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Metabolic Acidosis Is a Predictor of Mortality in Patients with Chronic Kidney Disease

With comments from poster co-author Nancy L. Reaven (Strategic Health Resources)

Maintenance of acid-base homeostasis is critical to normal cellular function. Metabolic acidosis is a condition that involves too much acid accumulation in the body. Acid is ordinarily generated in the body from dietary sources and daily metabolism and then non-volatile acid is excreted by the kidneys.

In chronic kidney disease (CKD), however, the kidneys lose the ability to completely excrete the acid that is generated through digestion of protein and daily metabolism, resulting in accumulation of acid in the body, which is manifested by low serum bicarbonate levels. Once serum bicarbonate is below 22 mEq/L, the patient has metabolic acidosis.¹

The number of functioning nephrons, the filtering units of the kidneys, declines with advancing kidney disease. The physiological response to acid retention results in increased acid excretion per remaining nephron, but, over time, this sustained adaptive response may result in inflammation and fibrosis, resulting in further damage to the kidney.²

A decrease in serum bicarbonate is what characterizes metabolic acidosis. Studies have shown that an increase in serum bicarbonate level to between 22 to 29 mEq/L slows estimated glomerular filtration rate (eGFR) decline in patients with CKD stages 3-5.

It is unknown the extent to which metabolic acidosis contributes to mortality in patients with CKD, so researchers conducted a study to investigate the impact of metabolic acidosis on mortality in a real-world population of patients with CKD who were not on dialysis.

“The serum bicarbonate test is a commonly performed



Nancy L. Reaven

laboratory test, but doctors who are treating patients for advanced kidney disease are managing so many other aspects of the condition that concerns about chronic metabolic acidosis may not be high on their priority list, particularly if there are no appropriate treatment options,” said Nancy Reaven, of Strategic Health Resources and a co-author of the study. “Our study was an opportunity to try to understand the extent to which this condition was impacting outcomes in patients with CKD.”

Study design

Researchers used deidentified electronic health record (EHR) data from Optum® that included a cumulative population of 81 million U.S. patients, including those with all insurance types and the uninsured. They identified 51,558 patients who had three or more eGFR values <60 mL/min/1.73 m² from 2007 to 2017. They included non-dialysis-dependent patients with stage 3-5 CKD at the index date who had two or more serum bicarbonate tests 28 to 365 days apart (first test was index date) and two or more years of follow-up data or those who died during the study interval. Patients without a qualifying pair of serum bicarbonate tests were excluded.

Patients were classified as having metabolic acidosis (n=17,350; defined as serum bicarbonate of 12 to <22 mEq/L) or normal serum bicarbonate (n=34,208; defined as 22 to 29 mEq/L). Researchers also assessed a

secondary population based on serum bicarbonate value cohorts: 12 to <22 mEq/L, 22 to <30 mEq/L, and 30 to 40 mEq/L. Patients with metabolic acidosis at baseline were younger (mean age, 70.3 years vs. 74.3 years), had more advanced stages of kidney disease (mean eGFR, 37.2 vs. 43.2 mL/min/1.73 m²), and had a higher Charlson Comorbidity Index (CCI) score (mean, 3.5 vs. 1.7) compared with patients with CKD with normal serum bicarbonate. The study oversampled for patients with metabolic acidosis to ensure a large enough study cohort.

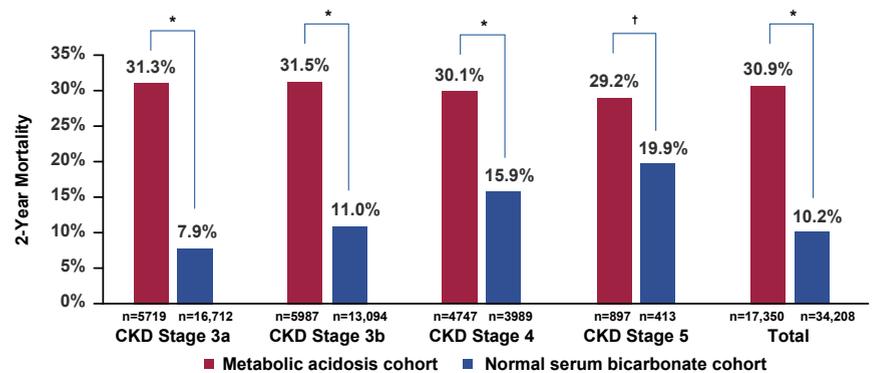
Researchers assessed all-cause mortality assigned by Optum using Social Security data. Time to all-cause mortality was assessed with a Cox proportional hazards model in all available post-index data (median four years, maximum 10 years). In the secondary population, two-year all-cause mortality was assessed at 1 mEq/L increments of serum bicarbonate (up to 40 mEq/L) by a restricted cubic spline model with knots at bicarbonate values of 20, 21, 24, 26, and 28 mEq/L.

Researchers assessed the impact of the covariates age, sex, race, baseline eGFR, diabetes, hypertension, heart failure, CCI score, and log albumin-to-creatinine ratio (ACR) on the relationship between serum bicarbonate and outcomes.

Mortality associated with metabolic acidosis

In unadjusted analysis, two-year all-cause mortality was significantly higher in the metabolic acidosis cohort compared with the normal serum bicarbonate cohort at all stages of CKD and in total. See **FIGURE 1**. In the adjusted model, serum bicarbonate was shown to be a significant

FIGURE 1 Two-Year Mortality by Index CKD Stage and in Total, Metabolic Acidosis Cohort vs Normal Serum Bicarbonate Cohort, Unadjusted



* $P < 0.0001$; † $P = 0.0004$.

independent predictor of all-cause mortality in patients with CKD.

Mortality over the two-year period increased steadily by CKD stage in the normal serum bicarbonate cohort from approximately 8% in stage 3 CKD to approximately 20% in stage 5 CKD. However, mortality in the metabolic acidosis cohort remained relatively consistent across CKD stages at a mean of approximately 30% to 31%. “Interestingly, the percentage of patients who died increased as kidney function declined, as we would expect, among patients with normal serum bicarbonate, but the rates of death were quite high irrespective of baseline CKD stage among patients with metabolic acidosis,” said Ms. Reaven. “This

suggested to us that metabolic acidosis itself is contributing to mortality, potentially independently of patients’ actual kidney disease status.”

“That was surprising because it’s generally thought that it is the state of the kidney that is most closely associated with the probability of mortality in these patients,” she continued. “Or it is the state of the kidney in combination with various comorbidities, like heart failure, that is primarily associated with mortality in these populations, so it was illuminating to understand that metabolic acidosis was actually an independent risk factor for mortality.”

In adjusted analyses, serum bicarbonate was a significant predictor of

“Chronic kidney disease is a public health problem of enormous proportion. Its prevalence is increasing, and the costs associated with it are soaring.”

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TABLE 1 Cox Proportional Hazards Ratio for Time to All-Cause Mortality in Patients with CKD 3–5 Evaluated Over a Median of 4 Years (Max 10 Yrs)

| | Cox HR (95% CI) | P value |
|---|-------------------------|-------------------------------|
| Continuous variables | | |
| Age, per 1 year increase | 1.04 (1.04–1.04) | <0.0001 ^a |
| Log ACR, per 1 mg/g increase | 1.07 (1.06–1.09) | <0.0001 ^a |
| Serum bicarbonate, per 1 mEq/L increase | 0.91 (0.90–0.91) | <0.0001^a |
| eGFR, per 1 mL/min/1.73 m ² increase | 0.99 (0.99–1.00) | <0.0001 ^a |
| Categorical variables | | |
| Male vs female | 1.13 (1.09–1.16) | <0.0001 ^a |
| Race: African American vs Caucasian | 1.16 (1.10–1.23) | <0.0001 ^a |
| Race: Asian vs Caucasian | 0.54 (0.46–0.62) | <0.0001 ^a |
| Race: Other/unknown vs Caucasian | 0.96 (0.89–1.02) | 0.2035 |
| Diabetes | 0.94 (0.90–0.98) | 0.0027 ^a |
| Heart failure | 1.81 (1.74–1.89) | <0.0001 ^a |
| Hypertension | 0.87 (0.83–0.91) | <0.0001 ^a |
| CCI score 1 vs 0 | 1.12 (1.05–1.20) | 0.0004 ^a |
| CCI score 2 vs 0 | 1.15 (1.08–1.22) | <0.0001 ^a |
| CCI score ≥3 vs 0 | 1.47 (1.39–1.56) | <0.0001 ^a |

^aP<0.05.

time to all-cause mortality (hazard ratio, 0.91; 95% confidence interval, 0.90-0.91; $P<0.0001$). For every 1 mEq/L increase in serum bicarbonate, there was a 9% decrease in all-cause mortality, as shown in **TABLE 1**. “What surprised me was the strength of that association,” said Ms. Reaven. “As serum bicarbonate increases, the risk of mortality decreases until you get to the point of alkalosis, which is a different condition. That’s typically where serum bicarbonate is greater than about 30 mEq/L. Then you start to see mortality increase again, so there is a sweet spot for serum bicarbonate that is representing normal and healthy pH balance in the body, which is generally thought to be between about 22 and 29 mEq/L.”

The spline analysis, also adjusted for covariates, showed declining mortality as serum bicarbonate rises from 12 to 21 mEq/L, and a j-shaped curve from 21 to 40 mEq/L, with a nadir at approximately 26 mEq/L. This means

that a serum bicarbonate value of 26 mEq/L was associated with the lowest mortality.

Metabolic acidosis as a significant predictor of all-cause mortality in this CKD patient population was independent of age, sex, race, preexisting comorbidities, and baseline eGFR and ACR. “We controlled for a host of other variables that are known or hypothesized to be risk factors for death in patients with advanced CKD,” said Ms. Reaven. Based on the findings that each 1 mEq/L increase in serum bicarbonate decreased mortality, “this indicated that there is a significant independent relationship between serum bicarbonate in the metabolic acidosis range and the risk of death. This tells us that metabolic acidosis has an impact on mortality that is independent from baseline CKD stage, and it’s actually worth paying attention to,” she said.

Ms. Reaven noted that a strength of the study design was its large, diverse patient population that was

distributed across the United States in community-based settings. “These are patients who were represented by EHRs and that were not attached to a single insurer. In fact, this represented patients who were covered by Medicare, private insurance, Medicaid, and even individuals who were uninsured,” she said.

The study is limited by its observational, retrospective design, “so it cannot prove causality,” she said. Ms. Reaven said the study also could not anticipate all variables and factors that might alter the relationships being studied.

Considerations for the healthcare system

“CKD is a public health problem of enormous proportion,” said Mrs. Reaven. “Its prevalence is increasing, and the costs associated with it are soaring. These patients progress to end-stage renal disease and end up on dialysis, which is not only debilitating but also enormously expensive. I think understanding that metabolic acidosis contributes independently to the poor outcomes for these patients and is a modifiable risk factor for these patients is an important takeaway because effective treatment could potentially delay progression and lower the risk of death.”

“Studies like this raise the awareness that as an independent risk factor for poor outcomes for these patients, serum bicarbonate should be much more closely monitored and interventions considered early in order to try to modify the clinical trajectories for these patients. Also, if research of this kind can be helpful in stimulating approaches to treatment, that could go a long way to mitigating the impact of metabolic acidosis,” she concluded.

Nancy L. Reaven is president and founder of Strategic Health Resources, a consulting firm specializing in health economics and outcomes research with a particular focus on investigating the clinical consequences of diseases in real-world settings. Previously, she was chief executive officer of a California-based physician-hospital delivery system, director of operations for Prudential Insurance Company, and director of development for Maxicare Health Plans. Ms. Reaven is a paid consultant on behalf of Tricida.

FEATURED POSTER

Tangri N, Reaven N, Funk SE, Mathur V. Metabolic acidosis is a predictive factor for all-cause mortality in patients with chronic kidney disease. Poster 263. Presented at the Virtual National Kidney Foundation 2020 Spring Clinical Meetings. The feature poster is sponsored by Tricida.

DISCLOSURES

NT, NR, SEF, VM are all consultants to Tricida, Inc.

VM is listed on granted or pending patents for Tricida, Inc.

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