Management of the Metabolic Acidosis of Chronic Kidney Disease

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Subjects with CKD and reduced glomerular filtration rate are at risk for chronic metabolic acidosis, and CKD is its most common cause. Untreated metabolic acidosis, even in its mildest forms, is associated with increased mortality and morbidity and should therefore be treated. If reduced glomerular filtration rate or the tubule abnormality causing chronic metabolic acidosis cannot be corrected, it is typically treated with dietary acid (H^+) reduction using Na^+-based alkali, usually $NaHCO_3$. Dietary H^+ reduction can also be accomplished with the addition of base-producing foods such as fruits and vegetables and limiting intake of H^+-producing foods like animal-sourced protein. The optimal dose of Na^+-based alkali that prevents the untoward effects of metabolic acidosis while minimizing adverse effects and the appropriate combination of this traditional therapy with dietary strategies remain to be determined by ongoing studies. Recent emerging evidence supports a phenomenon of H^+ retention, which precedes the development of metabolic acidosis by plasma acid-base parameters, but further studies will be needed to determine how best to identify patients with this phenomenon and whether they too should be treated with dietary H^+ reduction.

Key Words: Acid, Alkali, Bicarbonate, Chronic kidney disease, Diet

INTRODUCTION

Acidosis is a process defined by a net gain of hydrogen ion (H^+) and/or loss of base (usually HCO_3). Its metabolic variety is characterized by an initial decrease in plasma bicarbonate concentration ([HCO_3]) in a setting of a history and physical examination supportive of this diagnosis. As a single (as opposed to being a component of a mixed) acid-base disorder, it is additionally characterized by a decrease in plasma pH (equivalent to an increase in plasma [H^+]) and by a physiological response of increased ventilation reflected by decreased partial pressure of carbon dioxide (P_{CO_2}). Prevalence of metabolic acidosis in CKD increases with decreasing glomerular filtration rate (GFR).[1,2] Despite the daily acid (H^+) challenge from diet and metabolic processes, body buffer systems and the increased per nephron acidification, which occurs in response to a chronic (as opposed to an acute) decline in GFR, can prevent or mitigate the decrease in plasma [HCO_3] that heralds the onset of metabolic acidosis. As GFR chronically declines, some subjects ingesting a high H^+ diet might experience H^+ retention before its manifestation by decreased plasma [HCO_3].[3-5] It follows that over the course of progressive GFR decline, metabolic acidosis is a comparatively late complication of CKD. When defined as plasma [HCO_3] < 22 mEq/L, the level at which current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of metabolic acidosis in CKD,[6] metabolic acidosis was prevalent in 7% of stage 2, 13% of stage 3, and 37% of stage 4 CKD patients.[2]

THE DAILY ACID CHALLENGE

The body defends against acid challenges to acid-base balance by excreting volatile acid (CO_2 gas) through the lungs (about 15,000 mEq/d), by liver metabolism of base-producing food components (like plant-sourced protein) and some organic products of metabolism (eg, lactic acid) to yield HCO_3, and by urine excretion of "fixed" acid (about 50-100 mEq/d) with regeneration of new HCO_3 by the kidney. Diets typical of most developed societies on balance yield net production of H^+ when metabolized[7] because of the greater proportion of animal-sourced protein compared with plant-sourced protein. Net endogenous H^+ production of such diets averages about 1 mEq/kg/body weight/d.[8] Food components that yield H^+ when metabolized are animal protein including dairy products, most grains, and lentils.[9] Dietary sodium chloride (NaCl) also increases net acid production.[10] In contrast, food components that yield base when metabolized include most fruits and vegetables.[9]

Dietary H^+ challenges cause increases in plasma [H^+] with decreases in plasma [HCO_3] but even quantitatively large changes in dietary H^+ yield quantitatively small changes in plasma [H^+]/[HCO_3].[11] In addition, even large changes in dietary H^+ elicit plasma [H^+]/[HCO_3] changes that typically fall within the normal range for each[11] such that plasma [H^+]/[HCO_3] levels often provide little insight as to the magnitude of dietary H^+ or base. These data attest to the effectiveness of body buffers and kidney excretory capacity to maintain plasma [H^+]/[HCO_3] but also highlight the clinician's challenge to gauge dietary H^+ by plasma acid-base parameters. On the other hand, patients with CKD with reduced GFR can have greater increases in [H^+] and greater decreases in [HCO_3] in response to dietary H^+, even developing metabolic acidosis, at levels of dietary H^+ that do not cause metabolic acidosis in patients with higher GFR.[12] Consequently, clinicians are more likely to recognize metabolic acidosis in patients with lower GFR compared with higher GFR.

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When dietary H^+ is increased, the increment of kidney H^+ excretion is often less than the increment in dietary H^+,[13,14] even in individuals with normal GFR, consistent with retention of some of the ingested H^+.[15] Because this apparent H^+ retention is typically accompanied by only minor changes in plasma levels of $[H^+]$ and $[HCO_3]$,[11] much of this retained H^+ apparently titrates non-HCO_3 body buffers[13,14,15] and/or appears in non–plasma fluid compartments,[16] possibly in interstitial fluid.[17] Animal studies support that this purported H^+ retention is greater with reduced GFR compared with normal GFR[18] and some patients with reduced GFR appear to have H^+ retention.[3-5] These data support the existence of a continuum of H^+ stress in which H^+ retention is an earlier and metabolic acidosis is a later manifestation. Even so, early H^+ stress manifest by H^+ retention appears to cause tissue injury, particularly in the setting of reduced GFR.[18]

KIDNEY RESPONSE TO AN ACID CHALLENGE

Subjects with normal nephron mass given a dietary H^+ challenge increase urine net acid excretion (NAE) predominantly through an increment in urine ammonium (NH_4^+) excretion with smaller quantitative contributions from increased titratable acidity and decreased urine excretion of HCO_3.[19] Similarly, animals challenged with dietary H^+ increase urine NAE predominantly through increased urine NH_4^+ excretion,[16] which is associated with augmented distal nephron acidification.[20] Consequently, augmented distal nephron acidification with increased urine NH_4^+ excretion contributes importantly to the kidney response to dietary H^+.

Although metabolic acidosis is uncommon in early stage CKD, individuals with reduced GFR might nevertheless have H^+ retention when eating the high H^+-producing diets of developed societies.[3-5] With further GFR decline, patients with CKD typically develop a non–anion gap metabolic acidosis, which transitions to the anion gap variety as GFR nears levels at which kidney replacement therapy must be considered.[21] Even so, most patients with CKD with reduced GFR can effect steady-state H^+ excretion sufficient to avoid progressive metabolic acidosis while eating diets typical of developed societies.[13,22] More advanced GFR reduction in patients with CKD, however, is associated with reduced urine NH_4^+ excretion,[5] which likely contributes to their underlying H^+ retention and/or metabolic acidosis. These data suggest the need for further studies to better determine whether some patients with reduced GFR but without metabolic acidosis are nevertheless candidates for dietary H^+ reduction.

Experimental CKD models with GFR reduction low enough to be associated with metabolic acidosis[23] and those with less severe GFR reduction such that animals have H^+ retention without metabolic acidosis[24-27] can each achieve steady-state H^+ excretion sufficient to avoid progressive metabolic acidosis or progressive H^+ retention. This augmented acidification is accomplished in part by increased distal nephron acidification and increased urine NH_4^+ excretion. Augmented distal nephron acidification in these experimental CKD models is mediated by increased kidney levels of angiotensin II, endothelin, and aldosterone,[23,25,26] substances that also contribute to progressive GFR decline.[25,27] These data suggest that increased kidney levels of angiotensin II, endothelin, and aldosterone mediate the physiological, short-term benefit of increased urine H^+ excretion in response to an H^+ challenge yet, when the acid challenged is sustained, these substances also mediate the pathophysiological, long-term detriment of enhanced stages of kidney disease progression.

KIDNEY-RELATED CAUSES OF CHRONIC METABOLIC ACIDOSES FOR WHICH TREATMENT SHOULD BE CONSIDERED

Because of its untoward consequences including disturbed bone[14] and muscle[28] metabolism, possible exacerbation of stages of kidney disease progression[29-31] and increased mortality,[32] chronic metabolic acidosis, even when mild, should be treated.

CLINICAL SUMMARY

- Metabolic acidosis, even when mild, should be treated with dietary acid reduction to reduce its untoward consequences.
- Dietary acid reduction might be accomplished by: prescribing sodium-based alkali, adding base-producing food components, limiting acid-producing food components, or though a combination of these strategies.

RENAL TUBULAR ACIDOSES

Proximal Renal Tubular Acidosis

Patients with proximal renal tubular acidosis (PRTA) have defective proximal tubular HCO_3 reabsorption with excess terminal nephron HCO_3 delivery that overwhelms capacity of the distal nephron to completely reabsorb the high HCO_3 delivered load. Because urine NAE = urine NH_4^+ + urine titratable acidity − urine HCO_3, excess urine HCO_3 excretion reduces urine NAE. These patients reach a steady state of chronically low plasma $[HCO_3]$ at which the defective proximal tubule more completely reabsorbs the lower HCO_3 filtered load into the nephron (because of lower plasma $[HCO_3]$). This lower HCO_3 delivery to the terminal nephron allows the functionally intact distal nephron to effectively excrete NH_4^+ and titratable acidity without excess urine HCO_3 excretion. This steady-state scenario allows the kidney to maintain net acid balance, that is, match dietary H^+ intake with H^+ excretion. The steady-state price paid is that these patients have chronic metabolic acidosis manifest by low serum $[HCO_3]$ with a physiological response to decrease P_{CO_2}.

The most concerning consequence of the chronic metabolic acidosis of PRTA is the inhibited bone growth in children.[33] Chronic metabolic acidosis is also associated with