The kidney maintains the serum [HCO$_3^-$] at a normal value of 25 mEq/L by two distinct and highly regulated processes: (1) reabsorption of the filtered load of HCO$_3^-$ and (2) production and excretion of ammonium (NH$_4^+$). Production of NH$_4^+$ is primarily a function of the proximal tubule, and excretion is the result of the transport of NH$_4^+$ by the proximal convoluted tubule and thick ascending limb of Henle loop to facilitate the accumulation of NH$_3$ in the medullary interstitium and its transfer into the MCD to be trapped and excreted as NH$_4^+$. Both production and transport of NH$_3$/NH$_4^+$ are linked to changes in systemic pH and [K$^+$]. Ammoniagenesis is responsive to net endogenous acid production (NEAP) and thereby, dietary acid loads. In individuals ingesting a typical Western diet, NH$_3$/NH$_4^+$ produced in the proximal tubule and thick ascending limb of Henle loop are returned to the systemic circulation only if the NH$_4^+$ generated is excreted in the urine.$^1$

The possibility that NH$_3$/NH$_4^+$ accumulation in the renal interstitium could be potentially nephrotoxic per se or a representation of an inflammatory process was advanced by seminal studies from Hostetter and coworkers$^2$ in an animal model of chronic metabolic acidosis with elevated uNH$_4^+$ excretion that displayed accumulation of complement C5 in the interstitium. More recent evidence suggests that chronic metabolic acidosis activates signaling pathways in kidney cells$^3$ as well as other systems and cells$^4$ and that it may be associated with cell damage and fibrosis.$^5$ For example, the p53 gene, which is induced by acidosis, plays a role in the inhibition of glycolysis and increase in oxidative phosphorylation and activation of reactive oxygen species in cancer cells.$^5$ It is conceivable, therefore, that acidosis-induced inflammation and ER stress may represent important factors in cellular injury.

Evidence has accumulated from several clinical trials showing that patients with later-stage CKD and metabolic acidosis progress at a more rapid rate$^6$ and that high dietary acid load predicts ESRD among adults with CKD.$^7$ Moreover, a more rapid rate of progression of CKD has been documented in subjects with early-stage CKD eating a diet high in protein.$^7$ However, patients in this group typically have a compensatory increase in NEAP and consequently, do not develop frank metabolic acidosis. Importantly, in several studies, the rate of progression of CKD was retarded when supplementary alkali therapy was administered or additional fruits and vegetables were added to the diet.$^8,9$ Either maneuver can balance the generation of acids from dietary protein by adding alkali to the body balance equation as HCO$_3^-$ or producing citrate from dietary fruits and vegetables. The subsequent reduction in NEAP was observed in parallel with a significant reduction in urinary NAE, even in patients with early-stage CKD without frank metabolic acidosis. On the basis of these important findings, the concept of preclinical acidosis has been advanced to designate those patients with earlier-stage CKD, in whom by convention, higher dietary NEAP is matched by a higher NAE, preventing acidosis at this juncture. Avoidance of the development of overt clinical metabolic acidosis ([HCO$_3^-$]<22 mEq/L) requires, however, sufficient functional renal mass. The tradeoff for augmented ammoniagenesis and NH$_4^+$ excretion to preserve acid-base balance in these patients may activate potentially harmful signaling cascades in response to an “acid milieu” in the interstitium.$^3,4,10,11$ In this regard, studies have also shown that urine or serum levels of endothelin and angiotensinogen were elevated in nonacidotic patients with higher uNH$_4^+$ and, in addition, these levels declined with alkali administration.$^{10}$

In this issue of the *Journal of the American Society of Nephrology*, Raphael et al.$^{12}$ have examined the association between baseline NH$_4^+$ excretion and clinical outcomes in subjects participating in the African American Study of Kidney Disease and Hypertension (AASK). Patients without clinical metabolic acidosis at baseline were divided into tertiles on the basis of a metabolism into the ECF. The “new bicarbonate” produced in this pathway will be returned to the systemic circulation only if the NH$_4^+$ generated is excreted in the urine.$^1$
single measured urine NH$_4^+$+. Remarkably, patients with the lowest baseline NH$_4^+$+ excretion (<20 mEq/d) exhibited a 46% higher risk for adverse events (death and ESRD) as well as a future risk for metabolic acidosis at 1 year (table 6 in ref. 12) compared with participants in the high-NH$_4^+$+ excretion group (≥20 mEq/d). The authors propose that a lower uNH$_4^+$+ may be an “alternative and perhaps earlier indicator of risk than the serum [tCO$_2$].” 12

Although the assessment of uNH$_4^+$+ is of great interest and may prove beneficial, additional data are needed. For example, only baseline uNH$_4^+$+ values were available, and neither urine pH nor urinary biomarkers of tubule injury were reported. Moreover, none of the patients received alkali therapy. Although the authors correctly point to the study of Mahajan et al., 8 as evidence that alkali therapy slows progression of CKD in early hypertensive nephropathy, that study did not specifically evaluate patients with a low uNH$_4^+$+.

A sound pathophysiologic explanation for the key finding in this study is beyond the scope of the data available for analysis. The authors speculate that uNH$_4^+$+ is lower and that outcomes are poorer in patients with low uNH$_4^+$+ because of “poor excretory capacity (for NH$_4^+$+) and kidney function.” 12 Clearly, uNH$_4^+$+ fell significantly as mGFR declined (figure 3 in ref. 12) as expected. Accordingly, it might be helpful to consider the possible explanations for a decrease in uNH$_4^+$+ excretion. Urine NH$_4^+$+ excretion may be reduced because of (1) a physiologic response by the kidney to low levels of protein intake; (2) a reduction in ammoniagenesis and excretion due to metabolic or respiratory alkalosis or hyperkalemia; (3) a decrease in functional renal mass; or (4) a selective abnormality in NH$_4^+$+ transport and excretion, for example, transport of NH$_4^+$+ (or H$^+$+ ions) in the collecting duct or a defect in the medullary countercurrent multiplication system, either as a result of tubulointerstitial disease. 1–3

There was no evidence of metabolic alkalosis or hyperkalemia. By adjusting for NEAP and body mass index, the authors propose that the lower uNH$_4^+$+ cannot be discerned unequivocally, this study underscores the critical need for additional basic research using animal models to more fully explain the signal(s) linked to dietary acid loads that may initiate interstitial or tubule injury, and then to more clearly define its consequences in larger-scale multicenter prospective studies. Certainly, additional validation of the predictive utility of urine NH$_4^+$+ levels in patients with both early- and later-stage kidney disease is sorely needed. It seems that the time is past due for federal funding agencies to sponsor studies designed specifically to investigate the role of long-term alkali in slowing progression of CKD.

The availability of accurate measurement of uNH$_4^+$+ by clinical laboratories would be a welcome addition to evaluation of the integrity of kidney acid-base homeostasis in the patient with CKD. Moreover, for patients with possible renal tubular disorders, in whom surrogates for actual uNH$_4^+$+ measurements, such as the urine anion gap, are relied on by default, access to actual uNH$_4^+$+ determination is overdue.

Presently, it seems practical to provide alkali to patients with early- or later-stage CKD without metabolic acidosis who have a low or high uNH$_4^+$+ and recommend more universal adoption of administration of alkali to patients with CKD and clinical acidosis to correct the HCO$_3^-$ to values of approximately 24 mEq/L.

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DISCLOSURES

None.

REFERENCES


Turning the Tide: Improving Fluid Management in Dialysis through Technology

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Over the last decade, components of fluid management have emerged as some of the most important modifiable risk factors for morbidity and mortality among individuals on maintenance dialysis. Hypervolemia, either chronic from long-term volume overload or episodic from large interdialytic weight gains, may increase the risk of left ventricular hypertrophy and its adverse downstream cardiovascular consequences.1,2 Conversely, hypovolemia from either too voluminous or too rapid of fluid removal may lead to multiorgan ischemia and associated clinical sequelae.3,4 Experts recognize the need for balance between the extremes of volume status and ultrafiltration, but inter-relationships among volume-related components, lack of data on their relative importance, and absence of relevant clinical trials hinder consensus guideline development. Notwithstanding the paucity of trial evidence in this arena, international experts and United States dialysis organization leaders concur that putting “volume first” is essential if the dialysis community is to successfully “turn the tide” on the unacceptably poor outcomes experienced by our patients.5,6

Although the importance of volume control has been long appreciated in places like Tassin, France and Izmir, Turkey, the interest in fluid management in the United States has taken root in the last 5 years. The two largest United States dialysis providers recently implemented fluid management clinical programs. In 2013, DaVita launched FluidWise, a program advocating close attention to target weight prescription and attainment, BP control, standardized dialysate sodium, sodium and fluid dietary restrictions, and use of a clinic fluid advisor. The program includes risk stratification tools and individual-and facility-level fluid reports.7 In late 2016, Fresenius Medical Care, North America released the Fluid Management Dashboard, an electronic medical record tool that identifies patients with postdialysis weights >1 kg above or below their prescribed target weight and patients with ultrafiltration rates >13 ml/h per 1 kg in >30% of recent treatments. The dashboard, accessible on the hemodialysis machine, provides clinicians easy, single-screen access to recent pre- and postdialysis weights, prescribed target weights, prescribed and delivered treatment times, and postdialysis BPs.

Although each of these initiatives is important, the programs share two crucial deficiencies: (1) lack of tools that assess patient volume status objectively and (2) lack of randomized, controlled trial data showing that the proposed clinical interventions improve patient outcomes. Volume status estimation is essential for clinicians to accurately prescribe target weight, gauge ultrafiltration tolerance, and effectively balance the consequences of volume and fluid removal extremes. Physical examination findings contextualized with BP patterns and dialysis treatment tolerance are instructive but imprecise, and they often fall short in busy dialysis clinic environments. Objective volume assessment tools, such as biomarkers (e.g., B-type natriuretic peptide), relative plasma volume (RPV) monitoring, lung ultrasound, and bioimpedance (BIA) technology, exist. However, to date, clinical uptake has been restrained. Biomarker results have been disappointing. The one randomized, controlled clinical trial of RPV monitoring found that patients randomized to RPV monitoring had