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Acute Kidney Injury in CKD: Role of Metabolic Acidosis

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Chronic kidney disease (CKD) is the most common cause of chronic metabolic acidosis. It occurs because the diseased kidney can no longer compensate for the intake of dietary acids and production of acid from metabolism because of the CKD-related decreased renal excretion of metabolic acids and inadequate absorption and regeneration of bicarbonate. The prevalence of acidosis increases as kidney function decreases with a prevalence of approximately 5% in stage 2, 15% in stage 3, and 35% in stage 4 CKD. Metabolic acidosis has been associated with worsening of metabolic bone disease, sarcopenia and muscle weakness, and more rapid progression of CKD.[1]

Zhu *et al.*[2] recently reported a new potential adverse clinical consequence of metabolic acidosis in CKD, the occurrence of acute kidney injury (AKI). They performed a retrospective study using the Optum database (a US electronic health record) and the Manitoba Claims database. Subjects had an estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and a serum bicarbonate of 12 to 30 mEq/l, and they excluded those on dialysis or having a prior transplant or, in the US cohort, with an eGFR <10 ml/min per 1.73 m^2. In the US cohort, inclusion criteria required 2 consecutive eGFR <60 ml/min per 1.73 m^2 values 90 to 365 days apart, whereas inclusion in the Manitoba cohort required only 1 such value. They divided the population into 2 cohorts, namely those with metabolic acidosis, defined as serum bicarbonate ≥12 mEq/l and <22 mEq/l and those with a normal serum bicarbonate of ≥22 mEq/l and <30 mEq/l. The primary outcome of AKI during follow-up was based on ICD-9 and ICD-10 codes or the Kidney Disease: Improving Global Outcomes creatinine-based definition using inpatient or outpatient values.

Of all participants, 5.8% of the 136,067 individuals in the US database and 14.6% of the 34,957 individuals in the Manitoba database had metabolic acidosis. In the US cohort, the eGFR was 37.3 ± 13.3 ml/min per 1.73 m^2 in those with acidosis versus 45.1 ± 10.4 ml/min per 1.73 m^2 in those without acidosis, and in the Manitoba cohort, 33.4±16.4 versus 44.5±11.8 ml/min per 1.73 m^2. In both cohorts, individuals with metabolic acidosis were younger and more likely to have diabetes and stage G4 and G5 CKD than those without acidosis. The median follow-up time was 2.7 years in the US cohort and 3.9 years in the Manitoba cohort. Patients with metabolic acidosis had an increased rate of AKI (for those with and without acidosis, the AKI rate was 26.2 vs. 16.4 events per 100 person-years in the US database and 20.6 vs. 8.5 events per 100 person-years in the Manitoba database). In Cox models adjusting for age, sex, diabetes, hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, stroke, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, statins, eGFR, and additionally for race and geographic region in the US cohort, the hazard ratio was 1.57 (95% confidence interval 1.52–1.61) in the US and 1.65 (95% confidence interval 1.58–1.73) in the Manitoba populations. Patients with metabolic acidosis had a higher probability of AKI at all time intervals, and the probability increased with the severity of acidosis. The results were similar when serum bicarbonate was treated as a continuous variable and in a subgroup of patients with urine albumin-to-creatinine ratios.

The authors acknowledge the limitations of their study, including the possibility of residual confounding in an observational study; the inability to exclude chronic respiratory alkalosis as the cause of secondary metabolic acidosis; the fact that in the Manitoba database, patients were classified as having CKD or metabolic acidosis on the basis of 1 laboratory value, which might bias toward the null because of

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overinclusion of misclassified patients; and the possibility that in the Manitoba data set, sicker patients may have been more likely to use public laboratories or hospital sites, which comprise most of the data from outpatient tests, thereby leading to ascertainment bias. Nevertheless, the results have important implications for the pathophysiology of metabolic acidosis in CKD and its potential treatment.

The association of the severity of metabolic acidosis with the rate of progression of CKD is well recognized.[3] This association is thought to be due to the possibility that the kidney's adaptive response to maintain acid-base homeostasis may have adverse consequences on kidney function. The kidney has 2 primary mechanisms to maintain acid-base homeostasis, namely reabsorption of bicarbonate in the proximal tubule and the formation of new bicarbonate by proximal tubule ammonia generation and distal nephron hydrogen ion secretion, with ammonia as the primary urinary buffer. Increase in proximal tubule cell ammonia generation is the major mechanism for restoring bicarbonate levels in response to metabolic acidosis. There are also increases in endothelin-1 and angiotensin II production within the kidney. Endothelin-1, produced in the proximal tubule and collecting duct, stimulates the sodium-hydrogen exchanger exchange and increases aldosterone release, which increases distal tubular H^+-proton pump activity. Angiotensin II stimulates the sodium-hydrogen exchanger 3, H^+-proton pump activity, tubular ammoniagenesis, whereas systemic release stimulates aldosterone secretion leading to increased distal tubule hydrogen secretion.[4]

Animal studies have shown that renal adaptations to increase net acid excretion may be maladaptive because they also result in inflammation and increased fibrosis.[5,S1] Increased ammonia generation leads to high levels in the renal interstitium where it reacts with the C3 complement component with the formation of C3 convertase and complement activation. The subsequent inflammatory response results in tubulointerstitial injury and kidney fibrosis. Endothelin-1 is a vasoconstrictor and can induce oxidative stress, inflammation, and extracellular matrix accumulation in the kidney. Similarly, angiotensin II is a vasoconstrictor and promotes interstitial fibrosis in the kidney.

The increase in endothelin-1 and angiotensin II may also establish a hemodynamic milieu that increases the risk for ischemic AKI. Kendrick *et al.*[6] have shown that metabolic acidosis impairs endothelial function that can be ameliorated by alkali administration. In a 14-week, open-label crossover study, they studied the effect of bicarbonate administration on brachial artery flow–mediated dilation in 18 patients with an eGFR of 26 $\pm$ 8 ml/min per 1.73 m^2 and serum bicarbonate of 19.5 $\pm$ 2.3 mEq/l. Raising bicarbonate to 22.0 $\pm$ 3.1 mEq/l significantly improved flow-mediated dilation, whereas there was no change in the control period. Whether the observed impaired endothelial function would translate into an increased risk for ischemic AKI is unknown, but the study does provide a potential link between the metabolic acidosis of CKD and increased AKI risk.

Two recent animal studies provide additional evidence for an increased risk of AKI in the presence of metabolic acidosis. Magalhães *et al.*[7] studied an ischemia/reperfusion model in rats. They showed that induction of metabolic acidosis by adding ammonium chloride to the drinking water 2 days before ischemia/reperfusion leads to a more severe decline in GFR, higher tubular injury score, and increased mortality than sham controls or rats subjected to metabolic acidosis or ischemia/reperfusion alone. This increase in kidney injury was associated with high levels of NF-κB, a key mediator of acute and chronic inflammation, suggesting another pathway by which metabolic acidosis may exacerbate kidney injury.

Bugarski *et al.*[8] provide additional evidence linking metabolic acidosis directly to AKI. Metabolic acidosis increases proximal tubule glutamine uptake and ammoniagenesis, requiring a supply of the oxidized form of nicotinamide adenine dinucleotide (NAD), and NAD depletion has been identified as a key step in the pathogenesis of several models of AKI. Using intravital live cell imaging in a mouse model of ammonium chloride–induced metabolic acidosis, they found acute changes in mitochondrial NAD redox state, respiratory chain function, and lipid metabolism, which led to proximal tubule cell damage. Both the infusion of bicarbonate 2 hours after acidosis and pretreatment with a NAD precursor were protective. This study suggests a direct mechanism for metabolic acidosis and the role of NAD as a cause of tubular injury. Together, these animal studies provide additional mechanisms for a link between metabolic acidosis and AKI. Importantly, these studies used an acute metabolic acidosis model, although similar mechanism may well occur in chronic metabolic acidosis.

Acidosis may also be a marker of the severity of kidney function. The severity of CKD is typically assessed by glomerular function, usually by creatinine and

albuminuria measurements. But increasingly, investigators are recognizing impaired tubular function as an important contributor to the pathophysiology of CKD.[S2] As Zhu *et al.*[2] suggest, metabolic acidosis may be a marker for a vulnerable kidney, reflecting greater tubular damage and worse kidney function, and thereby a greater risk for AKI.

If metabolic acidosis in CKD is confirmed as a risk factor for AKI in further studies, it will provide another mechanism to explain its association with more rapid CKD progression. Substantial literature has confirmed that AKI, even with mild severity and apparent complete recovery, is a risk factor for incident CKD or CKD progression.[S3] Therefore, the association of AKI with metabolic acidosis in CKD may be linked to more rapid progression of CKD.

Animal models suggest that alkali may ameliorate the adverse pathophysiologic effect of metabolic acidosis, and several trials of alkali in patients suggest improvement in the rate of CKD progression.[9] However, the trials were small; usually single center; frequently unblinded; often excluded those with heart failure, edema, or hypertension; and did not always demonstrate the efficacy of alkali on the clinical outcomes; therefore, there has been a call for a large, multicenter, placebo-controlled trial. As Zhu *et al.*[2] recommend, including AKI as a secondary outcome would be worthwhile because the event rate was high, and it is relatively easy to ascertain. Although it may not be a patient-centered outcome of major importance, it may have relevance due to its association with more rapid progression of CKD.

The study of Zhu *et al.*[2] reminds us that acidosis in CKD has protean adverse consequences, and some may await further discovery. However, observational studies cannot strongly guide therapy. For those, we need randomized controlled trials. Treatment with sodium bicarbonate is inexpensive, and hopefully, future studies will provide an answer as to whether it should be part of our therapeutic armamentarium in CKD.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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