Adverse Effects of the Metabolic Acidosis of Chronic Kidney Disease

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The kidney has the principal role in the maintenance of acid-base balance, and therefore, a fall in renal net acid excretion and positive H^+ balance often leading to reduced serum [HCO_3^-] are observed in the course of CKD. This metabolic acidosis can be associated with muscle wasting, development or exacerbation of bone disease, hypoalbuminemia, increased inflammation, progression of CKD, protein malnutrition, alterations in insulin, leptin, and growth hormone, and increased mortality. Importantly, some of the adverse effects can be observed even in the absence of overt hypobicarbonatemia. Administration of base decreases muscle wasting, improves bone disease, restores responsiveness to insulin, slows progression of CKD, and possibly reduces mortality. Base is recommended when serum [HCO_3^-] is <22 mEq/L, but the target serum [HCO_3^-] remains unclear. Evidence that increments of serum [HCO_3^-] >26 mEq/L might be associated with worsening of cardiovascular disease adds complexity to treatment decisions. Further study of the mechanisms through which positive H^+ balance in CKD contributes to its various adverse effects and the pathways involved in mediating the benefits and complications of base therapy is warranted.

Keywords: Metabolic acidosis, CKD, Bicarbonate, Bone disease, Progression of chronic kidney disease, Muscle wasting

INTRODUCTION

The most common cause of chronic metabolic acidosis is CKD.[1] This form of metabolic acidosis develops as net acid excretion falls below net endogenous acid production causing acid retention. The retained acid appears to accumulate in interstitial and intracellular compartments of various tissues increasing their acidity; when sufficiently large, it also causes a detectable fall in serum [HCO_3^-] and systemic pH.[2] The phase when acid retention is present in the absence of a detectable fall in serum [HCO_3^-] has been termed subclinical or eubicarbonatemic metabolic acidosis. Importantly, even subclinical metabolic acidosis can impair the function of several organ systems.[1]

In the present review, we describe the nature of the cellular dysfunction engendered by the metabolic acidosis of CKD, its pathogenesis, and the impact of base treatment.

CELLULAR DYSFUNCTION

Although the cellular dysfunction caused by the metabolic acidosis of CKD is similar to that found with other chronic acidoses, CKD itself can potentially modify the cellular response to acidosis. For example, CKD is associated with abnormalities of parathyroid hormone (PTH) and insulin secretion, which will impact changes in these hormones driven by metabolic acidosis.[1]

The adverse effects of cellular function can take time to appear even if factors responsible for initiating damage are present soon after induction of metabolic acidosis. For example, processes promoting bone dissolution are activated promptly although overt bone disease might not be detectable for months or years.[3] Also, factors that can injure the kidney, such as increments of pro-inflammatory cytokines, are present early,[4] but fibrosis and a permanent reduction in glomerular filtration rate take time to occur.

The metabolic acidosis of CKD is associated with dysfunction of several organ systems as described subsequently.

Muscle Wasting

A loss of muscle mass or sarcopenia in CKD contributes to adoption of a sedentary lifestyle and increased mortality.[5] Sarcopenia is found at all stages of CKD, but its prevalence increases as GFR falls.[6,7] Thus, in the third National Health and Nutrition Examination Survey (NHANES III), the percentage of individuals with a normal skeletal mass index fell from 61% at a GFR of 60 to 89 mL/min/1.73 m^2 to 39.9% at a GFR <60 mL/min/1.73 m^2.[7] Metabolic acidosis has been implicated as an important factor contributing to the reduced muscle mass.[8,9] The NHANES III data revealed that individuals with a serum [HCO_3^-] <23 mEq/L had slower gait speed and decreased quadriceps strength[10] and young adults with lower serum [HCO_3^-] had lower cardiorespiratory fitness.[11]

Furthermore, administration of base to pre-dialysis patients with CKD or those with ESRD treated with chronic hemodialysis or peritoneal dialysis increased lean body mass, improved muscle strength, improved dietary protein intake, reduced protein catabolic rate, and increased serum albumin levels.[12-15]

Muscle wasting is characterized by increased muscle turnover rate and atrophy of type II muscle fibers. It is associated with increased muscle protein degradation without a change in muscle protein synthesis.[16-18] The mechanisms underlying muscle wasting are summarized in Figure 1. The degradation of muscle protein appears to be mediated by upregulation of the ubiquitin-proteasome pathway[19] and the caspase-3 protease.[20]

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Impaired insulin-like growth factor 1 (IGF-1) signaling,[20] increased levels of glucocorticoids,[21,22] and increased inflammation are considered important in activation of the ubiquitin-proteasome pathway.[23]

A reduction in systemic or intracellular pH contributes to increased glucocorticoid secretion, but a reduction in interstitial pH seems to be integral to muscle wasting.[20,24] Indeed, H^+ retention in paraspinal muscles has been observed via microdialysis in rats with CKD and a presumed reduction in interstitial pH even in the absence of a detectable fall in serum [HCO_3^-].[25,26] Also, administration of base to postmenopausal women with a normal serum [HCO_3^-] reduces urinary nitrogen excretion consistent with less muscle protein breakdown.[27] These findings suggest that accumulation of acid in interstitial compartments before a fall in serum [HCO_3^-] can induce muscle damage.

Hypoalbuminemia

Decreased albumin synthesis has been found with metabolic acidosis induced by 7, but not 2, days of NH_4Cl feeding.[28,29] The explanation for the divergent results is not clear, but since the metabolic acidosis of CKD is months to years in duration, the findings in patients with more prolonged acidosis seem more relevant.

Analysis of the NHANES III data in patients with CKD revealed that a serum [HCO_3^-] <22 mEq/L was associated with hypoalbuminemia (adjusted odds ratio of 1.54).[30] Also, administration of base to individuals with CKD (creatinine clearance 15-30 mL/min/1.73 m^2) and metabolic acidosis (serum [HCO_3^-] 16-20 mEq/L) led to an increase in serum albumin and lean body mass.[12] Thus, although proteinuria and inflammation (which enhances proteolysis and increases anorexia) are major contributors to hypoalbuminemia in CKD, improvement in acid-base balance will aid in optimizing albumin synthesis.

Bone Disease

Bone disease in patients with CKD is primarily attributed to abnormalities of vitamin D metabolism and excess PTH secretion,[31] but metabolic acidosis can also induce or exacerbate bone disease.[3,31,32]

Animal studies showed a correlation between metabolic acidosis induced by NH_4Cl and development of osteoporosis and osteomalacia.[33,34] In humans, approximately 20% of patients with distal renal tubular acidosis (RTA) develop osteomalacia.[35] A retrospective examination of acid-base parameters in patients with CKD revealed that those with a normal bone biopsy had a serum [HCO_3^-] close to normal (24-26 mEq/L), whereas those with bone disease had mild-to-moderate acidosis.[36] Chronic hemodialysis patients with a pre-dialysis serum [HCO_3^-] <21 mEq/L had a higher incidence of bone fractures,[37] suggesting that the metabolic acidosis contributes to brittleness of bone. Correction of metabolic acidosis results in healing of bone lesions in patients with distal RTA[35] and prevention of progression of kidney osteodystrophy in hemodialysis patients.[38]

Subclinical metabolic acidosis might also have injurious effects on bone. Feeding of an acid-producing diet to two-third nephrectomized rats is associated with bone injury (as shown by an increase in urine deoxypyridinoline excretion) in the absence of a reduction in serum [HCO_3^-].[39] Also, administration of base to postmenopausal women with a normal serum [HCO_3^-] was associated with biochemical evidence of bone accretion.[40]

The mechanisms underlying the adverse effect of metabolic acidosis on bone are summarized in Figure 2. *In vitro* studies showed that an acidic milieu causes dissolution of bone mineral directly, activates osteoclasts, and inhibits osteoblast function.[3,41,42] These effects have been linked to activation of the ovarian cancer G-protein-coupled receptor 1 (OGR-1)[43] and the transient receptor potential cation channel subfamily V member 1 (TRPV1),[44] 2 proton-sensing receptors or channels.

In animal studies, metabolic acidosis is associated with increased PTH secretion but blunting of the cAMP response to PTH.[45] A reduced concentration of 1,25-dihydroxyvitamin D caused by acidosis is an attractive inciting event, but serum concentrations of 1,25-dihydroxyvitamin D measured in humans with acidosis have not been consistently decreased.[35,46]

Fibroblast growth factor 23 (FGF23) induces phosphaturia, reduces systemic 1,25-dihydroxyvitamin D production, and inhibits PTH secretion.[47] In vitro studies showed metabolic acidosis increases the FGF23 concentration and RNA expression in mouse bone,[48] yet correction of metabolic acidosis in humans with CKD increases serum FG23 concentration.[47] Thus, a possible role of FG23 in the development of bone disease associated with metabolic acidosis remains to be clarified.

Children with distal RTA had a lower mean height and greater incidence of short stature than normal controls[49]

CLINICAL SUMMARY

- The metabolic acidosis of chronic kidney disease can produce or worsen bone disease, contribute to progression of chronic kidney disease, produce muscle wasting, induce inflammation, contribute to protein malnutrition and development of hypoalbuminemia, and increase mortality.
- Some of these adverse effects, particularly progression of chronic kidney disease, muscle wasting, and exacerbation of bone disease, can be observed even in the absence of hypobicarbonatemia.
- Retention of acid in the interstitial tissues leading to an increase in the acidity of this compartment is a major factor in the progression of chronic kidney disease and perhaps other adverse effects.
- Administration of base decreases muscle wasting, improves bone disease and augments growth in children, and slows progression of chronic kidney disease.