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Impact of Metabolic Acidosis on Clinical Outcomes in Patients with Chronic Kidney Disease

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Renal dietetics professionals routinely evaluate a range of laboratory values to monitor the status of patients with chronic kidney disease (CKD). These include serum albumin, one of a panel of indicators of nutritional status, and serum calcium- phosphorus, which provides information on bone metabolism and disease (1,2).

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines on Nutrition also recommend the monthly evaluation of sodium bicarbonate, a measure of hydrogen ion concentration in the blood (1). Low serum bicarbonate indicates metabolic acidosis and has been linked with adverse clinical outcomes, including negative nitrogen and total body protein balance, worsening secondary hyperparathyroidism and dissolution of bone (3). When metabolic acidosis is corrected, however, protein degradation decreases in patients undergoing maintenance dialysis therapy, and bone histology improves (2,4,5).

This column will review the underlying causes of metabolic acidosis in patients with CKD, summarize its potential adverse effects and discuss treatment recommendations.

Causes of metabolic acidosis in CKD

The human body produces approximately 70 mmol of hydrogen ions daily and maintaining an appropriate acid-base balance depends on equivalent net acid excretion (6). Dietary factors impacting acid-base balance include the protein, chloride, phosphorus, sodium, potassium, calcium and magnesium content of foods; differing absorption rates of these nutrients across the intestine; metabolic generation of sulfate from sulfur-containing amino acids and degree of phosphate dissociation (7).

Changes in the pH of the extracellular fluid (ECF) are prevented by the carbonic acid-bicarbonate buffer system (see Figure 1). When hydrogen ions (H^+) enter the ECF, they interact with bicarbonate ions (HCO3) forming carbonic acid (6).

Healthy kidneys support this buffer system by secreting hydrogen ions into the renal tubular fluid and reabsorbing bicarbonate ions. However, as glomerular filtration rate (GFR) declines in patients with CKD, bicarbonate ions are lost from the proximal tubule and acidosis begins to develop. Increasing severity of CKD is marked by failure to excrete inorganic and organic acids. A large proportion of patients with GFR below 30 mL/min/1.73m^2 (Stage 4 CKD) have acidosis, which progresses to affect most patients undergoing maintenance dialysis therapy (2).

Potential adverse effects of metabolic acidosis in patients with CKD

Studies in animals and humans indicate that CKD increases protein catabolism (8). When body composition and energy expenditure were compared in patients with CKD (mean GFR 23.9 ± 2.6 mL/min/1.73m2) with normal controls matched for age, gender, height and weight, lean body mass and basal energy expenditure was significantly lower in the patients with CKD (9). Since CKD patients were also more acidotic than the control group, acidosis may have contributed to protein catabolism (9,10).

For patients with CKD undergoing maintenance dialysis therapy, continuous ambulatory peritoneal dialysis (CAPD) may offer an advantage over hemodialysis (HD) by providing a continuous supply of buffer. However, in a cross-sectional study examining the relationship between acid-base balance and nutritional status in patients undergoing CAPD, almost 13% had metabolic acidosis (11). When a composite nutritional index (CNI) was

Continued on page 3

Figure 1. Response of the carbonic acid-bicarbonate buffer system to hydrogen ions.

Bicarbonate reserve: Extracellular fluid (ECF):

$NaHCO3 \rightarrow Na^+ + HCO3^- \text{------} > HCO3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$

continued from page 1

computed by grading these patients for clinical, biochemical and anthropometric parameters, mean CNI score was significantly lower in acidotic patients than in patients with normal acid-base balance.

Metabolic acidosis seems to increase muscle protein breakdown by stimulating an energy-dependent proteolytic pathway (12,13). Chronic metabolic acidosis also contributes to derangements in growth hormone sensitivity and thyroid hormone secretion (14). These changes negatively impact protein metabolism and play a significant role in the growth retardation seen in children with CKD (1,14).

Another effect of chronic metabolic acidosis is altered composition of bone tissue. Reduced synthesis of 1,25-dihydroxyvitamin D3 by the proximal kidney tubule in CKD is exacerbated by metabolic acidosis, thereby decreasing calcium absorption from the diet (2). In addition, compromised acid-base balance induces bone dissolution by stimulating bone resorption, inhibiting bone formation and increasing levels of parathyroid hormone (15,16). Thus, metabolic acidosis contributes to osteodystrophy and predisposes patients with CKD to bone fractures.

Following renal transplantation, metabolic acidosis may persist, and buffering of excess hydrogen ions by skeletal elements can lead to abnormalities in calcium-phosphorus balance, disorders of bone metabolism and post-transplant osteoporosis (2).

Recent preliminary studies suggest that metabolic acidosis also plays a part in the hypertriglyceridemia seen in CKD, and that normalization of acid-base balance in these patients may result in a significant decrease in serum triglyceride levels (3,17). The underlying mechanism may involve 1,25-dihydroxyvitamin D3 (18,19).

Clearly, metabolic acidosis in patients with CKD contributes to a wide range of adverse clinical outcomes, and these are summarized in Table 1.

When metabolic acidosis was corrected in nondialyzed elderly patients (ages 73 ± 6 years) with CKD, mean albumin increased significantly from 33.1 ± 2.1 g/L to 37.0 ± 2.5 g/L (20). Normalized protein catabolic rate (nPCR) decreased significantly in these patients, indicating reduced protein breakdown. Patients undergoing maintenance HD also show significantly decreased nPCR when their serum bicarbonate levels improve (21). Other studies on patients with CKD undergoing maintenance dialysis therapy have shown decreased protein breakdown and improved bone histology when metabolic acidosis is treated (2,4,5). The ability to alleviate adverse outcomes justifies an aggressive approach to the correction of metabolic acidosis.

Treatment recommendations for metabolic acidosis in CKD

The NKF-K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure recommend the measurement of serum bicarbonate once monthly in maintenance dialysis patients (1). These guidelines also recommend that pre-dialysis or stable serum bicarbonate levels should be at least 22 mmol/L in both adult and pediatric patients.

Normalization of low serum bicarbonate levels can be achieved in 2 ways. Increasing bicarbonate concentration in hemodialysate above 38 mmol/L is safe, effective and well tolerated (1,21,22). In patients undergoing peritoneal dialysis, serum bicarbonate levels may be raised by providing either higher dialysate bicarbonate or lactate levels (1).

Serum bicarbonate levels can also be increased by providing an oral dose of sodium bicarbonate (1,20). Sodium bicarbonate oral supplementation for adults with CKD usually comprises approximately 2-4 g daily. In children receiving maintenance dialysis therapy, use of high sodium bicarbonate concentrations in dialysate and oral administration of sodium bicarbonate should be individualized to maintain a steady serum bicarbonate level (1).

Summary

The renal dietetics professional can play an important part in managing metabolic acidosis in patients with CKD. Comparing the patient's serum bicarbonate level with the target range, recommending appropriate corrective therapies where indicated, and monitoring patient compliance with prescribed oral bicarbonate supplements are all within the renal dietitian's scope of practice and may alleviate the adverse effects of metabolic acidosis in this population.

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Continued on page 4

Table 1. Potential adverse effects of metabolic acidosis in patients with chronic kidney disease (CKD)

- Increased protein catabolism (8)
- Decreased composite nutritional index (CNI) score in patients on peritoneal dialysis (11)
- Growth retardation in children (1,14)
- Abnormalities in calcium and phosphorus metabolism (2,15,16)
- Worsening secondary hyperparathyroidism (3)
- Renal osteodystrophy (15,16)
- Post-transplant osteoporosis (2)
- Exacerbation of hypertriglyceridemia (3,17)

Impact of Metabolic Acidosis ...

continued from page 3

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