Regulation of Acid-Base Balance in Chronic Kidney Disease
Glenn T. Nagami and L. Lee Hamm

The kidneys play a major role in the regulation of acid-base balance by reabsorbing bicarbonate filtered by the glomeruli and excreting titratable acids and ammonia into the urine. In CKD, with declining kidney function, acid retention and metabolic acidosis occur, but the extent of acid retention depends not only on the degree of kidney impairment but also on the dietary acid load. Acid retention can occur even when the serum bicarbonate level is apparently normal. With reduced kidney function, acid transport processes in the surviving nephrons are augmented but as disease progresses ammonia excretion and, in some individuals, the ability to reabsorb bicarbonate falls, whereas titratable acid excretion is preserved until kidney function is severely impaired. Urinary ammonia levels are used to gauge the renal response to acid loads and are best assessed by direct measurement of urinary ammonia levels rather than by indirect assessments. In individuals with acidosis from CKD, an appropriately low degree of ammonia excretion points to the pathogenic role of impaired urinary acid excretion. The presence of a normal bicarbonate level in CKD complicates the interpretation of the urinary ammonia excretion as such individuals could be in acid-base balance or could be retaining acid without manifesting a low bicarbonate level. At this time, the decision to give bicarbonate supplementation in CKD is reserved for those with a bicarbonate level of 22 mEq/L, but because of potential harm of overtreatment, supplementation should be adjusted to maintain a bicarbonate level of <26 mEq/L.

Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
Key Words: Acid-base equilibrium, Acidosis, Ammonia metabolism, Bicarbonates, Renal insufficiency

THE ROLES OF THE KIDNEY IN MAINTAINING ACID-BASE BALANCE
One of the major functions of the kidney is the regulation of acid-base balance. The need for this regulation stems from acid-base challenges that the body faces on a daily basis. A diet that is rich in animal protein results in the production of acid. Two major processes allow the kidney to maintain acid-base balance: (1) prevention of loss of base from the body by reabsorbing the thousands of milliequivalents of bicarbonate that are filtered daily and (2) generation of new bicarbonate by secreting acid into the final urine through the excretion of titratable acids and by producing and excreting ammonia into the urine.

It has been said that in CKD, the kidney is able to maintain normal serum bicarbonate levels until the glomerular filtration rate (GFR) falls to low levels (lower than ~30 mL/min). In fact, the accumulation of acid in the body is not only dependent on the level of kidney function but also on the acid loads, which may overwhelm the capacity of the failing kidney to compensate and the presence of concurrent factors that preserve or impair acid excretion. In general, earlier degrees of CKD are associated with a mild nonanion gap metabolic acidosis because of preservation of renal phosphate and other anion excretion levels in the setting of reduced ammonia excretion. With late stages of CKD, a high anion gap metabolic acidosis may develop because of the retention of phosphate and other anions (see Fig. 1). It should be pointed out that not all patients with late stage CKD and acidosis have a high anion gap when the anion gap is calculated in a generally accepted way [anion gap = Na⁺ - (Cl⁻ + HCO₃⁻)]. Some individuals having a nonanion gap metabolic acidosis may be underestimated by examining serum bicarbonate concentrations alone. Measurement of tissue levels of acid have revealed that acid accumulation in tissues can occur with milder levels of CKD even before a detectable fall in serum bicarbonate level and, in humans with relatively mild CKD, a bicarbonate load appropriately reduced net acid excretion in individuals with normal estimated glomerular filtration rate but did not alter acid excretion rates in those with mild kidney disease (estimated GFR in the 60 to 90 mL/min/1.73 m² range). The interpretation of the latter study was that individuals with renal impairment retain enough acid so that the administered bicarbonate does not reduce net acid excretion or cause spillover of bicarbonate into the urine. Other recent studies suggest a positive acid balance in many patients with CKD who have a normal plasma HCO₃⁻. Seemingly, this initial chronic acid load may be undetectable with usual methods (eg, plasma HCO₃⁻ or arterial pH). A positive acid balance may be buffered by bone and tissues, surprisingly without affecting plasma HCO₃⁻.

THE DIETARY ACID LOAD
H⁺ and base (bicarbonate) are produced from the hepatic metabolism of ingested food. More than 200 mEq of

From the Nephrology Section 111L, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, Los Angeles, CA; and Tulane University School of Medicine, New Orleans, LA.
Conflict of interest: The authors have no conflict of medicine to declare.
Address correspondence to Glenn T. Nagami, MD, VA Greater Los Angeles Healthcare System, Nephrology Section 111L, 11301 Wilshire Boulevard, Los Angeles, CA 90073. E-mail: Glenn.Nagami@va.gov
Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
1548-5595/836.00
http://dx.doi.org/10.1053/j.ackd.2017.07.004

http://dx.doi.org/10.1053/j.ackd.2017.07.004


274
protons are generated daily from the metabolism of the sulfur-containing amino acids, methionine and cysteine, which are converted to sulfate and H\(^+\) ions, and the cationic amino acids, lysine, arginine, and some histidine residues, which are converted into neutral products and H\(^+\). More than 150 mEq/d of base is also generated from the metabolism of the amino acids, glutamate and aspartate, and organic anions such as citrate, gluconate, malate, acetate, and lactate. An additional 25 to 75 mEq of organic anions (half of which are metabolizable and could yield potential base) are excreted in the urine. Overall, the net endogenous acid production is approximately 50 to 70 mEq/d. Nevertheless, there can be a great variation in the net endogenous acid production that varies among patients with CKD even in studies in which the bicarbonate level was increased to normal levels of GFR (11 to 60 mL/min) or from net endogenous acid production measured in individuals with normal kidney function. When a constant diet is provided, individuals with kidney failure and metabolic acidosis ingesting a diet consisting of a purified formula displayed net endogenous acid production that was not significantly different from healthy individuals with normal kidney function. Others have found that net endogenous acid production markedly varies among patients with CKD who are not on a fixed diet and are not yet on dialysis. A third of individuals with CKD had an acid load <39 mEq/d, a third had an acid load of 39 to 55 mEq/d, and a third had an acid load >55 mEq/d. Thus, although some CKD patients who are not yet on dialysis appear to have normal net endogenous acid production, dietary variations can result in widely varied acid loads, which could affect the interpretation of the net endogenous acid production.

RENEAL BICARBONATE RECLAMATION AND GENERATION

In what ways is acid-base handling different in the kidneys of patients with CKD? Bicarbonate reclamation and generation are the major functions of the kidney that preserve normal acid-base balance in normal kidneys and may become disturbed in disease.

NOMRAL BICARBONATE REABSORPTION

Under dietary conditions that generate acid, the kidney needs to reclaim bicarbonate that is filtered at the glomeruli so that it is not wasted into the urine. With normal levels of GFR (150 to 180 L/d), the filtered load of bicarbonate (GFR × plasma bicarbonate concentration) is about 4000 mEq/d. Under most conditions, the kidney needs to reabsorb the filtered bicarbonate, otherwise the loss of bicarbonate would result in metabolic acidosis. Each of the segments of the nephron contributes to varying extent to bicarbonate reabsorption. The proximal tubule is the major site of bicarbonate reabsorption and normally accounts for 70% to 80% of bicarbonate reabsorption, the thick ascending limb of the loop of Henle for 15% and the collecting duct 5%. Bicarbonate reabsorption in the proximal tubule is mediated by a series of processes involving H\(^+\) secretion into the lumen (mostly via sodium-hydrogen exchange along with H\(^+\)-ATPase-mediated proton secretion), the formation of CO\(_2\) in the presence of luminal carbonic anhydrase (CA II), diffusion of CO\(_2\) into the cell, reconversion of CO\(_2\) to bicarbonate by intracellular carbonic anhydrase (CA IV), and transport of bicarbonate back into the blood via a basolateral sodium bicarbonate cotransporter (NBCe1-a). Several factors can increase bicarbonate reabsorption including acidosis and intracellular acid pH, hypokalemia, hypervolemia, increased bicarbonate delivery with euvolemia, and hormones such as angiotensin II, glucocorticoids, endothelin, and parathyroid hormone.

BICARBONATE REABSORPTION IN CKD

In most patients with CKD, the urine pH is acid (<5.5) but in studies in which the bicarbonate level was increased to normal some subjects spilled bicarbonate into the urine. These findings suggested that diseased kidneys in some individuals have a lower threshold for urinary bicarbonate wasting as can occur in individuals with proximal renal tubular acidosis. It should be noted, however, that when nephrons are lost from disease or surgical removal, the remaining nephrons display higher single nephron GFRs. In other words, each remaining filtering unit filters more plasma. Indeed, in micropuncture studies in rats with reduced renal mass (5/6th nephrectomy), the single nephron GFR was increased so that although the serum bicarbonate concentration was lower in 5/6th nephrectomized rats than in control subjects, the filtered load of bicarbonate per nephron (bicarbonate concentration × single nephron GFR) was higher. By the end of the