

Eubicarbonatemic Hydrogen Ion Retention and CKD Progression

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Small-scale trials in patients with chronic kidney disease (CKD) 3-5 have shown that hypobicarbonatemic metabolic acidosis promotes progression of CKD. Accordingly, the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guideline suggests base administration to patients with CKD when serum bicarbonate concentration ($[\text{HCO}_3^-]$) is <22 mEq/L (~15% of non-dialysis-dependent patients with CKD). However, individuals with milder CKD largely maintain serum $[\text{HCO}_3^-]$ within the normal range (eubicarbonatemia) and yet can manifest hydrogen ion (H^+) retention. Limited data in eubicarbonatemic patients with CKD 2 suggest that base administration ameliorates CKD progression. Furthermore, most patients with moderate and advanced CKD maintain a normal serum $[\text{HCO}_3^-]$, and of those, the vast majority most likely harbor masked H^+ retention. The present review probes this expanded concept of metabolic acidosis of CKD: the eubicarbonatemic H^+ retention or subclinical metabolic acidosis of CKD. It focuses on the high prevalence of the entity, its pathophysiologic features, its clinical course, and recent work on potential biomarkers of the condition. Further, it puts forward the urgent task of investigating definitively whether treatment with alkali of eubicarbonatemic H^+ retention delays CKD progression. If proven true, such knowledge would trigger a paradigm shift in the indication for alkali therapy in CKD.

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Metabolic acidosis of chronic kidney disease (CKD) develops when net acid (hydrogen ion $[\text{H}^+]$) excretion lags behind net endogenous H^+ production, causing H^+ retention. Numerous adverse effects are associated with this entity, including bone disease, muscle wasting, protein catabolism, CKD progression, and increased mortality.^{1,2} Base administration or dietary modifications tend to ameliorate or correct these deleterious effects.¹⁻³

Focusing on CKD progression, the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guideline suggests base administration to patients with CKD when serum bicarbonate concentration ($[\text{HCO}_3^-]$) is <22 mEq/L.⁴ This threshold reflects the fact that interventional studies on the role of metabolic acidosis in CKD progression have mainly involved hypobicarbonatemic patients with CKD 3-5.^{3,5} However, rats and humans with milder CKD largely maintain serum $[\text{HCO}_3^-]$ within the normal range (eubicarbonatemia) and yet can manifest H^+ retention.^{6,7} In both settings, limited data suggest that base administration ameliorates CKD progression, pointing to the pathophysiologic significance of this masked H^+ retention.^{6,8} Furthermore, most patients with moderate and advanced CKD maintain normal serum $[\text{HCO}_3^-]$, and of those, the vast majority most likely harbor masked H^+ retention.^{3,5} Identification of this highly prevalent state of eubicarbonatemic H^+ retention, dubbed the subclinical metabolic acidosis of CKD, puts forward the urgent task of investigating definitively whether its treatment with alkali delays CKD progression.^{5,9-11}

Here, the eubicarbonatemic H^+ retention of CKD is probed, focusing on its high prevalence, clinical features and course, potential biomarkers, and pathophysiologic prospect in CKD progression.

SERUM $[\text{HCO}_3^-]$: THE NORMAL RANGE

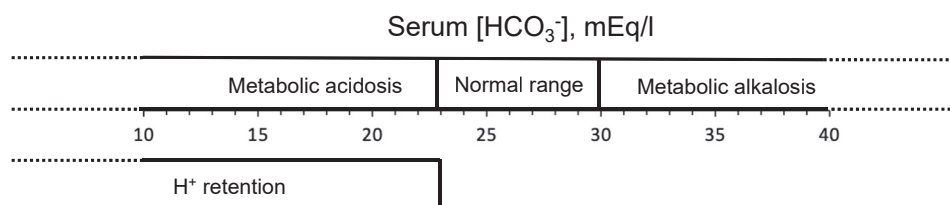
First, a clarification about nomenclature is in order. When clinicians use the term “serum $[\text{HCO}_3^-]$,” they usually refer to “serum [total carbon dioxide] ($[\text{TCO}_2]$) in venous blood.” Serum TCO_2 is largely composed of HCO_3^- but also includes dissolved CO_2 and carbonic acid, as well as negligible amounts of carbonate and carbamino compounds.¹² Clinical laboratories list this parameter as “ TCO_2 ” or “carbon dioxide” and measure its moieties collectively after acidifying the specimen; because HCO_3^- represents ~95% of TCO_2 (serum $[\text{TCO}_2]$ being higher by 1.0-1.5 mEq/L than serum $[\text{HCO}_3^-]$), the terms are usually used interchangeably, most clinicians preferring “serum $[\text{HCO}_3^-]$.” Clinical trials have largely measured serum $[\text{TCO}_2]$, and practice guidelines are based on serum $[\text{TCO}_2]$ measurements but use the term “serum $[\text{HCO}_3^-]$.” A blood gas device quantitates $[\text{HCO}_3^-]$ itself by measuring pH and Pco_2 and calculating $[\text{HCO}_3^-]$ by applying the Henderson-Hasselbalch equation. Despite the inherent inaccuracy, to avoid confusion, “serum $[\text{HCO}_3^-]$ ” in this article refers to measured serum $[\text{TCO}_2]$ in venous blood.

The normal range of serum $[\text{HCO}_3^-]$ is 23 to 30 mEq/L.¹² This 8-digit span is substantial, with the largest source of variance being the variance in Pco_2 .¹²⁻¹⁴ Recently, a frequent large variation in the normal range of serum $[\text{HCO}_3^-]$ among clinical laboratories was reported, with deviations at one or both ends of the above range (to as low as 18-20 mEq/L and as high as 33-35 mEq/L) and an overall span that can encompass 10 to 13 digits.¹² These substantial deviations from the 23- to 30-mEq/L range are bound to impart confusion to clinicians regarding the diagnosis and management of the metabolic acidosis of CKD. A call for standardization of the normal range of serum $[\text{HCO}_3^-]$ in clinical laboratories has been made.¹²

Metabolic Acidosis of CKD

A. Classical concept

Hypobicarbonatemic H⁺ retention



B. Expanded concept

Hypobicarbonatemic or eubicarbonatemic H⁺ retention

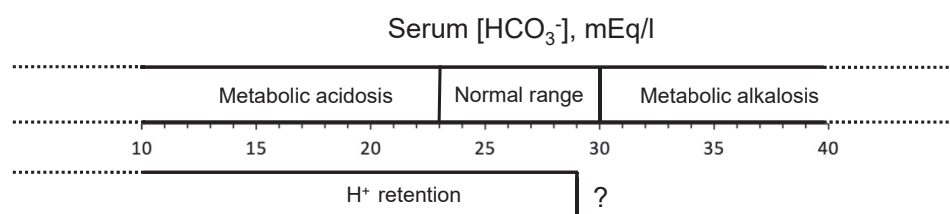


Figure 1. Metabolic acidosis of chronic kidney disease (CKD). (A) Classic concept; metabolic acidosis and H⁺ retention occur when serum bicarbonate concentration ([HCO₃⁻]) decreases to less than the normal range (hypobicarbonatemic H⁺ retention). (B) Expanded concept; in addition to hypobicarbonatemic H⁺ retention, metabolic acidosis includes H⁺ retention manifesting within the normal range of serum [HCO₃⁻] (hypobicarbonatemic or eubicarbonatemic H⁺ retention). Reproduced from Madias⁵ with permission of the American Society of Nephrology.

Moreover, studies are required to assess the variability of serum [HCO₃⁻] in stable patients with CKD. Such knowledge is necessary to inform implementation of practice guidelines.

CLASSIC CONCEPT OF THE METABOLIC ACIDOSIS OF CKD

The classic concept of the metabolic acidosis of CKD derives from the general definition of metabolic acidosis, that is, the acid-base disorder expressed as primary decrease in serum [HCO₃⁻] below the normal range (23–30 mEq/L).^{12,15} Consequently, the presence of metabolic acidosis of CKD and the associated H⁺ retention requires a reduction in serum [HCO₃⁻] to <23 mEq/L (Fig 1A).

Rats subjected to severe 5/6 subtotal nephrectomy (5/6-Nx rats) and fed H⁺-producing casein develop hypobicarbonatemic metabolic acidosis and a large reduction in ammonium and net H⁺ excretion.^{16,17} The prevailing hypobicarbonatemia evidences H⁺ retention. Figure 2 depicts putative mechanisms through which H⁺ retention mediates CKD progression.^{1–3,18} Acidification of the kidney's interstitial and intracellular compartments presumably activates molecular mechanisms of acid sensing, which trigger increases in kidney levels of endothelin 1, angiotensin II, and aldosterone.^{18–20} By stimulating the kidney's

proximal and distal acidification, these hormones tend to lessen H⁺ retention; however, they also promote tubulointerstitial inflammation, oxidative stress, and fibrosis.^{1–3,18} Additionally, kidney acidification stimulates ammoniogenesis per residual nephron even if ammonium excretion decreases progressively. Like the injurious hormones, increased ammoniogenesis is adaptive from the H⁺-retention viewpoint but proves maladaptive for the injured kidney by activating complement that promotes kidney fibrosis.^{18,21} Further, an acidic environment stimulates production of proinflammatory cytokines by kidney tubular cells, which could cause kidney injury and fibrosis.²² This pathophysiologic paradigm is supported by demonstrating that alkali administration slows the glomerular filtration rate (GFR) decline while reducing levels of these injurious hormones and ammonium excretion.^{16,17} Feeding 5/6-Nx rats HCO₃⁻-producing soy instead of H⁺-producing casein prevents the development of hypobicarbonatemic metabolic acidosis and GFR decline.¹⁷

Outcomes of interventional trials in patients with moderate and advanced CKD ingesting the typical H⁺-producing diet of Western countries parallel the animal evidence. Small single-center studies in patients with CKD 3–5 and hypobicarbonatemic metabolic acidosis (serum [HCO₃⁻] < 22 mEq/L) revealed that alkali therapy delays CKD progression while decreasing ammonium excretion

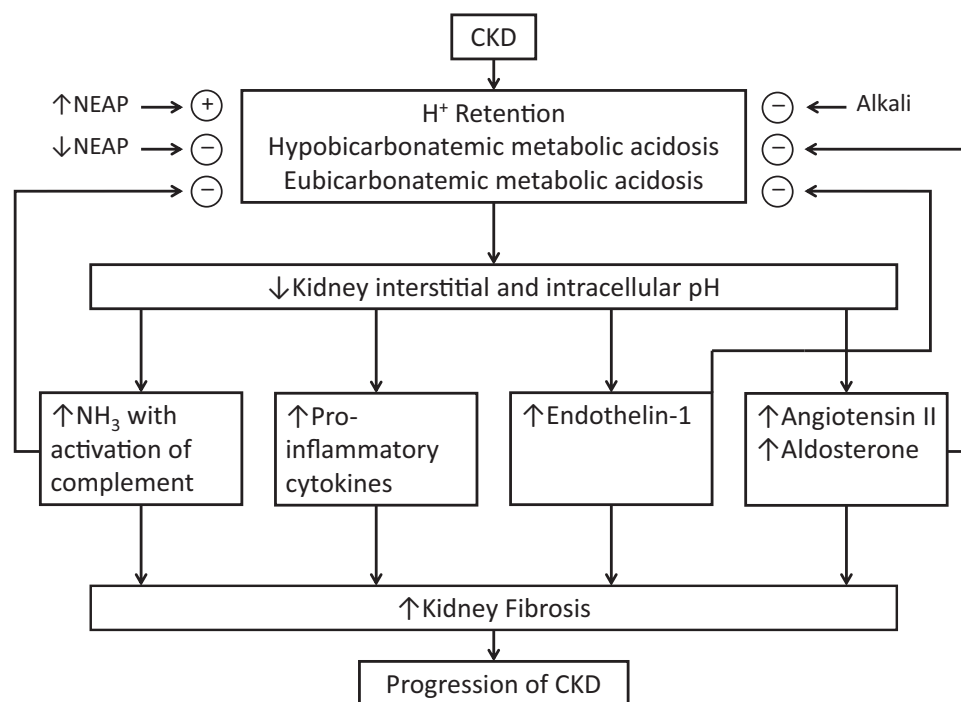


Figure 2. Putative mechanisms induced by metabolic acidosis (hypobicarbonatemic or eubicarbonatemic H⁺ retention) that produce kidney injury and promote progression of chronic kidney disease (CKD). H⁺ retention in CKD decreases the pH of the kidney interstitial and intracellular compartments, causing stimulation of ammoniogenesis per residual nephron, increased production of proinflammatory cytokines, and an increase in kidney levels of endothelin 1, angiotensin II, and aldosterone. These changes lead to kidney injury and fibrosis. Increased ammoniogenesis and increased levels of endothelin 1, angiotensin II, and aldosterone stimulate kidney acidification, decreasing H⁺ retention. Increased dietary net endogenous acid production augments H⁺ retention, whereas decreased dietary net endogenous acid production or administration of alkali lessens H⁺ retention. Abbreviations: NEAP, net endogenous acid production; NH₃, ammonia. Reproduced from Kraut and Madias³ with permission of Springer.

and urinary levels of endothelin 1 and markers of kidney damage.^{23,24} These outcomes prompted the 2012 guideline suggesting base administration to patients with CKD with serum [HCO₃⁻] < 22 mEq/L to slow CKD progression.⁴ Subsequently, additional small-scale trials of alkali administration or dietary modification have been completed in CKD 3-5 and hypobicarbonatemic metabolic acidosis that are concordant with the guideline.²⁵⁻²⁹ A 1,600-participant trial is being conducted in hypobicarbonatemic patients with CKD 3-4 using veveimer, a novel agent that adds endogenous bicarbonate to body fluids ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03710291) Identifier: NCT03710291).³⁰

Observational studies have identified hypobicarbonatemia as a risk factor for CKD progression congruent with outcomes of interventional trials.¹⁻³ In both settings, hypobicarbonatemia signifies metabolic acidosis, a reasonable assumption given the kidney's role in excreting the dietary H⁺ load. However, a recent retrospective study of patients with CKD (n = 1,058; baseline estimated GFR [eGFR] < 60 mL/min/1.73 m²) casts doubt on this assumption.³¹ At baseline, only 59% of patients in the lowest serum [HCO₃⁻] quartile (≤21.5 mEq/L) were acidemic (pH < 7.32 by venous blood gas), whereas 38% were normohydric (pH 7.32-7.42) and 3% were alkalemic (pH > 7.42). The latter 2 groups

presumably reflected metabolic acidosis with increased ventilatory adaptation and respiratory alkalosis. During a median follow-up of 3 years and after adjustment for potential confounders (including eGFR, ventilatory adaptation capacity, cardiovascular and pulmonary comorbid conditions, and medications), acidemic patients in the lowest [HCO₃⁻] quartile had a 2.29-fold higher hazard for incident kidney failure requiring replacement therapy than the highest quartile (≥26.6 mEq/L). Among nonacidemic patients, the hazard for kidney failure requiring replacement therapy was not significantly different between these [HCO₃⁻] quartiles. The study has several limitations and confirmatory work is required.^{31,32} Nonetheless, it introduces the plausible concept that measurement of blood pH might be needed for risk stratification of hypobicarbonatemic patients with CKD.

Defined as serum [HCO₃⁻] < 22 mEq/L, metabolic acidosis is observed in only ~15% of non-dialysis-dependent patients with CKD.^{33,34} Expectedly, its prevalence increases with the severity of CKD. For example, in Chronic Renal Insufficiency Cohort participants (n = 3,904; CKD 2-4), it was observed in 7%, 13%, and 37% of patients with CKD 2, CKD 3, and CKD 4, respectively.³⁵

Limited data suggest that of such hypobicarbonatemic patients, only a relatively small fraction is being treated with

Table 1. Changes in eGFR_{cys}, Serum [HCO₃⁻], H⁺ Retention, and Urinary Citrate Excretion in Eubicarbonatemic Patients With CKD 2 Undergoing UC or Treatment With NaCl or NaHCO₃

Parameter	UC (n = 26)	NaCl (n = 29)	NaHCO ₃ (n = 31)	Intergroup P
eGFR _{cys} , mL/min/1.73 m ²				
Baseline	73.9 ± 6.4	73.7 ± 6.6	72.9 ± 6.3	NS
Year 10	52.3 ± 4.1	52.1 ± 5.9	59.6 ± 4.8	<0.01, higher in NaHCO ₃
P	<0.01	<0.01	<0.01	
Serum [HCO ₃ ⁻], mEq/L				
Baseline	24.9 ± 0.6	24.6 ± 0.5	24.7 ± 0.6	NS
Year 10	23.9 ± 0.6	23.7 ± 0.5	24.8 ± 0.7	<0.01, higher in NaHCO ₃
P	<0.01	<0.01	0.62	
H ⁺ retention, mEq				
Baseline	17.7 ± 10.9	18.2 ± 15.3	16.1 ± 15.1	NS
Year 10	24.8 ± 11.3	26.5 ± 13.1	14.2 ± 13.5	NS
P	<0.01	<0.01	1.00	
Urinary citrate, mg/8 h				
Baseline	186 ± 42	196 ± 52	203 ± 49	NS
Year 10	153 ± 41	162 ± 47	212 ± 45	<0.01, higher in NaHCO ₃
P	<0.01	<0.01	0.74	

Note: Values are mean ± standard deviation. Serum [HCO₃⁻] values calculated from measured venous blood pH and Pco₂.

Abbreviations: CKD, chronic kidney disease; eGFR_{cys}, estimated glomerular filtration rate calculated using serum cystatin C level; NS, not significant; UC, usual care. Created from data included in reference 42.

alkali (2.7%, 6%–10%, and 24.4% in 3 studies).^{31,36–38} This degree of poor following of the guideline is notable given that base therapy, mainly sodium bicarbonate (NaHCO₃), is an effective, low-cost, and largely safe therapy.^{1–3,10} The substantial variance in the normal range of serum [HCO₃⁻] prevailing among laboratories likely undermines adherence to the guideline.¹² Notwithstanding, many clinicians justifiably remain unconvinced about the utility of countering H⁺ retention. Beyond their small scale, available trials on alkali administration are all non–placebo controlled and nonblinded,^{23–25,27,28} and one is even nonrandomized.²⁴ Large-scale and properly controlled trials are required to produce definitive evidence about the efficacy and safety of alkali therapy in CKD.

EXPANDED CONCEPT OF THE METABOLIC ACIDOSIS OF CKD

Rats subjected to less severe 2/3 subtotal nephrectomy (2/3-Nx rats) and fed H⁺-producing casein develop milder CKD than 5/6-Nx rats while maintaining serum [HCO₃⁻] within the normal range.^{6,18} The prevailing eubicarbonatemia notwithstanding, H⁺ retention in the kidney and muscle interstitium of 2/3-Nx rats has been documented by microdialysis, pointing to its systemic occurrence.^{6,18,39–41} Acidification of the kidney interstitium and tubular cells activates the same pathways described for hypobicarbonatemic rats with both adaptive and damaging consequences (Fig 2).^{6,18,40} With some delay, the 2/3-Nx rats achieve steady-state net H⁺ excretion similar to sham animals, which prevents progressive H⁺ retention and maintains eubicarbonatemia; however, this is predicated on underlying H⁺ retention. Alkali treatment repairs H⁺ retention, reduces kidney levels of injurious hormones and

urinary ammonium excretion, and preserves kidney function. Placing 2/3-Nx rats on HCO₃⁻-producing soy decreases H⁺ retention in the tissues and prevents GFR decline.^{6,18,39–41}

The 2/3-Nx rat appears to be a good model of humans with milder CKD.⁷ In a prospective study, 120 patients with CKD 2 and serum [HCO₃⁻] > 24.5 mEq/L (mean, 26.2 mEq/L) were randomly assigned to NaHCO₃ supplement (0.5 mEq/kg of lean body weight), equimolar sodium chloride (NaCl), or usual care (UC; n = 40 in each group).⁸ Like their rat counterparts, such eubicarbonatemic patients with CKD display H⁺ retention as determined by the serum [HCO₃⁻] response to an acute NaHCO₃ load.⁷ By 5 years, the yearly change in eGFR_{cys} (calculated using serum cystatin C level and the CKD Epidemiology Collaboration [CKD-EPI] equation) was lower in the NaHCO₃ group than in the NaCl or UC group (–1.34 vs –2.19 vs –2.37 mL/min, respectively; P < 0.003). Urinary endothelin 1 excretion and markers of tubulointerstitial injury increased in the NaCl and UC groups but decreased in the NaHCO₃ group.⁸

The 10-year follow-up of participants in that trial,⁸ who continued treatment in a blinded fashion under their original group, was recently reported.⁴² The 10-year eGFR_{cys} was higher in the NaHCO₃ group than in the NaCl and UC groups (Table 1). Baseline H⁺ retention was not different among the 3 groups; however, at the 10-year mark, H⁺ retention was unchanged in the NaHCO₃ group but increased from baseline in the NaCl and UC groups. Accordingly, serum [HCO₃⁻] was not different from baseline in the NaHCO₃ group but it decreased in the NaCl and UC groups, although still remaining within the normal range (Table 1).⁴²

Table 2. Changes in Serum $[\text{HCO}_3^-]$, H^+ Retention, and Urinary Citrate Excretion in Eubicarbonatemic Patients With CKD 1 and CKD 2 After 30-Day Administration of Fruits and Vegetables

Parameter	CKD 1 (n = 26)	CKD 2 (n = 40)	Intergroup P
Serum $[\text{HCO}_3^-]$, mEq/L			
Baseline	26.4 ± 0.6	25.9 ± 0.8	<0.01
30-d F+V	26.6 ± 0.3	26.2 ± 0.6	<0.01
P	0.08	<0.01	
H^+ retention, mEq			
Baseline	5.2 ± 12.0	28.1 ± 9.4	<0.01
30-d F+V	4.7 ± 15.6	18.4 ± 17.4	<0.01
P	0.88	<0.01	
Urinary citrate, mg/8 h			
Baseline	335 ± 125	187 ± 40	<0.01
30-d F+V	369 ± 125	245 ± 70	<0.01
P	<0.02	<0.01	

Note: Values are mean ± standard deviation.

Abbreviations: 30-d F+V, 30-day administration of fruits and vegetables; CKD, chronic kidney disease. Created from data included in reference 48.

Taken together, the animal and human data of milder CKD define an expanded concept of metabolic acidosis of CKD that includes H^+ retention manifesting within the normal range of serum $[\text{HCO}_3^-]$ (Fig 1B). Eubicarbonatemic H^+ retention presumably resides in both the extracellular and intracellular spaces and, according to the isohydric principle, it must challenge both bicarbonate and nonbicarbonate buffers. The data suggest remarkable sensitivity of putative extracellular and intracellular acid sensors to meager acidification signals that induce mechanistic responses, such as those depicted in Fig 2.^{9-11,18-20} The findings are consistent with the interpretation that initial H^+ retention in milder CKD and subclinical metabolic acidosis triggers augmentation of acidification per residual nephron; consequently, achieved steady-state net H^+ excretion is similar to that of controls with normal GFRs (sham animals and patients with CKD 1), thereby reestablishing external H^+ balance (ie, $\text{H}^+_{\text{in}} = \text{H}^+_{\text{out}}$) but under conditions of H^+ retention.^{7,41}

Beyond accelerating CKD progression, eubicarbonatemic H^+ retention might harm other organs, such as bone and muscle. Switching 2/3-Nx rats from HCO_3^- -producing soy to H^+ -producing casein increased eubicarbonatemic H^+ retention in kidney interstitium and urinary excretion of deoxy-pyridinoline, a biomarker of bone matrix injury.⁴¹ Similar evidence exists in human aging, a state of subclinical metabolic acidosis.⁴³ Administration of KHCO_3 (potassium bicarbonate) to postmenopausal eubicarbonatemic women reduced urinary nitrogen excretion (indicative of lowered muscle wasting) and promoted bone accretion.^{44,45} Base supplementation to elderly men and women with eubicarbonatemia decreased bone resorption, increased bone density, and improved bone microarchitecture.^{46,47}

SUBCLINICAL METABOLIC ACIDOSIS OF CKD: PREVALENCE AND COURSE

Approximately 85% of non-dialysis-dependent patients with CKD have serum $[\text{HCO}_3^-] \geq 22$ mEq/L.³³⁻³⁵ How

many of those manifest H^+ retention thereby qualifying as having subclinical metabolic acidosis? In 2 recent studies, virtually all eubicarbonatemic patients with CKD 2 tested at baseline had an estimated H^+ retention > 0 mEq that averaged ~17 mEq and 28 mEq, with substantial variability (Tables 1 and 2). In comparison, H^+ retention averaged a nonsignificant 5 mEq in patients with CKD 1 (Table 2).^{42,48} Thus, if we adopt the expanded definition of the disorder, metabolic acidosis is an early CKD complication. However, the number of tested individuals is small and additional studies are required. One would predict that estimated H^+ retention would be larger and essentially universal in eubicarbonatemic patients with CKD 3 and 4.⁴⁹ Although its precise prevalence remains to be determined, subclinical metabolic acidosis is most likely present in most patients with CKD 2-4 consuming the typical H^+ -producing diet of Western countries.

There is no systematic information on the course of serum $[\text{HCO}_3^-]$ in patients with CKD 2 with subclinical metabolic acidosis, but data suggest that eubicarbonatemia can last for many years (Table 1).⁴² At the 10-year mark, serum $[\text{HCO}_3^-]$ in the NaCl and UC groups had decreased from baseline but still remained within the normal range. Because the prevalence of hypobicarbonatemic metabolic acidosis increases as CKD advances, it appears that accumulating H^+ retention in certain eubicarbonatemic patients eventually transitions their serum $[\text{HCO}_3^-]$ to the hypobicarbonatemic domain.^{10,11,33-35}

Several factors can affect the duration of subclinical metabolic acidosis and its trajectory to hypobicarbonatemia. Among these is the baseline serum $[\text{HCO}_3^-]$; other factors being equal, the higher the baseline serum $[\text{HCO}_3^-]$, the longer the duration of eubicarbonatemia. Worsening CKD is the chief factor for transitioning to hypobicarbonatemia; despite the gradual increase in ammoniogenesis of residual nephrons, ammonium excretion progressively diminishes, thereby augmenting H^+ retention.^{10,11,35} Dietary H^+ load is another important factor, as it interacts with GFR in generating H^+ retention;

its downward adjustment, by decreasing H^+ -producing animal-sourced protein or increasing HCO_3^- -producing fruits and vegetables, would tend to lengthen the eubicarbonatemic stage.^{35,50,51} Hyperkalemia lowers serum $[HCO_3^-]$ by reducing kidney ammoniogenesis and collecting duct ammonia transport.⁵² Progressive exhaustion of the body's nonbicarbonate buffers, especially those in bone and muscle, would accelerate the transition to hypobicarbonatemia.^{2,5,11,18} Finally, some medications (thiazide and loop diuretics and calcium carbonate) tend to increase serum $[HCO_3^-]$, whereas others (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and sevelamer HCl) promote H^+ retention.

It is not surprising that virtually all patients with CKD 2 ingesting a typical H^+ -producing diet would retain H^+ . Increases in dietary H^+ up to 120 to 150 mEq/d in healthy humans cause meager changes in serum $[HCO_3^-]$ and blood pH, but the increase in kidney H^+ excretion falls short of the dietary H^+ increment signifying H^+ retention.^{50,53,54} Animals and humans with CKD have increased difficulty excreting H^+ loads.^{55,56} Epidemiologic studies show that high dietary H^+ loads increase CKD risk.^{57,58} In effect, patients with CKD 2 are reminiscent of normal aging, in which a low-grade subclinical metabolic acidosis also exists.⁴³ Age, largely through the associated kidney function decline, and dietary H^+ load codetermine the small but significant decreases in serum $[HCO_3^-]$ and blood pH that characterize this life stage evidencing H^+ retention.⁵⁹

SUBCLINICAL METABOLIC ACIDOSIS OF CKD: RISK FACTOR FOR CKD PROGRESSION?

Trials on the role of H^+ retention in CKD progression have largely examined hypobicarbonatemic metabolic acidosis in patients with CKD 3-5.²³⁻²⁹ Only a single small study has tested the impact of alkali (0.5 mEq/kg of lean body weight) in patients with CKD 2 with subclinical metabolic acidosis yielding a positive outcome at 5 and 10 years of follow-up (Table 1).^{8,42} Moreover, higher serum $[HCO_3^-]$ within the normal range is associated with lower risk for CKD progression.⁶⁰

In a recent trial, 149 patients with CKD 3 and 4 and serum $[HCO_3^-]$ bridging the hypobicarbonatemic and eubicarbonatemic domains (20-26 mEq/L; mean, 24.0 mEq/L) were randomly assigned to $NaHCO_3$ supplement (0.4 mEq/kg of lean body weight) or placebo. Forty-five participants dropped out during the course of study. Over 2 years, no difference in eGFR was detected.⁶¹ By contrast, a longer trial of patients with CKD bordering the low end of the eubicarbonatemic range had a positive outcome. One hundred eight patients with CKD 3 and serum $[HCO_3^-] > 22$ mEq/L and < 24 mEq/L (mean, 23.0 mEq/L) were randomly assigned to $NaHCO_3$ supplement (0.3 mEq/kg of lean body weight), base-producing fruits and vegetables (like the $NaHCO_3$ supplement, designed to

reduce dietary H^+ load by 50%), or UC. By 3 years, the decrease in eGFR was less by 6 to 8 mL/min in the $NaHCO_3$ and the fruits-and-vegetables groups than the UC group ($P < 0.01$). Excretion of urinary angiotensinogen (a marker of kidney angiotensin II) and markers of kidney tubulointerstitial injury increased in the UC group but decreased in the $NaHCO_3$ and the fruits-and-vegetables groups.⁶²

The enormity of the eubicarbonatemic CKD population coupled with the expected H^+ retention in its large majority call for an urgent examination of the pathophysiologic significance of subclinical metabolic acidosis in CKD progression.⁵ Although studying such patients with advanced CKD would be welcome, potentially more consequential would be trials involving patients with CKD 2 and 3a with subclinical metabolic acidosis. The rationale behind this view is potential modification of the CKD course before diffuse kidney fibrosis develops. Because progression at earlier CKD stages is relatively slow, demonstration of benefit would take longer. To potentially shorten study duration, future trials should enroll eubicarbonatemic patients with low-normal serum $[HCO_3^-]$ (eg, < 26 mEq/L) and relatively high H^+ retention (eg, > 20 mEq).

The procedure currently used for estimating H^+ retention in eubicarbonatemic patients entails measuring baseline serum $[HCO_3^-]$ followed by an oral $NaHCO_3$ load (0.5 mEq/kg of body weight) and a 2-hour urine collection. On completing the collection, serum $[HCO_3^-]$ is remeasured.⁴² Quantifying urinary HCO_3^- excretion serves to calculate retained HCO_3^- . Estimation of H^+ retention is based on the difference between the expected and observed increase in serum $[HCO_3^-]$ assuming an apparent space of distribution of retained HCO_3^- of 50% of body weight.⁶³ Increased consumption of retained HCO_3^- by accumulated H^+ on nonbicarbonate buffers would limit the observed increase in serum $[HCO_3^-]$ evidencing H^+ retention. The procedure is pathophysiologically sound but clearly cumbersome, invasive, and time consuming. Although reasonable for investigative purposes, it is ill suited for clinical practice. A practical, simple, and noninvasive procedure for estimating H^+ retention in patients with CKD with subclinical metabolic acidosis is needed.

In reflecting on this need, I inferred that measuring urinary citrate excretion might be such a procedure. Citrate is the most abundant organic base-equivalent in urine, its excretion being determined by the extent of its proximal tubule reabsorption.⁶⁴⁻⁶⁶ Reabsorbed citrate is metabolized to glucose or CO_2 and H_2O , generating HCO_3^- in the process.⁶⁷ Therefore, citrate reabsorption equals base gain, whereas its excretion represents base loss.⁶⁸

H^+ retention causes hypocitraturia by increasing citrate reabsorption and metabolism, thereby decreasing the loss of base equivalents.^{65,66,69-72} The signal triggering these adaptations appears to be intracellular acidification. Thus, chronic potassium depletion (intracellular metabolic

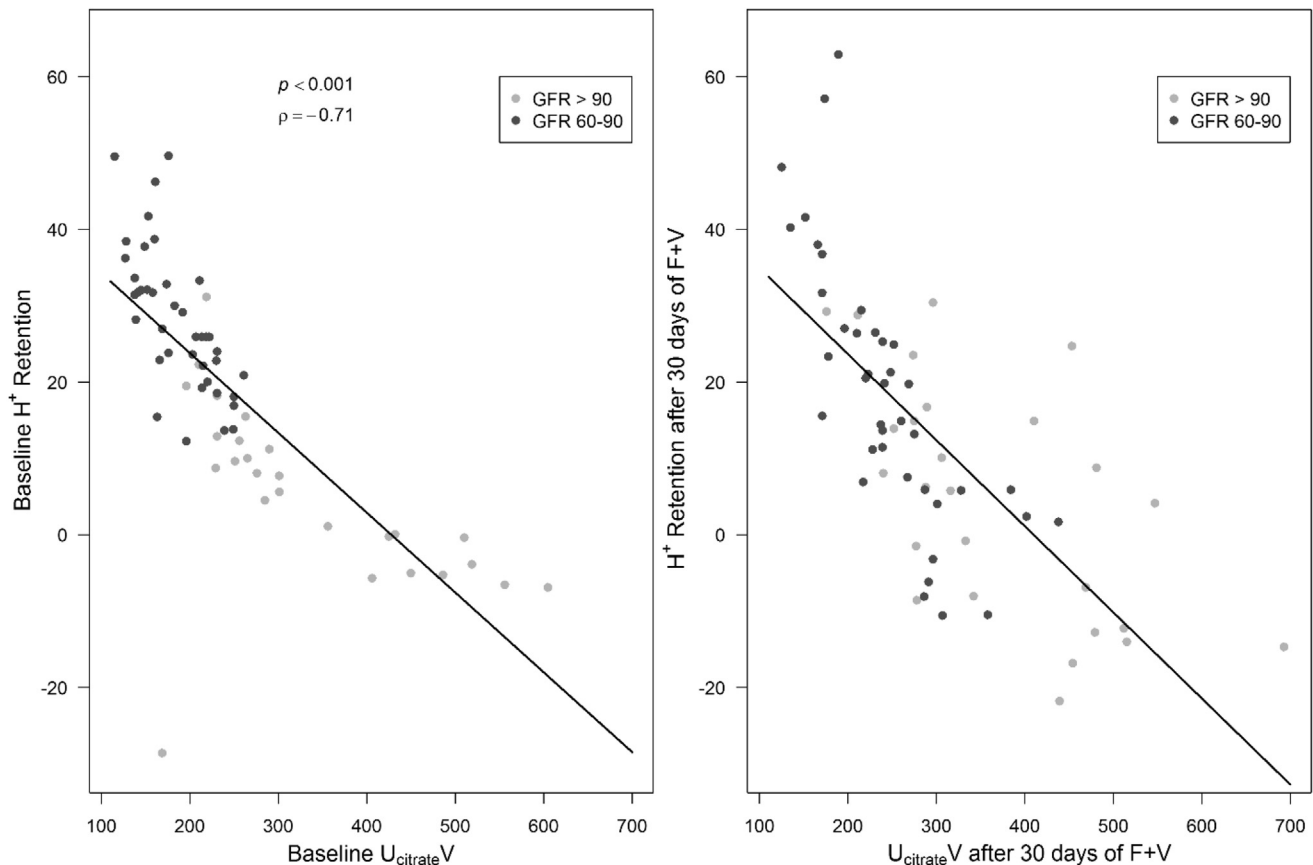


Figure 3. Relationship of H^+ retention (mEq) versus urinary citrate excretion ($U_{\text{citrate}}V$; mg/8 h) combining the data for the 2 studied groups, chronic kidney disease (CKD) 1 (glomerular filtration rate [GFR] > 90 mL/min/1.73 m²) and CKD 2 (GFR, 60-90). Left, baseline relationship; right, relationship after 30 days of eating base-producing fruits and vegetables (F + V). Reproduced from Goraya et al⁴⁸ with permission of Elsevier.

acidosis but extracellular metabolic alkalosis) is also associated with hypocitraturia, whereas chronic respiratory acidosis in the rat (extracellular respiratory acidosis but normal intracellular pH) is not.^{73,74}

It has long been recognized that decreased urinary citrate excretion is a sensitive indicator of H^+ retention.^{9,75} Adaptive hypocitraturia occurs in hypobicarbonatemic metabolic acidosis (eg, H^+ feeding, diarrhea, and distal renal tubular acidosis). However, it also occurs in eubicarbonatemic metabolic acidosis, such as increased meat intake (high dietary H^+ production) and incomplete distal renal tubular acidosis.^{9,75,76} Drawing on this body of evidence, I proposed measuring urinary citrate excretion as an index of H^+ retention in eubicarbonatemic patients with CKD.

In collaboration with Dr Wesson's group, this proposal was evaluated in eubicarbonatemic patients with CKD 1 and CKD 2 with hypertensive nephropathy before and after 30-day administration of HCO_3^- -producing fruits and vegetables.⁴⁸ As shown in Table 2, patients with CKD 2 had higher baseline H^+ retention and lower baseline 8-hour urinary citrate excretion than patients with CKD 1. Fruits and vegetables decreased H^+ retention in patients with CKD 2 and increased urinary citrate excretion in both

groups. A mixed-effects regression model showed that urinary citrate excretion was strongly predictive of H^+ retention and reliably verified a reduction in H^+ retention following fruits and vegetables (Fig 3). Using 90th percentile H^+ retention in CKD 1 (19.5 mEq) as the comparison level, urinary citrate excretion of 230 mg/8 h in patients with CKD 2 had sensitivity of 93.7%, specificity of 62.5 %, positive predictive value of 90.9%, negative predictive value of 71.4%, and accuracy of 87.5% for predicting H^+ retention. Area under the receiver operating characteristic curve of 0.78 indicated that urinary citrate excretion of 230 mg/8 h in patients with CKD is a fair cutoff for predicting high H^+ retention. When this cutoff was applied to another cohort of patients with CKD 2, it performed very similarly.⁴⁸

A second study showed that urinary citrate excretion identifies changes in H^+ retention as eGFR declines in eubicarbonatemic patients with CKD 2.⁴² Table 1 depicts that baseline 8-hour urinary citrate excretion was not different among the 3 groups ($NaHCO_3$, $NaCl$, and UC), similar to their baseline H^+ retention. At the 10-year mark, both urinary citrate excretion and H^+ retention were not different from baseline in the $NaHCO_3$ group. By contrast, urinary citrate excretion was lower than baseline in both

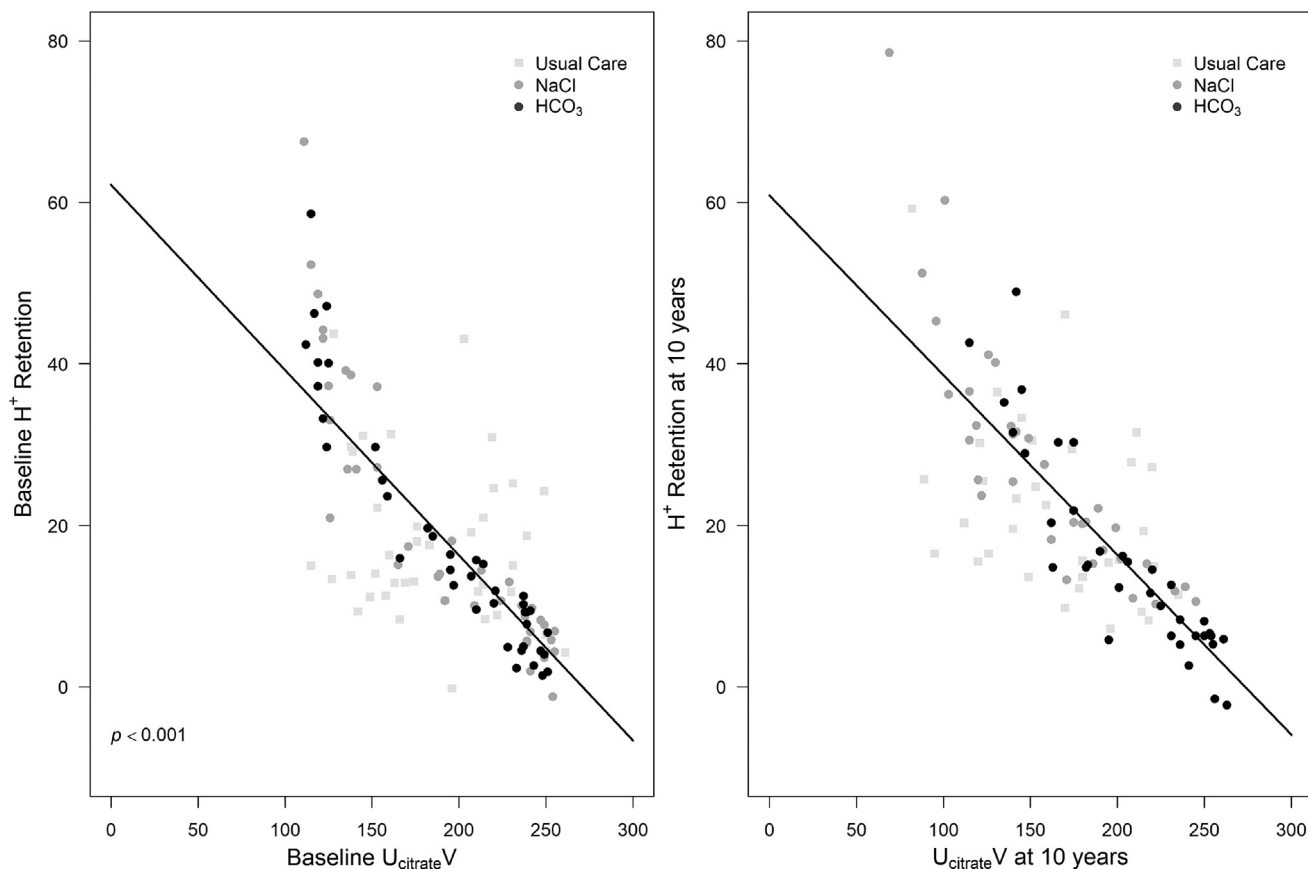


Figure 4. Generalized linear model for repeated measures, adjusted for time, for H^+ retention (mEq) versus urinary citrate excretion ($U_{\text{citrate}}V$; mg/8 h) combining the data for the 3 studied groups, usual care, NaCl, and NaHCO_3 (HCO_3^-). Left, baseline relationship; right, 10-year relationship. Reproduced from Goraya et al⁴² with permission of the American Physiological Society.

the NaCl and UC groups, whereas H^+ retention was higher than baseline in both groups. Urinary citrate excretion at 10 years was not different between the NaCl and UC groups but it was higher than both in the NaHCO_3 group. A generalized linear model for repeated measures, adjusted for time, showed that urinary citrate excretion predicted H^+ retention overall when the data for all 3 groups were combined (Fig 4).⁴²

The evidence indicates that urinary citrate excretion holds promise as a marker of H^+ retention in eubicarbonatemic patients with CKD to guide initiation of alkali therapy and monitor its effectiveness. Decreased urinary citrate excretion while on therapy would signal consideration of intensifying the intervention. Additional studies are required to optimize the procedure (eg, expression of urinary citrate per milligram of creatinine) and further document its utility.

LOW URINARY AMMONIUM EXCRETION

Recent studies have identified low urinary ammonium excretion as a risk factor for progression to end-stage kidney disease. In the prospective NephroTest cohort ($n = 1,065$; CKD 1-4; 69% with measured $\text{GFR} \geq 30$ mL/

min/1.73 m^2 ; 92% with eubicarbonatemia), after a median follow-up of 4.3 years, those in the lowest tertile of urinary ammonium excretion at baseline had an increased hazard ratio for end-stage kidney disease and higher odds ratio of fast decline ($>10\%$ per year) in measured GFR than patients in the highest tertile. Those associations were independent of measured GFR and other confounders.⁴⁹ Similar findings were obtained in a retrospective analysis of the African American Study of Kidney Disease and Hypertension (AASK; $n = 1,044$; 84% with measured $\text{GFR} \geq 30$ mL/min/1.73 m^2 ; 88% with eubicarbonatemia) that included adjustment for measured GFR and additional confounders, including net endogenous H^+ production. For the entire cohort or those with eubicarbonatemia at baseline, those in the lowest tertile of baseline urinary ammonium excretion had an increased hazard ratio of the composite outcome of death or dialysis. Moreover, among eubicarbonatemic participants at baseline, those in the lowest tertile of urinary ammonium excretion had higher adjusted odds of incident hypobicarbonatemia at 1 year.⁷⁷

The data suggest that low urinary ammonium excretion in eubicarbonatemic CKD identifies patients with high-level H^+ retention. Comparison studies of urinary citrate versus ammonium excretion as biomarkers of H^+ retention

Box 1. Recommendations for Future Studies

- Large-scale and properly controlled trials are required to establish the efficacy and safety of base therapy in hypobicarbonatemic metabolic acidosis regarding CKD progression.
- Eubicarbonatemic H⁺ retention in CKD is highly prevalent and limited data suggest that it contributes to CKD progression.
- Investigative focus should now be applied to examining the impact of base treatment on CKD progression in eubicarbonatemic H⁺ retention in patients with CKD 2 and 3a.
- These studies should also quantitate baseline urinary citrate and ammonium excretion to further assess their utility as biomarkers of H⁺ retention and CKD progression.

Abbreviation: CKD, chronic kidney disease.

in eubicarbonatemic patients with CKD should be performed, aiming at risk stratification for CKD progression. However, a crucial barrier to the utility of urinary ammonium excretion in practice is that clinical laboratories generally do not offer such measurement.

CONCLUSION

Additional small-scale studies on base treatment of the hypobicarbonatemic metabolic acidosis of CKD 3-5 have strengthened the evidence supporting the 2012 KDIGO guideline that NaHCO₃ be administered to patients with serum [HCO₃⁻] < 22 mEq/L for delaying CKD progression. Notwithstanding, large-scale and properly controlled trials are required to produce definitive evidence about the efficacy and safety of base therapy. These trials should include determination of blood pH at baseline. Most important, investigative focus should now be applied to examining the impact of base treatment in eubicarbonatemic H⁺ retention in patients with CKD 2 and 3a. Such trials should target patients with low-normal serum [HCO₃⁻] and relatively high-level H⁺ retention, as estimated by the serum [HCO₃⁻] response to an acute NaHCO₃ load. These studies should also quantitate baseline urinary citrate and ammonium excretion to further assess their utility as biomarkers of H⁺ retention and CKD progression (Box 1). Demonstration that base administration delays progression of CKD in eubicarbonatemic H⁺ retention would trigger a paradigm shift in the indication of alkali therapy in CKD.

ARTICLE INFORMATION

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