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Adverse Clinical Outcomes in Patients With Chronic Kidney Disease and Metabolic Acidosis: A Longitudinal Analysis

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During the National Kidney Foundation 2019 Spring Clinical Meetings, Nancy L. Reaven, MA, president and founder of Strategic Health Resources, and Vandana Mathur, MD, president of MathurConsulting, presented the results of a longitudinal analysis of data from a large population of patients with chronic kidney disease (CKD) and metabolic acidosis.

CHRONIC KIDNEY DISEASE AND METABOLIC ACIDOSIS

Declining kidney function is a common cause of chronic metabolic acidosis, a condition in which the body accumulates too much acid due to a disruption in homeostasis.¹ In patients with impaired kidney function, metabolic acidosis is defined as a persistent bicarbonate level less than 22 mEq/L.² Metabolic acidosis is associated with muscle wasting, loss of bone density, impaired cardiac function, and increased mortality risk, and it is a risk factor for the progression of CKD.^{1,2}

Increasing evidence has shown that metabolic acidosis contributes to the progression of CKD because of the body's inability to maintain acid–base balance, resulting in increased production of certain peptides and hormones—for example, endothelin, aldosterone, and angiotensin II. The overproduction of these peptides and hormones leads to renal fibrosis and inflammation, contributing to the progression of CKD.^{2,3} The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines recommend maintaining a serum bicarbonate level above 22 mEq/L.⁴

PREVIOUS ANALYSES DEMONSTRATING THE IMPACT OF METABOLIC ACIDOSIS ON MORTALITY

The results of cross-sectional analyses demonstrate that metabolic acidosis is associated with increased mortality and that the prevalence of metabolic acidosis increases with advancing stages of CKD.^{5,6} However, data from longitudinal analyses of large populations of patients with CKD and metabolic acidosis are limited.^{6,7}

LONGITUDINAL ANALYSIS BY REAVEN ET AL

To address this gap in knowledge, Reaven et al conducted a longitudinal analysis of data from a large US community-based population, with the goal of evaluating the impact of metabolic acidosis on mortality and adverse kidney outcomes. The results of the analysis showed that metabolic acidosis was associated with an increased risk of the composite outcome DD40, which was defined as death, initiation of chronic kidney dialysis, kidney transplant, or at least a 40% decline in estimated glomerular filtration rate (eGFR) compared with the baseline level. These results were independent of patient age, sex, race, other comorbidities, overall comorbidity burden, and baseline eGFR and log urine albumin-to-creatinine ratio. During a follow-up period of up to 10 years, each increase of 1 mEq/L

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in serum bicarbonate level was associated with a 5% incremental decrease in risk of DD40 in patients younger than 65 years and an 8% incremental decrease in risk of DD40 in patients 65 years and older.⁷ •

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ASK THE INVESTIGATORS

An editor from The American Journal of Managed Care® (AJMC®) conducted a question-and-answer session with Nancy L. Reaven, MA, along with the other investigators, to gain additional insight on the current management of metabolic acidosis in patients with chronic kidney disease (CKD), the gap in knowledge the study by Reaven et al¹ was designed to address, and the implications of the results for managed care professionals.

AJMC®: What is metabolic acidosis, and what causes it?

Investigators: Metabolic acidosis is a pathologic process in which an increase in hydrogen ions results in a depletion of bicarbonate, the most available buffer in the body. Metabolic acidosis can be caused by an addition of an acid, a reduction in base, or failure to excrete acid. In patients with kidney disease, acid derived from the diet and metabolism is not fully excreted by the kidneys. Metabolic acidosis in patients with CKD can be identified by an abnormally low serum bicarbonate level, as determined by a common blood test. Metabolic acidosis is a complication of CKD and also a cause of its progression.²

This study highlights the independent contribution of metabolic acidosis to adverse kidney outcomes.

AJMC®: What are some of the complications of metabolic acidosis in patients with CKD?

Investigators: Metabolic acidosis is associated with more rapid progression of CKD to later stages, necessitating dialysis and kidney transplantation. Treatment of metabolic acidosis appears to improve kidney outcomes, as evidenced by data from several single-center, randomized, controlled trials.³⁻⁵ A number of pathogenetic mechanisms related to metabolic acidosis may result in kidney damage. For example, decreased acid secretion by the kidneys in patients with CKD leads to an increase of peptide hormones such as endothelin 1, aldosterone, and angiotensin II, as well as activation of the complement system, resulting in kidney fibrosis, inflammation, and proteinuria.²

Acidosis directly leads to bone loss and muscle wasting. As kidney function declines, acid accumulation is buffered by bone and muscle tissue breaks down. This leads to bone demineralization, with an increased risk of fractures, and protein catabolism resulting in reduced muscle mass.^{2,6} These factors may contribute to worsening of physical function and frailty.

AJMC®: How is metabolic acidosis currently treated?

Investigators: Currently, there is no FDA-approved treatment available for chronic metabolic acidosis in the United States. Patients are sometimes treated with oral alkali (sodium bicarbonate or sodium citrate) or diets very low in acid-producing animal protein and/or high in base-producing fruits and vegetables.⁷⁻⁹ Sodium-containing treatments may not be options for patients with conditions that may be aggravated by increased sodium intake, such as heart failure, hypertension, and edema.⁹ Increased dietary ingestion of fruit and vegetables, with their higher potassium content, is not always feasible in patients with chronic kidney disease because they often have hyperkalemia.⁹

AJMC®: Prior to this study, what was known about metabolic acidosis in patients with CKD?

Investigators: Retrospective studies have shown that higher serum bicarbonate values are associated with lower kidney failure risk.^{4,10-12} The risk of CKD progression is 3% to 8% lower for each 1 mEq/L increase of serum bicarbonate.¹⁰⁻¹³ Additionally, prospective studies have shown that metabolic acidosis is a key risk factor in the progression of CKD.^{3-5,14-16} Therefore, treating metabolic acidosis has the potential to be a disease-modifying intervention.

AJMC®: Why was this study conducted? What knowledge gap does it address?

Investigators: The burden of illness associated with metabolic acidosis has not been well characterized. Although several cross-sectional

studies have shown that metabolic acidosis is a risk factor for CKD progression, its independent association with the wider range of adverse outcomes, including mortality, is not well understood. This study is a useful next step in advancing that understanding.¹

AJMC®: How was the study performed?

Investigators: We obtained electronic medical records for patients with advanced CKD (stages 3a-5) for 10 years (2007-2017). We identified patients who had metabolic acidosis and compared their health outcomes (adverse renal outcomes and death) with those of patients whose serum bicarbonate levels were in the normal range, while controlling for a number of other factors that are known to affect renal outcomes, including age, level of kidney function, albuminuria, and comorbid conditions such as diabetes.¹

AJMC®: What were the results?

Investigators: The results of the analysis showed that the unadjusted 2-year event rates for death, chronic dialysis, renal transplant, $\geq 40\%$ decline in eGFR [estimated glomerular filtration rate], and the composite endpoint DD40 [defined as death, initiation of chronic kidney dialysis, kidney transplant, or at least a 40% decline in eGFR compared with baseline level] were significantly higher in patients with metabolic acidosis versus those with normal serum bicarbonate ($P < .0001$ for all outcomes, regardless of age group). Additionally, in adjusted results over a follow-up period of up to 10 years, every 1 mEq/L increase in serum bicarbonate was associated with a 5% decrease in the risk of DD40 in the < 65 years population (HR, 0.95 per 1 mEq/L; 95% CI, 0.94-0.96) and an 8% decrease in the risk of DD40 in the ≥ 65 years population (HR, 0.92 per 1 mEq/L; 95% CI, 0.91-0.92). The analysis adjusted for a number of other risk factors, including age, gender, preexisting diabetes, hypertension, and heart failure; comorbidity burden (measured by the Charlson Comorbidity Index); baseline eGFR; and baseline log urine albumin-to-creatinine ratio.¹

AJMC®: What is the relevance of these results for managed care professionals, and how could this information be used?

Investigators: This study highlights the independent contribution of metabolic acidosis to adverse kidney outcomes.¹

AJMC®: What are some of the strengths and limitations of this study?

Investigators: One of its strengths is the size and nature of the study population. The study includes medical records from over 50,000 community-based patients with advanced CKD from a diverse, geographically distributed database.¹ Thus, its results provide insight into the effects of metabolic acidosis in a community-based population. However, there are inherent limitations with retrospective, observational study designs. Hopefully, the results of this study are intriguing enough to stimulate other research into this condition and its effects.

“Interventional studies are needed to determine if successful treatment of metabolic acidosis can reduce mortality and slow CKD progression.”

AJMC®: Based on the results of this study, what are the next steps? For example, should additional research be done?

Investigators: Interventional studies are needed to determine if successful treatment of metabolic acidosis can reduce mortality and slow CKD progression.¹

AJMC®: Is your team involved in additional research in this area?

Investigators: We have conducted additional analyses using this rich data source, including investigations into the relationship between serum bicarbonate and adverse muscle, bone, and cardiovascular outcomes, and the direct healthcare costs of metabolic acidosis in patients with CKD. •

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