# 18 Metabolic Acidosis and Chronic Kidney Disease

Jeffrey A. Kraut and Glenn T. Nagami

**Before You Start: Facts You Need to Know**

- A decrease in bicarbonate generation with chronic kidney disease (CKD) leads to acid retention in the body. Initially this acid is retained in interstitial tissues without causing a change in systemic acid-base parameters, a stage termed eubicarbonatemic metabolic acidosis. Eventually as CKD progresses, a fall in the systemic bicarbonate level is also observed (overt metabolic acidosis).
- Eubicarbonatemic metabolic acidosis can be observed as early as stage II CKD (GFR 60–90 mL/min). Overt metabolic acidosis usually occurs when the estimated glomerular filtration rate (eGFR) falls below 25–30 mL/min, but may occur at higher levels of eGFR, particularly in the presence of concurrent disorders which affect renal bicarbonate generation such as hyporeninemic hypoaldosteronism or damage to the kidney collecting duct or with excessive dietary acid loads.
- Major adverse effects of both untreated eubicarbonatemic and overt metabolic acidosis include muscle wasting, bone disease, progression of CKD, and increased mortality.
- Acid-base parameters including pH, $PCO_2$, and [$HCO_3^-$] should be checked upon first evaluation, and then serum [Total $CO_2$] should be checked at least annually in stage 3a CKD, every 4–6 months for stage 3b CKD and approximately every 1–3 months in stages 4 and 5 CKD.
- Treatment of metabolic acidosis with base and/ or reduction in net endogenous acid production to reduce interstitial acidity slows the progression of CKD, decreases muscle wasting, and improves bone disease.
- New recommendations are to initiate base treatment when serum bicarbonate is ≤24 mEq/L with the goal of raising it to between 24 and 26 mEq/L.
- Guidelines for the detection and treatment of eubicarbonatemic metabolic acidosis are under investigation.

## 18.1 Introduction

Acid is produced from metabolism of ingested foodstuffs each day. The kidneys are responsible for generating a sufficient quantity of base to

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M. Arıcı (ed.), *Management of Chronic Kidney Disease*,
https://doi.org/10.1007/978-3-031-42045-0_18

neutralize this acid and thereby maintaining normal acid-base balance. With the development of chronic kidney disease (CKD), base generation rates can fall below acid production rates leading to hydrogen ion retention and positive acid balance [1]. The acid retained can cause the progression of CKD, development or exacerbation of bone disease, and wasting and dysfunction of muscles. Furthermore, in children it can impair growth [2].

In this chapter, we review the pathophysiology of the metabolic acidosis of CKD, the characteristics of the metabolic acidosis, the nature and mechanisms of cellular dysfunction, and the present recommendations for its treatment.

## 18.2 Pathophysiology

The serum bicarbonate (traditionally measured by the laboratory as [total $CO_2$]) is normally maintained between 23 and 29 mEq/L (mean, 24 mEq/L) and blood pH between 7.38 and 7.42 (mean, 7.40). The kidney is responsible for maintaining a normal serum bicarbonate concentration by reclaiming the large quantity of bicarbonate which is filtered by the glomeruli (approximately 4500 meq/d with normal GFR, and generating sufficient bicarbonate to match the daily net endogenous acid production rate (NEAP). The NEAP is derived from the metabolism of mostly animal proteins with their content of sulfur-containing and cationic amino acids. Dietary base is derived from the metabolism of fruits and vegetables. NEAP may vary in individuals with chronic kidney disease and largely depends on the nature of the diet.

Estimates of NEAP from diet recall of thousands of individuals participating in the Third National Health and Nutrition Examination Survey (NHANES) [3] revealed that the median acid load was 47 meq/d with 25% of individuals having less than 39 meq/d and 25% having greater than 59 meq/d of acid load. Thus, the necessary response of the kidney to maintain acid-base balance by generating sufficient quantities of base to neutralize NEAP will vary according to the diet. Generation of base by the kidneys occurs as a result of urinary excretion of hydrogen ions, in the form of titratable acid excretion ($H_2PO_4^-$) (approximately 1/3 of the acid load) and the generation of bicarbonate from the metabolic and transport processes resulting in ammonium excretion (approximately 2/3 of the acid load). However, with acid challenges from diet or disease, an increase in urinary ammonium excretion ($NH_4$) accounts for the majority of the increased acid excretion. Figure 18.1 illustrates the need for a balance between acid production from diet and acid excretion by the kidneys for maintaining a normal acid-base status.

Impairment in the kidney response to acid challenges in CKD could theoretically occur from a defect in bicarbonate reabsorption or in the generation bicarbonate. A defect in renal bicarbonate reabsorption occurs in a minority of patients with CKD. The major cause of acid retention in CKD is decreased ammonium excretion (from the usual quantity of 40 mEq/d to less than 20 mEq/d). This decrease in ammonium excretion is primarily a consequence of a reduction in the number of functioning nephrons, as ammonium excretion per residual nephron is actually increased above normal. As a result, rates of net acid excretion fall below rates of acid production leading to hydrogen ion retention. Studies in patients with a stable, albeit reduced GFR, have demonstrated that they are in continual positive hydrogen balance despite having a stable serum bicarbonate concentration [4]. The stability of serum bicarbonate at any given level of GFR has been attributed to buffering of retained hydrogen by tissue buffers, primarily those residing in bone, muscle, and kidney [5].

In some patients, superimposed defects in tubular hydrogen secretion and/or ammonia production can lead to more severe metabolic acidosis or its appearance earlier in the course of CKD especially in individuals who have a large NEAP. The most common cause for this exacerbation of metabolic acidosis is a reduction in aldosterone synthesis found with hyporeninemic hypoaldosteronism [6]. However, it can also be due to impaired proton excretion resulting from damage to the tubules residing in the renal medulla such as can found in patients with sickle

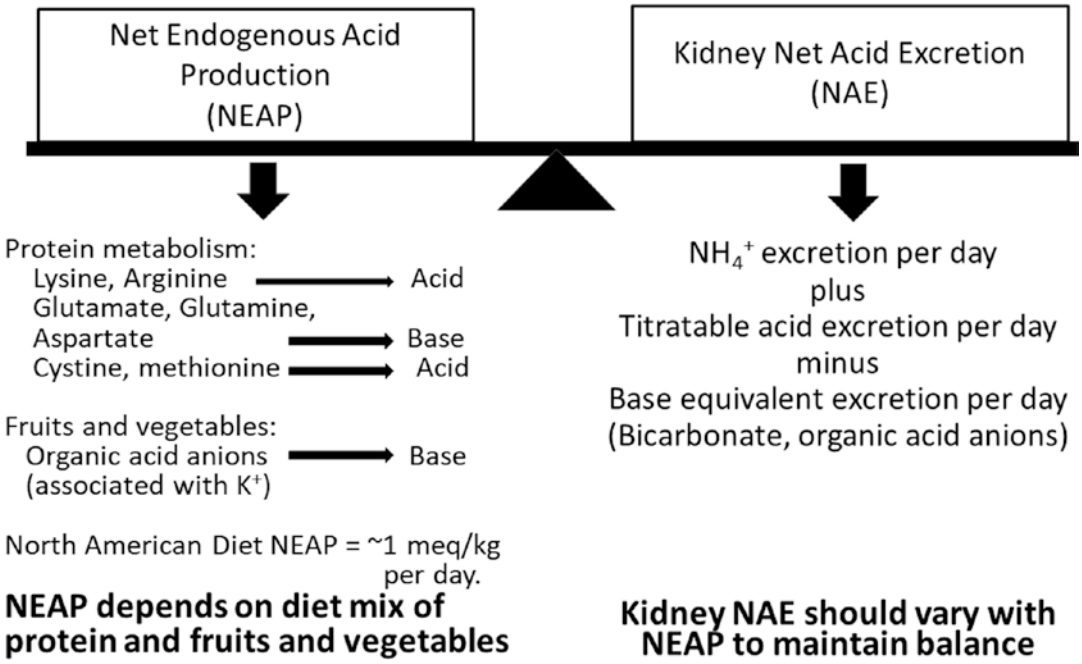


**Fig. 18.1** Normal acid-base homeostasis is maintained by balancing Net Endogenous Acid Production (NEAP) from metabolism and Net Acid Excretion (NAE) by the kidney. In general, increased protein intake relative to fruits and vegetables will result in more acid production which will need to be compensated for by the kidney, but the degree of compensation may be limited in chronic kidney disease

cell disease. Hyperkalemia out of proportion to the decrease in GFR which often accompanies these disorders contributes to the suppression of ammonia production and thereby to the development of metabolic acidosis. [7] Studies indicate that acid retention and positive acid balance can be observed with only mild reductions in GFR from the normal value of around 100–125 mL/min to between 60 and 90 mL/min (stage 2 CKD) [8]. At this stage, serum bicarbonate and blood pH are normal, and the acid appears to be sequestered in muscle, bone, and kidney. This stage has been termed normobicarbonatemic or eubicarbonatemic metabolic acidosis. [8] As kidney function declines further, hydrogen retention may become more extensive and a fall in systemic blood pH and bicarbonate can be observed. When overt metabolic acidosis develops, the reduction in serum [$HCO_3^-$] is usually mild (4–6 mEq/L), with serum bicarbonate ranging between 17 mEq/L and 22 mEq/L.

## 18.3 Clinical and Laboratory Characteristics

As noted above, acid retention without hypobicarbonatemia can be observed with only mild reductions in GFR. The exact prevalence of eubicarbonatemic metabolic acidosis is unknown. However, a recent survey of veterans (primarily male) revealed that approximately 25% of the patients had a GFR at which eubicarbonatemic metabolic acidosis has been described (stage 2 or more CKD). As renal function declines further, hypobicarbonatemia becomes more frequent. Thus, in the CRIC study [9], a serum bicarbonate less than 22 mEq/L (the definition of metabolic acidosis espoused by the National Kidney Foundation until 2020) was found in approximately 7% in individuals with stage 2 CKD rising to 35% in individuals with eGFR of 15–30 mL/min (stage 4) . Looked at another way, the majority of patients will develop hypobicar-

**Table 18.1** Disorders associated with metabolic acidosis in patients with CKD

| Disorder | Serum electrolyte pattern | Urine $NH_4$ | Urine pH | Urine anion and osmolal gap | Comments |
|---|---|---|---|---|---|
| Chronic kidney disease | Normal anion gap early; mixed high and normal and then high anion gap | <20 mEq/d | <5.5 | Abnormal | Acid retention can lead to eubicarbonatemic acidosis with stage 2 CKD and overt metabolic acidosis with stages 3 to 5 |
| Hyporeninemic Hypoaldosteronism | Normal anion gap | <20 mEq/d | <5.5 | Abnormal | Most common in diabetic patients; hyperkalemia out of proportion to reduction in eGFR; low renin low aldosterone levels present; treatment with mineralocorticoid or diuretics indicated |
| Tubular injury with tubular resistance to aldosterone | Normal anion gap | <20 mEq/d | >5.5 | Abnormal | Common in patients with significant interstitial renal disease including patients with sickle cell disease; renin and aldosterone values are normal |

Urine anion gap is defined as $Na^+ + K^+ - Cl^-$. In patients with ability to excrete acid appropriately, it is approximately—30 mEq/L, whereas it is positive in patients with impaired ability to excrete acid such as those with CKD. The urine osmolal gap is defined as measured urine osmolality—$2 \times Na^+ + K^+$ + urea nitrogen/2.8 + glucose/18. The difference if divided by 2 gives an approximation of $NH_4$ excretion. In normal patients it increases from 30 to 40 mEq/day to more than 150 mEq/day. In patients with CKD, it is usually <20 mmol/day

bonatemia once eGFR falls below 25–30 mL/min [10]. A small percentage of patients will maintain a normal serum bicarbonate concentration even in the presence of severe kidney failure (eGFR < 15 mL/min). The explanation for this occurrence is unclear.

The laboratory characteristics of the metabolic acidosis of CKD are summarized in Table 18.1. The metabolic acidosis can be of the normal anion gap variety early in the course of CKD, and then as CKD progresses excretion of phosphate and sulfate and organic anions become impaired so that they accumulate in the serum leading to the transition from a non-anion gap metabolic acidosis to a mixed non-anion gap and high anion gap metabolic acidosis, and finally to a high anion gap variety alone. The sensitivity of detecting an anion gap can be improved by adding a correction for albumin such that patients with earlier stages of CKD may be discovered to have an elevated anion gap [11] and such patients with adjusted anion gap levels had higher rates of mortality [11]. The presence of an anion gap is associated with larger dietary acid loads and with a higher risk for developing end-stage kidney disease [12]. Nevertheless, the general evolution of the type of acidosis is not uniform and may vary at different stages of CKD.

Hyperkalemia can be a pathogenetic factor in the development of a non-anion gap metabolic acidosis by its inhibitory effect on renal ammoniagenesis. Hyperkalemia is common with severe reductions of eGFR (<25–30 mL/min). However, it can also be observed with less severe reduction in eGFR, particularly when hyporeninemic hypoaldosteronism or significant tubular damage is present, such as observed in some cases of diabetes mellitus and urinary obstruction, or in sickle cell disease. Correction of hyperkalemia in patients with hyporeninemic hypoaldosteronism can result in the correction of metabolic acidosis [7].

Urine pH is appropriately acidic (<5.5) in the majority of patients with CKD reflecting their ability to acidify the urine. While titratable acid excretion is preserved due to enhanced excretion of phosphate until severe CKD supervenes, the excretion of ammonium is impaired earlier in the CKD course and is the major factor contributing the positive acid balance and metabolic acidosis.

## 18.4 Assessment of Acid-Base Balance in CKD

Since hypobicarbonatemia is often mild in patients with CKD, it sometimes can be difficult to distinguish the metabolic acidosis of CKD from chronic hypocapnia. Indeed, in one study a significant number of patients with CKD and hypobicarbonatemia had respiratory alkalosis [13]. Therefore, we recommend blood gas analyses be obtained upon first evaluation of these patients, even if the serum bicarbonate concentration is minimally perturbed. Although arterial blood gases are traditionally utilized for this purpose, recent studies have demonstrated that venous blood gases may suffice [14]. Measurement of urine pH in patients with a reduced serum bicarbonate concentration (obtained immediately upon voiding to prevent dissipation of $CO_2$) can be helpful in distinguishing patients with CKD alone or in combination with hypoaldosteronism (urine pH will be <5.5) from those with medullary tubular damage (urinary pH will be >5.5). Therefore, it can be worthwhile obtaining a measurement of urine pH in patients with hypobicarbonatemia.

Urinary ammonium excretion will be low in all patients with metabolic acidosis arising from kidney dysfunction, and therefore, estimates of urinary ammonium excretion are helpful in distinguishing the acidosis related to the presence of kidney disease to that caused by nonrenal mechanisms. Either indirect estimates of urinary ammonium excretion, such as those obtained using the urine anion gap or osmolal gap [15] or direct determination of urinary ammonium excretion [16] have been utilized. However, given the complexity of indirect estimates of urinary ammonium excretion, several investigators have found direct measurement of urinary ammonium excretion to be the most cost-effective and accurate method of assessing the kidney's contribution to acid-base balance [15]. In patients in whom kidney dysfunction is the only mechanism underlying the metabolic acidosis, urine ammonium excretion will be considerably less than the normal value of 40 mEq/day. On the other hand, if there is an increased acid load, urinary ammonium excretion can be greater than this value but substantially less than the 200 mEq/day which can be observed in healthy individuals with chronic mild metabolic acidosis and normal kidney function [17, 18]. Once acid-base parameters have been assessed and the presence of metabolic acidosis has been confirmed, blood gases need not be obtained again, but rather serum [Total $CO_2$] alone can be monitored. The recommended appropriate time of assessment for this parameter is given in Table 18.2. If patients are being treated with base or there is a subsequent reduction in GFR, more frequent determinations of serum bicarbonate might be necessary.

**Table 18.2** Recommended frequency of measurements of acid-base parameters in patients with CKD

| CKD stage | eGFR mL/min/1.73 $m^2$ | Frequency of measurements | Comments |
|---|---|---|---|
| 2 | 60–90 | At least once per year | Patients can manifest eubicarbonatemic metabolic acidosis at this stage and a small percentage, <10% can have hypobicarbonatemia |
| 3a | 45–59 | At least every 6 months | Hypobicarbonatemia begins to be more prevalent at this stage: In approximately 15% of patients. In acidemic patients hypobicarbonatemia can lead to severe kidney failure and needs to be treated aggressively |
| 3b | 30–44 | At least every 3–4 months | |
| 4 | 15–29 | At least every 2–3 months | Hypobicarbonatemia is frequent: Seen in at least 35% of patients. Normalization of acid-base parameters is important to prevent complications and improve clinical condition for initiation of dialysis |
| 5 | <15 | Once per month in dialysis patients; once 4–8 weeks in patients not on dialysis | A large majority of patients will be on chronic dialysis either hemodialysis or peritoneal dialysis |

Measurements of venous blood gases should be done initially or when hypobicarbonatemia is present. Once metabolic acidosis has been established serum [total $CO_2$] can be obtained

In patients with eubicarbonatemic metabolic acidosis, the presence of acid retention might not be easily identified given the normal acid-base parameters. Recent studies in a small cohort of patients with presumed eubicarbonatemic metabolic acidosis have shown that a spot urinary citrate/creatinine ratio determination might be an effective way of detecting these patients as patients with acid retention should also retain citrate and have low rates of urinary citrate excretion [8, 19]. One study was limited to patients with stage 1 and 2 CKD [19], and it is unclear whether this would apply to lower levels of eGFR. Studies involving a larger number of patients are necessary to determine the role of an urinary citrate measurement in the evaluation of patients with CKD.

## 18.5 Adverse Effects of the Chronic Metabolic Acidosis of CKD and Rationale for Treatment

The adverse effects of acid retention are summarized in Box 18.1. As noted above, acid retained with CKD is first sequestered in muscles, bones, and kidney. During this early phase, as noted, systemic acid-base parameters might be within the normal range. However, even in this early phase adverse effects can be observed including acceleration of the progression of CKD [8, 20]. Although not well studied, it seems that as the metabolic acidosis becomes more profound that the adverse effects become more extensive. The mechanisms underlying the progression of CKD with acid retention are summarized in Fig. 18.2.

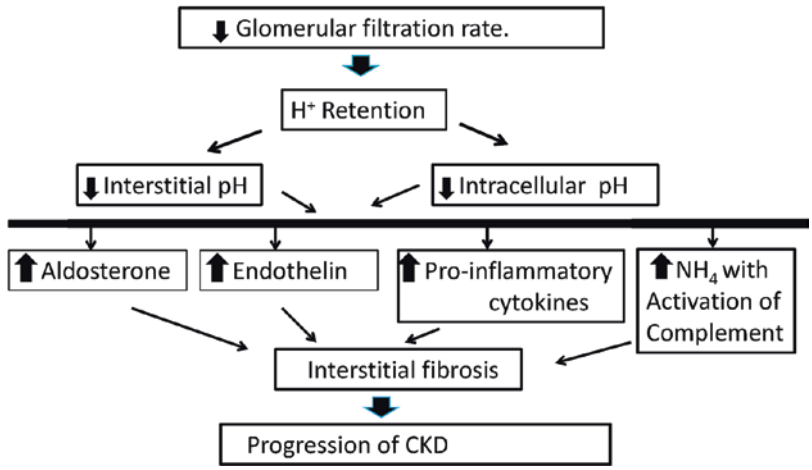


**Fig. 18.2** Factors contributing to kidney interstitial fibrosis and progression of CKD with chronic metabolic acidosis. A reduction in interstitial pH causes excess production of endothelin, aldosterone, and proinflammatory cytokines. The accumulation of acid also causes the kidney to produce more ammonium which activates a complement-dependent inflammatory cascade. All of these factors lead to increase kidney fibrosis and a decline in kidney function

**Box 18.1 Major Adverse Effects of Metabolic Acidosis**

| Effect | Stage of occurrence | Comments |
|---|---|---|
| Bone disease | Usually seen with later stages of CKD when significant hypobicarbonatemia is present | Both osteomalacia and osteitis fibrosa cystica described; lesions healed with base therapy |
| Stunted growth in children | Described in children with more severe hypobicarbonatemia; occurrence with less severe hypobicarbonatemia unclear | Growth improved with base therapy; impact of eubicarbonatemic metabolic acidosis not well studied |
| Acceleration in the progression of CKD | Can be seen with eubicarbonatemic metabolic acidosis, but more pronounced with hypobicarbonatemic metabolic acidosis | Base therapy slows progression |
| Muscle wasting with reduced muscle strength | Reported only in patients with hypobicarbonatemic metabolic acidosis | Base therapy reduces muscle wasting and improves muscle strength |
| Increased mortality | Reported in patients with significant acidemia | Impact of base therapy not studied |

A reduction in interstitial pH and/or intracellular pH appears to be the primary signals inducing alteration in the factors causing cellular damage. The increased acidity in these compartments increases the tissue concentrations of angiotensin II, aldosterone, endothelin, and proinflammatory cytokines. Also, the augmented $NH_4$ production per remaining nephron causes activation of the complement pathway and cellular damage. All four of these factors cause increased renal fibrosis. Administration of base to lessen acid retention reduces the concentration of the hormones and the activation of complement slowing the progression of CKD.

Acid retention also exacerbates or produces damage to the bones. Both osteitis fibrosa and osteomalacia have been described with metabolic acidosis which is ameliorated by administration of base. Whether eubicarbonatemic metabolic acidosis is associated with bone damage is not known. However, since bone is an important buffering site for acid, this would be expected. Acid retention and metabolic acidosis is associated with muscle wasting and reduced muscle strength. Again, base administration reduces muscle wasting and improves muscle strength [21, 22].

Many factors affect mortality in patients with CKD. Several studies in patients with CKD, both before and after initiation of chronic maintenance dialysis, have shown a correlation between metabolic acidosis and increased mortality [23] . The mechanism(s) underlying this effect is unclear.

In summary, the development of metabolic acidosis is associated with a myriad of adverse effects which can have a dramatic effect on the quality of life and mortality of patients with CKD. The impact of acidosis on progression of CKD has been the effect most studied. The impact of acidosis on bone and muscle have been less broadly examined, and therefore further studies involving large cohorts of patients are desirable. The clinical studies performed so far indicate base therapy is beneficial in ameliorating many of these adverse effects providing a strong rationale for aggressive prevention and/ or treatment of the acidosis [2].

## 18.6 Treatment

Based on evidence that metabolic acidosis is associated with progression of chronic kidney disease, production or worsening of bone disease, and increased mortality, several kidney organizations including the National Kidney Foundation (NKF) have recommended administration of base to patients with hypobicarbonatemia. Initially the recommendation for base administration was the presence of a serum [$HCO_3^-$] concentration of less than or equal to 22 mEq/L. However, in 2019 the NKF changed

the criteria to recommend administration of base when serum bicarbonate was less than 24–25 mEq/L. Most experts and renal organizations now recommend that the serum bicarbonate should be raised to values between 24 mEq/L and 26 mEq/L. No randomized controlled studies have determined whether this criterion is appropriate, and this remains an important issue to assess. The potential adverse effects of over-correction of too high of a bicarbonate level have also to be raised. Therefore, the clinician should be vigilant to prevent over-correction of the acidosis.

An added layer of complexity has been added by the recognition that patients with eubicarbonatemic metabolic acidosis can have deleterious effects from the acidosis that are ameliorated by the administration of base [8]. Therefore, there could be a reason to initiate base therapy in patients with CKD even with minimal or no reductions in serum [$HCO_3^-$]. On the other hand, there remains potential risk of base therapy should it rise even slightly above normal. A recent randomized study indicated that although base therapy slowed progression of CKD, a serum bicarbonate above 24 mEq/L even when produced by measures other than base therapy was associated with a higher prevalence of congestive heart failure [9]. Moreover, others have suggested that an increased serum bicarbonate might provide an alkaline milieu that would predispose to deposition of calcium and phosphorus in tissues with resultant organ dysfunction. Be that as it may, we conclude that until randomized controlled studies which evaluate the risks and benefits of base therapy in patients with eubicarbonatemic metabolic acidosis and CKD are published, we are cautious about the use of base in the treatment of patients with eubicarbonatemic metabolic acidosis. Identifying individuals who may be at higher risk for developing acid retention may be helpful in choosing who needs special attention and validating newer ways to monitor treatment responses could add to the safety and effectiveness of more aggressive approaches to treatment. Individuals with a tendency to hyperkalemia from hyporeninemic hypoaldosteronism or those who consume a heavy animal protein intake may need dietary counseling about reducing dietary acid load. Clearly given the potential large numbers of individuals with this disorder, this remains a critical area of study.

In treatment of patients with base, the clinician should be very vigilant to assess patients for possible complications such as volume overload with exacerbation of hypertension and congestive heart failure. Also, strong emphasis should be given on control of serum calcium and phosphorus to lessen the risk of soft tissue and vascular calcifications. An increase in serum bicarbonate above normal should be prevented at all costs because of concern for exacerbation of heart failure or promotion of tissue calcifications.

Administration of sodium bicarbonate, sodium citrate (Shohl's solution), or an increase in the consumption of dietary fruits and vegetables are all effective in raising serum bicarbonate concentration. Sodium bicarbonate is inexpensive, but has the complication of producing excess carbon dioxide in the stomach which can be uncomfortable for the patient. The use of enteric-coated tablets might lessen this complication. The administration of sodium citrate (Shohl's solution) is effective and relatively inexpensive, but caution should be advised in patients who are taking aluminum-containing compounds such as sucralfate and AlOH-containing antacids. Citrate enhances the gastrointestinal absorption of aluminum which can accumulate and cause toxicity when kidney function is impaired.

Changes in dietary habits rather than administration of supplements might be the most cost-effective means of raising serum bicarbonate concentration. A reduction in animal protein intake in concert with increased intake of fruits and vegetables has been shown to be successful in raising serum bicarbonate with little complications [24]. Given the high potassium content of fruits and vegetables, however, one should be cautious about a possible increase in serum potassium with this regimen. Controlled studies up to now, however, have not found a significant increment in the appearance of this complication.

Recently a new drug, Veverimer has been developed that raising serum bicarbonate by

binding hydrogen ions in the stomach and causing their excretion in the stools. In contrast to sodium containing buffers, it does not deliver any sodium to the patient. In controlled studies, it raised serum bicarbonate by approximately 4 mEq/L in a matter of days and maintained it for several months [25]. The drug remains under study and is not yet approved by the FDA, but could be an attractive addition to the clinician armamentarium in the treatment of patients with CKD.

No matter what regimen is utilized, an estimate of base deficit should be obtained before embarking on therapy. This can easily be accomplished by subtracting the prevailing serum bicarbonate from the desired serum bicarbonate and multiplying this value by the approximate volume of distribution of administered bicarbonate, usually 50% body weight as shown below:

Bicarbonate deficit (mEq) = goal serum $[HCO_3^-]$ − prevailing serum $[HCO_3^-]$ × 50% bd wt (kg).

The calculation assumes no significant addition of acid or generation of base and so is only a very rough estimate. This calculation will allow the clinician to estimate not only how much base should be given, but also how long it will take before the target bicarbonate is reached. The serum $[HCO_3^-]$ can be raised slowly over a matter of days while observing the patient for evidence of various complications particularly exacerbation of hypertension or congestive heart failure. Once the target serum bicarbonate has been reached, base administration can be reduced to values that approximate the estimated rate of net endogenous acid production. This precaution will aid in ensuring the clinician does not overshoot the target serum bicarbonate concentration. The above approaches to treatment are summarized in Box 18.2.

**Box 18.2 Recommendations for Treatment of Metabolic Acidosis with Chronic Kidney Disease**

Reduce dietary protein intake to decrease acid generation. Consider substituting plant protein for animal protein. Be sure to maintain sufficient protein to preserve muscle mass and protein stores.

Provide base in various forms. Increase intake of fruits and vegetables while monitoring patients carefully for development of hyperkalemia. This might reduce the quantity of oral base required or eliminate it completely. See American Heart Association and National Kidney Foundation diets.

In patients with CKD not yet on dialysis, base can be provided in the form of sodium bicarbonate or sodium citrate. Calculate the bicarbonate deficit prior to administration of base to get an estimate of bicarbonate requirements. Use 50% body weight as the space of distribution of administered base. Once goal serum [total $CO_2$] of 24–26 mEq/L is reached reduce base administration to quantity required to neutralize NEAP.

Monitor patients' volume status and blood pressure carefully. Although sodium retention appears to be less than with sodium chloride there still can be volume overload or exacerbation of hypertension. Restrict dietary sodium intake to less than 1000 mg/day if possible.

If it receives FDA approval, veverimer given orally with sodium-restricted diet might be an effective method or raising serum [total $CO_2$] without giving sodium or potassium.

## 18.7 Conclusions and Future Directions

Acid retention with its adverse effects on cellular function is an important complication of CKD. Base administration is effective in preventing or treating the progression of CKD, muscle wasting, and bone disease that accompany the development of metabolic acidosis. The new agent Veverimer could provide an alternative to sodium bicarbonate and citrate that could raise serum [$HCO_3^-$] without adding a sodium load.

Further study of the most effective methods of treating metabolic acidosis in CKD are ongoing. Also, the exact prevalence and how to detect and treat patients with eubicarbonatemic metabolic acidosis remains an important focus of study.

**Before You Finish: Practice Pearls for the Clinician**

- Full acid-base parameters from venous blood including pH, $pCO_2$, and [$HCO_3^-$] should be obtained in patients with CKD, particularly if they have hypobicarbonatemia.
- Alkali therapy in the form of sodium bicarbonate or sodium citrate or increased intake of fruits and vegetables should be used to maintain a serum bicarbonate concentration between 24 and 26 mEq/L. The dose should be determined based on the estimated bicarbonate deficit.
- During alkali therapy, patients should be monitored carefully for the development of adverse effects and to ensure serum bicarbonate is maintained within the recommend level.

**Acknowledgments** This work was supported in part by unrestricted funds from UCLA (JK) Dr. Kraut reports no financial conflict of interest. Dr. Nagami reports no financial conflict of interest.

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