Perspective

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Metabolic Acidosis and CKD Progression

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Metabolic acidosis of CKD develops when net acid (H^+) excretion falls short of net endogenous H^+ production, resulting in H^+ retention. It is associated with numerous adverse effects, including acceleration of CKD progression. Regarding this adversity, the 2012 Kidney Disease Improving Global Outcomes guideline suggests base administration to patients with CKD and serum [HCO_3^-] <22 meq/L. However, limited data show that patients with CKD 2 and normal serum [HCO_3^-] (eubicarbonatemia) manifest H^+ retention, and base administration ameliorates CKD progression. Further, most patients with CKD 3 and 4 also harbor masked H^+ retention. Recognition of this subclinical metabolic acidosis calls for examination of its pathophysiologic significance regarding CKD progression.

Metabolic Acidosis of CKD: Classic Concept

The classic concept of metabolic acidosis of CKD reflects the conventional definition of metabolic acidosis (*i.e.*, the acid-base disorder expressed as primary decrease in serum [HCO_3^-] below the normal range [23–30 meq/L]) (1). Accordingly, metabolic acidosis of CKD and associated H^+ retention require reduction in serum [HCO_3^-] to <23 meq/L (Figure 1A).

Rats with 5/6 subtotal nephrectomy develop hypobicarbonatemic metabolic acidosis and large reduction in net H^+ excretion. Hypobicarbonatemia is *prima facie* evidence of H^+ retention; pointing to its systemic occurrence, microdialysis documented H^+ retention in kidney and muscle interstitium (2). Cogent mechanisms through which H^+ retention accelerates CKD progression were proposed. Countering H^+ retention slows GFR decline and reduces putative culprits of kidney fibrosis, validating the pathophysiologic construct (2).

Small, single-center studies in patients with CKD 3–5 and hypobicarbonatemic metabolic acidosis revealed that alkali therapy delays CKD progression (3), prompting the 2012 guideline. Subsequently, additional trials have been completed, strengthening the corroborative evidence (4,5).

How prevalent is hypobicarbonatemic metabolic acidosis? In one study, metabolic acidosis (serum [HCO_3^-] <22 meq/L) was present in 7%, 13%, and 37% of patients with CKD 2, CKD 3, and CKD 4, respectively, with aggregate prevalence of 15% (6). Such prevalence was only 8% in the NephroTest cohort (CKD 2–4). Limited data suggest that the treatment guideline has a poor following: only 10%–20% of eligible patients are administered alkali in the United States and Europe. Many clinicians likely remain unconvinced or assign low priority to countering H^+ retention. More education is required, especially in light of the effectiveness and safety of base administration in the Use of Bicarbonate in Chronic Renal Insufficiency (UBI) trial (4). Striking variance in the normal range of serum [HCO_3^-] among laboratories likely undermines adherence to the guideline (1).

Metabolic Acidosis of CKD: Expanded Concept

Rats with 2/3 subtotal nephrectomy develop milder CKD than 5/6 nephrectomized rats while maintaining eubicarbonatemia; notwithstanding, microdialysis documented H^+ retention in kidney interstitium. Alkali treatment repairs H^+ retention and preserves kidney function (2).

Patients with CKD 2 and eubicarbonatemia also display H^+ retention. One trial randomized eubicarbonatemic patients with CKD 2 to $NaHCO_3$ supplement, equimolar NaCl, or usual care. At both 5 and 10 years, eGFR calculated using the serum cystatin C level and the CKD-EPI equation was higher in the $NaHCO_3$ group than the other groups. By 10 years, H^+ retention remained unchanged in the $NaHCO_3$ group but increased in the other groups, and serum [HCO_3^-] was unchanged in the $NaHCO_3$ group but decreased in the other groups, although remaining within the normal range (7,8).

These animal and human data of milder CKD frame an expanded concept of metabolic acidosis of CKD that encompasses H^+ retention occurring during eubicarbonatemia (Figure 1B). Initial H^+ retention augments acidification per residual nephron such that achieved steady-state net H^+ excretion is similar to controls with normal GFR (sham animals or patients with CKD 1); consequently, external H^+ balance is reestablished but under conditions of H^+ retention (2,8). Subclinical H^+ retention should challenge both bicarbonate and nonbicarbonate buffers residing in extracellular and intracellular spaces.

Studies have shown that 85%–90% of patients with CKD 2–4 have serum [HCO_3^-] ≥22 meq/L. Virtually all eubicarbonatemic patients with CKD 2 tested at baseline had H^+ retention of variable severity (8). Therefore, metabolic acidosis is an early, not late, complication of CKD. It is anticipated that H^+ retention would be larger and essentially universal in eubicarbonatemic patients with CKD 3 and 4. Nonetheless, the

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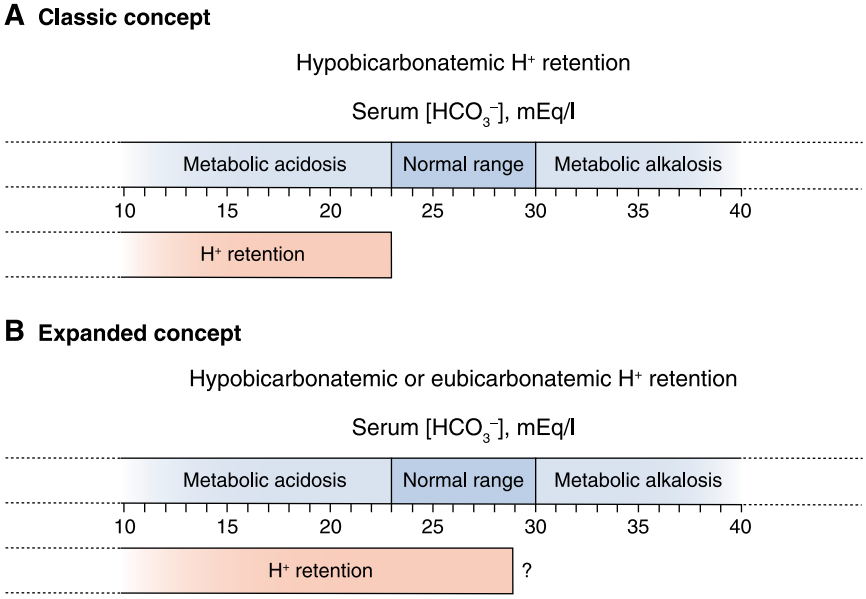

Figure 1. | **Metabolic acidosis of CKD.** (A) Classic concept. (B) Expanded concept.

precise prevalence of H^+ retention in eubicarbonatemic patients with CKD 2–4 remains to be determined.

Experience with patients with CKD 2 suggests that eubicarbonatemia can last for many years (8). Putative factors affecting the duration of subclinical metabolic acidosis include the baseline serum [HCO_3^-]; the higher the level, the longer the duration of eubicarbonatemia, other factors being equal. The dietary acid load is another factor; decreasing H^+-producing, animal-sourced protein or increasing HCO_3^--producing fruits and vegetables would tend to prolong the eubicarbonatemic phase. Despite progressive augmentation of ammoniagenesis of residual nephrons, ammonium excretion variably diminishes as CKD advances, increasing H^+ retention and accelerating transition to hypobicarbonatemia. Gradual exhaustion of nonbicarbonate buffers, including those in bone and muscle, would speed shifting to hypobicarbonatemia. Finally, some medications (*e.g.*, loop diuretics) increase serum [HCO_3^-], whereas others (*e.g.*, angiotensin converting enzyme [ACE] inhibitors) promote H^+ retention (5,6).

Subclinical Metabolic Acidosis and CKD Progression

Despite its anticipated very large prevalence in patients with CKD 2–4, only a small trial has examined the role of subclinical metabolic acidosis in CKD progression—a positive study (7,8). Thus, research should now shift toward subclinical metabolic acidosis with a focus on CKD 2 and 3a. The underlying rationale is potential amelioration of the CKD course before diffuse kidney fibrosis ensues. To maximize demonstration of benefit, trials should enroll eubicarbonatemic patients with relatively high H^+ retention.

The current procedure for estimating H^+ retention in subclinical metabolic acidosis (*i.e.*, the serum [HCO_3^-] response to oral $NaHCO_3$ load) is pathophysiologically sound but cumbersome, invasive, and time consuming; therefore, it is unsuitable for clinical practice (2,8). Might there be a practical and noninvasive alternative? In pondering this question, measurement of urine citrate emerged as a possibility. Hypocitraturia has long been recognized as a sensitive indicator of H^+ retention (9). It occurs in hypobicarbonatemic metabolic acidosis (H^+ feeding, diarrhea, distal renal tubular acidosis) but also in eubicarbonatemic metabolic acidosis (increased meat intake, incomplete distal renal tubular acidosis). Sensing of meager intracellular acidification seems to induce the physiologic adaptations that result in increased proximal reabsorption of citrate and hypocitraturia, the conserved citrate yielding HCO_3^- during its metabolism. Drawing on this evidence, the association between H^+ retention and urine citrate excretion in eubicarbonatemic patients with CKD 1 and 2 was evaluated before and after a 30-day administration of HCO_3^--producing fruits and vegetables. A mixed effects regression model showed that urine citrate excretion was strongly predictive of H^+ retention and reliably verified reduction in H^+ retention after fruits and vegetables (10). Furthermore, changes in urine citrate excretion identified changes in H^+ retention as eGFR declines in eubicarbonatemic patients with CKD 2 (8). Thus, urine citrate holds promise as an index of H^+ retention in eubicarbonatemic patients with CKD to guide initiation of base therapy and monitor its longitudinal effectiveness.

Not surprisingly, urine ammonium excretion has been identified as a risk factor for progression to ESKD. In both the NephroTest cohort (n=1065; 69% with measured GFR ≥30 ml/min per 1.73 m^2, 92% with eubicarbonatemia) and the African American Study of Kidney Disease and Hypertension cohort (n=1044; 84% with measured GFR ≥30 ml/min per 1.73 m^2, 88% with eubicarbonatemia), those in the lowest tertile of baseline urine ammonium excretion had an increased hazard ratio of ESKD. Moreover, in the latter analysis, among eubicarbonatemic

participants at baseline, those in the lowest tertile of urine ammonium excretion had higher adjusted odds of incident hypobicarbonatemia at 1 year. It would be interesting to compare urine citrate excretion and urine ammonium excretion as indicators of H^+ retention in eubicarbonatemic patients with CKD. However, a major obstacle to the utility of urine ammonium excretion is that clinical laboratories generally do not offer such measurement.

In conclusion, research should now shift toward examining the effect of base treatment on CKD progression in eubicarbonatemic patients with CKD 2 and 3a. Such trials should target patients with higher H^+ retention, as estimated by the serum [HCO_3^-] response to oral $NaHCO_3$ load. Baseline urine citrate and ammonium excretion should also be obtained to further evaluate their utility as markers of H^+ retention and CKD progression.

Disclosures

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