18 mEq/L, it is reasonable to begin alkali therapy without confirming a low value, assuming there is no short-term condition that might account for the low tCO<sub>2</sub> concentration.



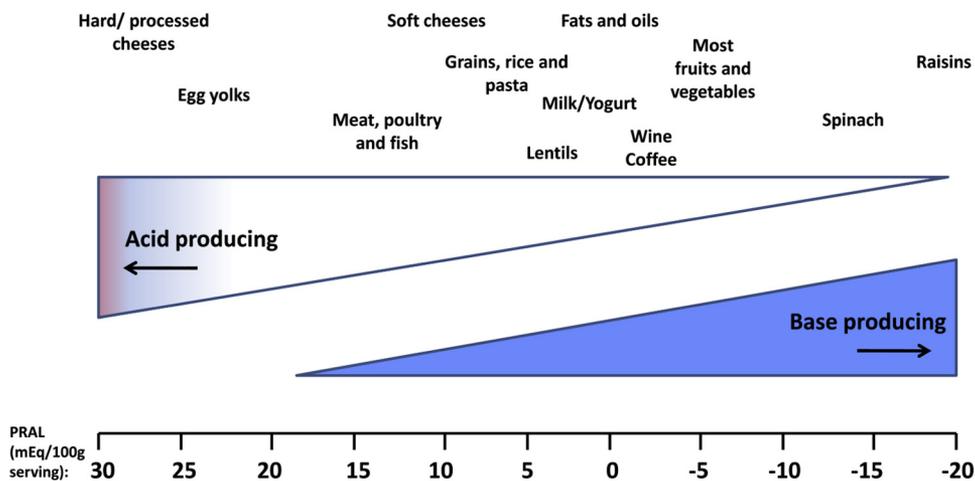
**Figure 5.** Author’s approach to the management of chronic metabolic acidosis (MA) in chronic kidney disease using sodium bicarbonate (NaHCO<sub>3</sub>). The NaHCO<sub>3</sub> dose should be reduced if total carbon dioxide (tCO<sub>2</sub>) is > 26 mEq/L. The dose of HCO<sub>3</sub><sup>-</sup> in mEq/day is shown in parentheses; the dose of citrate-based formulations can be approximated using these values. Adapted from Raphael (*Am J Kidney Dis.* 2016;67(4):696-702) with permission of the National Kidney Foundation.

**Treatment of Metabolic Acidosis in CKD**

Dietary strategies should be considered in the management of metabolic acidosis in CKD. This can include a combined approach of reducing acid-producing and increasing base-producing foods and beverages. In addition to providing alkali, the potassium, fiber, and other nutrients in fruits

and vegetables may have benefit in CKD. Serum potassium concentration should be < 4.5 mEq/L if fruits and vegetables are recommended and should be closely monitored. Dietary protein reduction also increases serum tCO<sub>2</sub> concentration and can be incorporated in dietary recommendations. Decreasing consumption of other acid-producing foods such as grains and cheeses can be considered. Given the time required to gather a detailed dietary history, the complexity of these dietary recommendations and their impact on potassium, phosphate, and protein balance, a kidney nutrition specialist should be intimately involved if dietary strategies are recommended. Figure 6 shows the potential renal acid load of common foods and can be used to help counsel patients.

If dietary changes are ineffective, contraindicated (eg, because of hyperkalemia), or unlikely to be adhered to by patients, pharmacologic treatment should be used. Potassium- and sodium-based preparations are available; however, potassium-based agents should be avoided unless hypokalemia is also present. Table 1 presents characteristics of commonly prescribed alkalinizing agents. Although citrate-based agents may enhance aluminum absorption, as long as aluminum-based binders are not used, this probably does not pose a safety concern. Less expensive than citrate-based therapies is sodium bicarbonate, which should be dosed taking into consideration the potential for gastrointestinal intolerance or other side effects, as well as serum tCO<sub>2</sub> concentration. A reasonable starting dose is 650 mg twice daily if serum tCO<sub>2</sub> concentration is 19 to 21 mEq/L. If serum tCO<sub>2</sub> concentration is ≤ 18 mEq/L, a dose of 1,300 mg twice daily can be considered. Some patients prefer over-the-counter sodium bicarbonate powder (baking soda) dissolved in water instead of consuming tablets. One-eighth of a teaspoon of sodium bicarbonate powder provides an equivalent amount of bicarbonate as one 650-mg tablet. The powder should be dissolved in approximately 8 to 12 ounces of water. It is critical that patients understand that the unit of



**Figure 6.** Estimated potential renal acid load (PRAL) of common foods per 100-g serving. Reproduced from Scialla et al (*Adv Chronic Kidney Dis.* 2013;20(2):141-149) with permission of the National Kidney Foundation.

## Core Curriculum

**Table 1.** Commonly Prescribed Alkalinizing Agents, Dosages, and Considerations

Agent	Dose	mEq of HCO <sub>3</sub> <sup>-</sup>	Considerations
Sodium bicarbonate tablets	325 mg 650 mg	3.9 7.7	<ul style="list-style-type: none"> <li>Inexpensive</li> <li>Non-potassium based</li> <li>Conversion of HCO<sub>3</sub><sup>-</sup> to CO<sub>2</sub> causes upper GI symptoms, rarely stomach perforation</li> </ul>
Sodium bicarbonate powder	1/8 teaspoon (600 mg)	7.1	<ul style="list-style-type: none"> <li>Powder should be dissolved in water or other liquid; may be mixed with food</li> </ul>
Sodium citrate/citric acid solution	500 mg/334 mg per 5 mL 490 mg/640 mg per 5 mL	1 per mL	<ul style="list-style-type: none"> <li>Fewer GI symptoms than sodium bicarbonate</li> <li>Non-potassium based</li> <li>Enhances aluminum absorption</li> <li>Conversion of citrate to HCO<sub>3</sub><sup>-</sup> impaired in liver disease</li> </ul>
Potassium citrate tablets	540 mg 1,080 mg 1,620 mg	5 10 15	<ul style="list-style-type: none"> <li>10- &amp; 15-mEq tablets deliver more mEq of HCO<sub>3</sub><sup>-</sup> than NaHCO<sub>3</sub> tablets</li> <li>Solution delivers more mEq/mL of HCO<sub>3</sub><sup>-</sup> than sodium citrate</li> </ul>
Potassium citrate/citric acid solution	1,100 mg/334 mg per 5 mL	2 per mL	<ul style="list-style-type: none"> <li>GI ulceration is rare</li> <li>Enhances aluminum absorption</li> </ul>
Potassium citrate/citric acid packet	3,300 mg/1,002 mg	30 per packet	<ul style="list-style-type: none"> <li>May cause hyperkalemia</li> <li>Packets should be dissolved in water</li> <li>Conversion of citrate to HCO<sub>3</sub><sup>-</sup> may be impaired in liver disease</li> </ul>

Abbreviations: CO<sub>2</sub>, carbon dioxide; GI, gastrointestinal; HCO<sub>3</sub><sup>-</sup>, bicarbonate; NaHCO<sub>3</sub>, sodium bicarbonate.

Adapted from Raphael (*Am J Kidney Dis.* 2016;67(4):696-702) with permission of the National Kidney Foundation.

measurement is **teaspoons**, not tablespoons. Each form of **sodium bicarbonate**, tablets and powder in water or other liquid, is unpalatable for some patients, with some preferring one or the other. Baking soda may also be mixed in food to increase palatability.

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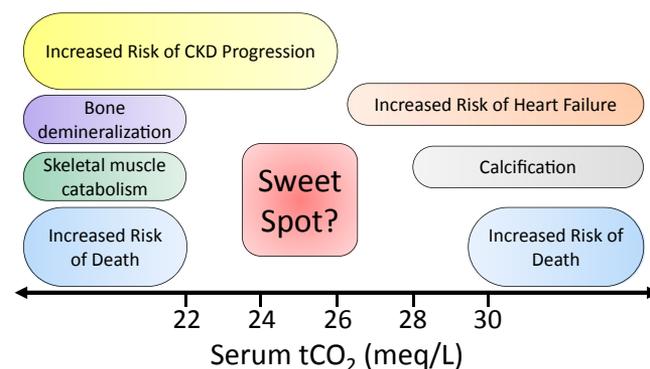
### Therapy Considerations

#### Dose Titration

Although guidelines recommend maintaining serum **tCO<sub>2</sub> concentrations at ≥ 22 mEq/L**, the ideal target may be **24 to 26 mEq/L**. The mean achieved tCO<sub>2</sub> concentration in de Brito-Ashurst et al and Phisitkul et al, studies that reported a beneficial effect of treating metabolic acidosis on eGFR, was ~24 mEq/L. Also, several observational studies have found an association between improved kidney outcomes and patient survival with tCO<sub>2</sub> concentrations of 26 to 28 mEq/L. However, results from CRIC suggest that values > 26 mEq/L are associated with higher risk for heart failure, and in other studies, values ≥ 30 mEq/L are associated with higher risk for death. Thus, targeting serum tCO<sub>2</sub> levels > 26 mEq/L may

not be warranted. These observations form the basis to consider targeting serum tCO<sub>2</sub> concentrations of 24 to 26 mEq/L in CKD (Fig 7).

To achieve the desired serum tCO<sub>2</sub> goal, the alkali dose can be titrated every few months as long as the dose is not excessive such that it impairs adherence and there are no side effects of treatment. In de Brito-Ashurst et al, the mean dose of sodium bicarbonate to achieve a mean serum tCO<sub>2</sub> concentration of ~24 mEq/L was 1.82 g/d. However, the maximum dose of sodium bicarbonate to



**Figure 7.** Rationale to target serum total carbon dioxide (tCO<sub>2</sub>) concentration of 24 to 26 mEq/L in chronic kidney disease (CKD). The optimum serum bicarbonate concentration in CKD is unknown. tCO<sub>2</sub> levels < 22 mEq/L are associated with bone demineralization, skeletal muscle catabolism, CKD progression, and mortality, while tCO<sub>2</sub> levels > 26 mEq/L are associated with higher risk for incident heart failure, and levels ≥ 30 mEq/L are associated with higher mortality. Targeting levels above the normal range may predispose to kidney and cardiovascular calcification.

prescribe in CKD is uncertain. Figure 5 shows one approach in which the sodium bicarbonate dose is titrated up to 1,950 mg twice daily to achieve a  $t\text{CO}_2$  target of 24 to 26 mEq/L. If the  $t\text{CO}_2$  concentration remains  $< 22$  mEq/L, confirming the presence of metabolic acidosis with an arterial or venous blood gas should be performed if possible. Doses up to 1,950 mg thrice daily can be considered if  $t\text{CO}_2$  concentration remains  $< 22$  mEq/L; however, doses above this are not used with this approach, even if  $t\text{CO}_2$  concentration remains low. This approach is not based on experimental evidence and the dose prescribed should take into account patient safety and tolerability. An approach using equimolar amounts of citrate-based formulations can be used as well.

### Complications of Pharmacologic Alkali Therapy

The primary concern with sodium-based alkali is fluid retention, elevation of blood pressure, and peripheral and pulmonary edema (Box 2). To date, results from small studies in CKD showed that differences in blood pressure, weight, and hospitalizations for heart failure were not significantly different between sodium bicarbonate/citrate-treated patients and controls. This is not entirely unexpected because sodium-related fluid retention is more substantial when sodium is accompanied by the chloride anion and not with other anions. Although the mechanisms for this are complex and multifactorial, hyperchloremia induces renal vasoconstriction through tubuloglomerular feedback. The reduction in GFR leads to increased sodium and water reabsorption.

Alkali therapy may also cause hypokalemia if bicarbonaturia occurs. Potassium-based formulations can cause hyperkalemia in CKD, although they can be used if hypokalemia is present. Hence, close monitoring of potassium is warranted. Ionized hypocalcemia may be observed if alkalemia develops, and increasing urine pH may theoretically predispose to calcium phosphate nephrolithiasis, although this has not been reported in clinical trials of alkali therapy in CKD. This may be because correcting metabolic acidosis reduces proximal citrate reabsorption (citrate reabsorption is increased in metabolic acidosis), and higher urinary citrate levels are expected to prevent hydroxyapatite formation.

Some patients have gastrointestinal side effects with sodium bicarbonate. Rupture of the stomach after consuming sodium bicarbonate is an extremely unusual but life-threatening complication. This appears to be due to increased intragastric pressure from a combination of factors, including the amount of  $\text{CO}_2$  gas produced after ingestion and the quantity of food and liquids in the stomach at the time of consumption. For this reason, sodium bicarbonate should be taken on an empty stomach and the total daily dose should not be taken at one time. Bloating and burping are more common gastrointestinal side effects, and switching to sodium

citrate should be considered if these limit adherence. Enteric-coated sodium bicarbonate preparations, which deliver bicarbonate to the intestine for absorption, may reduce these symptoms and are available in some countries.

There is a theoretical possibility that correcting metabolic acidosis may promote vascular and kidney calcification in humans. Uremic animals for which metabolic acidosis was treated with sodium bicarbonate had significantly greater vascular calcification than untreated animals. Furthermore, uremic animals with untreated metabolic acidosis had similar levels of vascular calcification as healthy animals. These findings raise the possibility that metabolic acidosis prevents and correcting metabolic acidosis provokes vascular calcification in CKD. Metabolic acidosis also prevents renal calcification in uremic animals on a high-phosphate diet; thus, withholding alkali therapy in patients with hyperphosphatemia may be warranted. These are theoretical but potentially significant complications that have not been thoroughly evaluated in clinical trials with sufficient sample size.

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### What to Do When Serum $t\text{CO}_2$ Fails to Normalize or Worsens With Treatment

Poor adherence and intolerance, particularly gastrointestinal intolerance, should be considered if  $t\text{CO}_2$  concentration remains  $< 22$  mEq/L after several months of treatment. Dissolving sodium bicarbonate powder in water can be tried if the number of pills affects adherence, and citrate-based agents should be tried if gastrointestinal symptoms occur with sodium bicarbonate. A detailed dietary history to assess dietary acid load may be helpful as well. Because some medications contain acid equivalents (ie, sevelamer hydrochloride), base-containing alternatives (ie, sevelamer carbonate) are worth considering.

## Core Curriculum

Acute illness, with or without a reduction in eGFR, can worsen serum tCO<sub>2</sub> concentrations in patients receiving alkali therapy. Inquiring about recent illnesses, particularly diarrheal illness, is important and can help guide clinical decision making.

**Summary**

Metabolic acidosis is a common complication of CKD and is associated with a number of clinically important adverse outcomes. These include higher risks for CKD progression, mortality, and impaired musculoskeletal health. Despite a century of knowledge that metabolic acidosis is a complication of CKD, convincing evidence that correcting metabolic acidosis benefits patients is lacking. Results from small studies support the notion that treating metabolic acidosis preserves kidney function and improves musculoskeletal health. Although pharmacologic therapy appears to be safe, there are potential risks of correcting metabolic acidosis. Large-scale clinical trials to determine whether

alkali therapy is efficacious and safe in CKD are long overdue.

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**Support:** Dr Raphael receives support from VA Merit Award I01-CX001695 from the US Department of Veterans Affairs Clinical Sciences Research and Development Service and the National Institute of Diabetes and Digestive and Kidney Diseases U01DK0099933 Research Project Cooperative Agreement.

**Financial Disclosure:** Dr Raphael received a 1-time consulting fee from Tricida, Inc.

**Peer Review:** Received July 11, 2018, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form January 23, 2019.