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The Balance of the Evidence on Acid-Base Homeostasis and Progression of CKD

Julia J. Scialla, MD, MHS[1,2]

[1]Division of Nephrology, Duke University School of Medicine, Durham, NC

[2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

Abstract

Normalization of acid-base homeostasis in CKD holds promise for mitigating disease progression, but whether efforts should focus on patients with low serum bicarbonate or high dietary acid load is not known. In this issue Vallet *et al* contribute to this debate with a report that low urinary ammonia excretion independently associates with increased progression in moderate CKD. Whether this finding implicates differences in endogenous acid production or the ability to excrete an acid load in the pathogenesis of progression requires further study.

Keywords

metabolic acidosis; chronic kidney disease; nutrition

The role of disordered acid-base homeostasis in the progression of chronic kidney disease (CKD) has been hypothesized for decades.[1] In recent years interest in the field has grown due, in large part, to the exciting findings of two small randomized studies that reported slower rates of disease progression after treatment with alkali.[2,3] In one randomized study, use of sodium bicarbonate to treat frank metabolic acidosis in patients with late CKD delayed the need for renal replacement therapy[2]; In the other, sodium bicarbonate slowed glomerular filtration rate decline in patients with early CKD and without overt acidosis.[3] Numerous observational studies have reported associations between lower levels of serum bicarbonate and progression of CKD in a variety of settings.[4] Collectively, these studies laid the groundwork for current hypotheses positing that the observed beneficial effects of alkali therapy may be due to either: (1) correction of harmful systemic acid-base derangements versus (2) reducing demand for acid excretion that may otherwise stimulate pro-fibrotic factors, such as high cortical ammonia concentrations, renal endothelin production or activation of the renin-angiotensin-aldosterone system[1-5] (Figure A). Determining between these possibilities is clinically important because they imply different biochemical treatment targets and patient populations. For instance, the former may focus on treating patients with

Correspondence to: Julia J. Scialla, MD, MHS, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715, (919) 668-8764, Julia.scialla@duke.edu.

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largely late CKD to an optimal circulating bicarbonate concentration, while the latter suggests targeting acid load even early in kidney disease when serum bicarbonate and acid-base homeostasis generally appear normal.

In this issue of *Kidney International*, Vallet *et al* [6] add important new data to this field. The authors evaluated the associations of venous total CO_2 (tCO_2) concentration and urinary ammonia excretion with the risk of disease progression in a cohort of approximately 1,000 patients with CKD identified within the health care system. The median measured glomerular filtration rate (mGFR) was 38 ml/min/173m^2. Despite the relatively advanced kidney disease, mean tCO_2 was 26 mmol/l and only 8% of the cohort had evidence of overt metabolic acidosis, defined as tCO_2 <22 mmol/l. In this setting 24 hour urinary ammonia excretion was generally low (mean 18.5 mEq). In their longitudinal analyses, both low tCO_2 and lower urinary ammonia excretion were associated with greater risk of progressive kidney disease, as either progression to end-stage renal disease (ESRD) or fast decline in mGFR. The authors infer that low urinary ammonia in their study population largely represents an impaired ability to excrete the daily acid load and hence their results implicate abnormal acid balance in CKD progression. However, a major challenge to interpreting the meaning of the urinary ammonia and the associated findings is that the “appropriateness” of the urinary ammonia depends on the context of the dietary acid load and overall acid-base status.

To address the role of acid load in urinary ammonia excretion the authors calculated traditional measures of net acid excretion (NAE) and estimates of acid load, as the net endogenous acid production (NEAP) in a subset of 160 participants in the study. They find that although NAE and tCO_2 are lower in participants with lower mGFR, NEAP was not. In fact the difference between NEAP and NAE in the lowest mGFR group implied a median of 20 mEq/day net positive acid balance. We should exercise caution in making conclusions about balance in an observational study in which input variables were not tightly controlled or directly measured. In fact, equations used to *estimate* NEAP in this study represent a model for expected NAE developed in healthy individuals under the explicit assumption that in steady state NEAP≈NAE.[7] Stated another way, the results indicate that the acid excretion in patients with moderate to advanced CKD is less than what would be expected in an individual without CKD despite similar dietary intake. While one possible explanation is that patients with CKD have ongoing daily acid imbalance, another may be that diet-independent components of endogenous acid production differ in CKD. Diet-dependent determinants of acid excretion include the intake of sulfur containing amino acids and direct alkali precursors in the diet, whereas diet-independent determinants include the load of otherwise combustible organic anions that are lost in the urine.[4] Rates of organic anion excretion are known to be modified by acid-base disorders, suggesting the possibility that endogenous acid production, and not acid balance, may also be modulated in CKD.[8,9] In the setting of the only minor reductions in tCO_2 observed in the study population the latter may be a more satisfying hypothesis. Thus, although they cannot be definitively answered by the current observational study, the findings in this study raise intriguing questions about how fully we understand acid excretion and production in CKD.

Interestingly, two methods were used to quantify urinary ammonia excretion and resulted in slightly different results: fasting urinary ammonia concentration and the ratio of urinary ammonia to creatinine ratio in a 24 hour urine collection. Although the direction of effect was generally similar for risk of ESRD, the relationship between fasting urinary ammonia concentration and risk was more obviously graded. Furthermore, in contrast to fasting urinary ammonia, urine ammonia to creatinine ratio was not associated with fast mGFR decline. It is possible that factors other than urinary ammonia excretion contribute to the different findings with these metrics. For instance, a low creatinine generation rate may raise apparent ammonia excretion using the urinary ammonia to creatinine ratio, whereas a urine concentrating defect may lower the fasting urinary ammonia concentration through dilution. Although the authors adjust for body mass index and urine osmolality in their analyses, these factors may plausibly contribute to differences in results using these metrics. Alternatively diurnal variation in urinary ammonia excretion or analytic instability of urine ammonia as measured in a 24 hour urine collection could contribute and will be important to understand if these measurements are to be used clinically.

Despite the inability to make definitive conclusions regarding balance or the optimal methods to quantify urinary ammonia in CKD, the results in this study add important insights about the role of these metrics in the care of patients with CKD. At first glance, the data appear inconsistent with the existing hypothesis that augmented urinary ammonia excretion as a result of acid loading contributes to CKD progression (Figure A). It is important to recognize that although global ammonia excretion may be depressed, ammonia excretion on a per nephron basis, and therefore cortical ammonia concentrations in functioning nephrons, may be still be high.[1] Nonetheless, based on these results high urinary ammonia excretion does not appear to be a useful metric to connote risk and guide therapy. The authors conclude that a defect in ammonia excretion, presumably reflected in low urine ammonia, could help identify patients for alkali supplementation in earlier stages of CKD. However, in this study both venous tCO_2 and urinary ammonia appear to decrease with mGFR in a similar fashion. The use of urinary ammonia as a guide for alkali therapy is limited by the fact that in any individual CKD patient low urinary ammonia excretion could represent either impaired acid excretion or low acid load in which addition of alkali is unnecessary, or worse, inappropriate. To determine between these scenarios use of tCO_2 remains the most logical current tool. Regardless the current data nicely demonstrate that high urinary ammonia concentration or even NAE are unlikely to be direct targets for interventions in patients with moderate CKD. An alternative conclusion from this study is that low tCO_2 and urine ammonia may be powerful markers of renal tubular functions that can predict disease progression and ESRD independent of mGFR (Figure B). This and other studies highlight our need to better understand the physiology of moderate CKD and think about kidney ‘function’ more broadly and not merely indexed to its rate of filtration.

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References

1. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. J Clin Invest. 1985; 76(2):667–675. [PubMed: 2993363]
2. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status. J Am Soc Nephrol. 2009; 20(9):2075–2084. [PubMed: 19608703]
3. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int. 2010; 78(3):303–309. [PubMed: 20445497]
4. Scialla JJ, Anderson CAM. Dietary Acid Load: A Novel Nutritional Target in Chronic Kidney Disease? Adv Chronic Kidney Dis. 2013; 20(2):141–149. [PubMed: 23439373]
5. Scialla JJ, Appel LJ, Astor BC, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. Kidney Int. 2012; 82(1):106–112. [PubMed: 22475819]
6. Vallet M, Metzger M, Haymann JP, et al. Urinary ammonia and long-term outcomes in CKD. Kidney Int. 2015 In Press.
7. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr. 1998; 68(3):576–583. [PubMed: 9734733]
8. Hood V, Tannen R. Protection of acid-base balance by pH regulation of acid production. N Engl J Med. 1998; 339(12):819–826. [PubMed: 9738091]
9. Halperin M, Dhadli S, Kamel K. Physiology of acid-base balance: links with kidney stone prevention. Seminars in Nephrology. 2006; 26(6):441–446. [PubMed: 17275581]

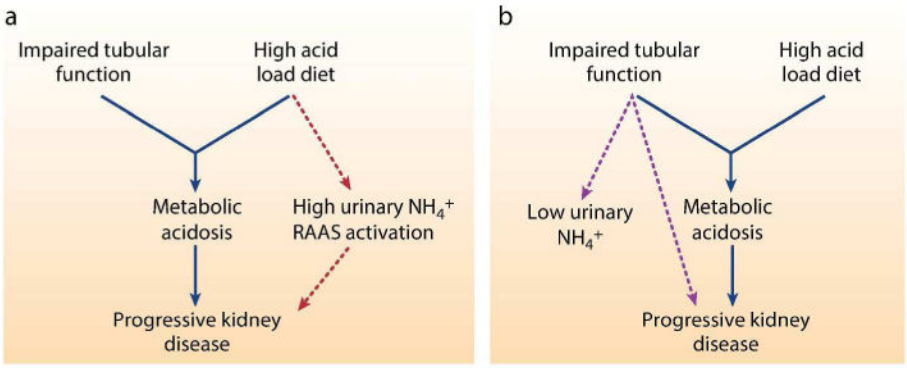

Figure. Framework for interpreting relationship between urine ammonia and CKD progression

Panel **A** depicts the pre-existing working hypothesis, whereby high dietary acid load coupled with impaired tubular function result in metabolic acidosis and CKD progression (Blue arrows). In this framework, interventions that reduce acid load via dietary changes or alkali supplements may slow CKD progression via changes in acid base status. Red dashed arrows represent an alternative hypothesis whereby high acid load may promote CKD progression by increasing renal ammoniagenesis and stimulating renin-angiotensin-aldosterone system (RAAS) activation even in the absence of metabolic acidosis. Panel **B** depicts an alternative framework for interpreting the study in this issue of Kidney International that reports a relationship between low, as opposed to high, urinary ammonia excretion with CKD progression.[6] Low urinary ammonia excretion may be a powerful marker of tubular function that is at least partially independent of GFR and associated independently with outcomes (Dashed purple arrows). Lower urinary ammonia may indicate a proclivity toward development of metabolic acidosis, but the “appropriateness” of the urinary ammonia can only be fully understood relative to the acid-base status and the acid load.