

Treatment of Acidosis in CKD

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Metabolic acidosis (MA) in advanced CKD results from a progressive reduction in the capacity of the kidneys to generate sufficient ammonia to excrete the daily production of hydrogen ions (equivalent to approximately 1 mmol/kg body weight) leading to the formation of a new steady state at the cost of a reduction in blood pH.

MA is a relatively common complication in patients with advanced CKD, particularly when GFR falls below 30 ml/min (1). MA adversely affects protein and muscle metabolism and bone turnover, compounding the mineral-bone disorder of uremia. In addition, MA is also associated with increased inflammatory mediators, insulin resistance, and corticosteroid and parathyroid hormone production. This may result in growth restriction in children, loss of bone and muscle mass, negative nitrogen balance, and possibly an accelerated decline in renal function (2).

Currently, there is good experimental but limited clinical evidence that MA contributes to protein energy wasting (PEW) in CKD patients (3). Several clinical trials in patients with ESRD, albeit of small size and limited follow-up, have demonstrated a benefit from the correction of acidosis on serum albumin and prealbumin levels, a reduction in the normalized protein catabolic rate (4–6), as well as an increase in the concentrations of branched chain and total essential amino acids (7,8).

The evidence supporting a role for MA in the progression of CKD is less convincing. Some preclinical studies have indicated that the MA is associated with a worsening of proteinuria, tubulointerstitial fibrosis, and a more rapid decline in renal function (9–12). However, other studies in rodents have been unable to reproduce these detrimental effects (13). Furthermore, in rodents with CKD receiving a high-phosphate diet, MA actually reduced the rate of progression of renal failure. This unusual but interesting finding was attributed to the inhibition of calcium phosphate deposition in the kidney (14).

Few studies have examined the effects of correction of MA on renal function in humans. Lyon *et al.* (15), in a seminal study from 1931, treated 17 patients with moderate renal failure with both low-acid diets and sufficient oral supplementation with sodium bicarbonate and potassium citrate to maintain an alkaline urine pH for weeks to months. This observation was instrumental in propagating the idea that reducing acid burden on the kidney may stabilize or temporarily improve renal function.

Recently, a randomized controlled clinical trial to examine the effect of administering oral sodium bicarbonate on progression of CKD in patients with nondialysis-dependent CKD was reported (16). In this study, the researchers randomized 134 patients with CKD and a mean creatinine clearance (CrCl) of around 20 ml/min to standard patient care plus administration of oral sodium bicarbonate titrated to reach a serum bicarbonate level of >23 mmol/L. After 2 years, the rate of CrCl decline was significantly lower in the bicarbonate-treated group compared with controls, despite similar BP and proteinuria, suggesting that this inexpensive and readily available intervention could potentially be beneficial for patients with nondialysis-dependent CKD. In addition, improvements in anthropometric measurements, protein intake, potassium levels, and other biochemical markers of nutritional status were seen in patients who received bicarbonate supplementation. In light of the known association of various markers of PEW with mortality in patients with both moderate and advanced CKD, this finding raises the hope that the administration of sodium bicarbonate might also increase survival.

More recently, a 5-year prospective, randomized, placebo-controlled blinded interventional study tested if daily oral sodium bicarbonate slowed GFR decline in patients with hypertensive nephropathy with reduced but relatively preserved estimated GFR (eGFR) (mean 75 ml/min per 1.73 m²). Participants matched for age, ethnicity, albuminuria, and eGFR received either daily placebo (*n*=40), equimolar sodium chloride (*n*=40), or sodium bicarbonate (*n*=40) while being maintained on their antihypertensive regimens (including angiotensin-converting enzyme [ACE] inhibition) treated to conventional BP targets. In keeping with their relatively preserved renal function, participants were not acidotic at enrollment with a mean total CO₂ in ≥26 mmol/L. After 5 years, the rate of eGFR decline, estimated using plasma cystatin C, was slower and eGFR significantly higher in patients receiving sodium bicarbonate (baseline cysGFR [in ml/min per 1.73 m²], 73.2; after 5 years, 66.4) than in those given placebo (baseline, 73.5; after 5 years, 60.8) or sodium chloride (baseline, 73.5; after 5 years, 62.7). This interesting study calls for use of sodium bicarbonate in patients with early CKD even in the absence of overt acidosis (17).

However, concerns regarding the potential to increase the sodium load with the widespread use of sodium bicarbonate and the adverse consequences that

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this may have persist within the renal community. In this issue of *CJASN*, Goraya *et al.* (18) tested the hypothesis that base-inducing fruits and vegetables would have an equivalent effect to correction of acidosis with oral sodium bicarbonate and result in a similar beneficial effect on the rate of decline in renal function in patients with hypertension-associated kidney disease, high urine protein excretion, and moderate MA with total plasma carbon dioxide (PTCO₂) levels of 22–24 mmol/L. Participants received antihypertensive therapy with ACE inhibitors to a target of <130/80 mmHg. Their dietary acid consumption was assessed using food diaries and net urinary acid excretion.

Patients were randomly assigned to receive fruits and vegetables (F+V group) that reduce the potential renal acid load by 50% ($n=36$) or to receive oral NaHCO₃ at 1 mEq/kg body weight per day to reduce it by the same amount ($n=35$). The study supplied fruits and vegetables sufficient to feed all family members of patients randomized to the F+V group. Relevant clinical measurements were taken at study entry and at 1 year.

Plasma cystatin C–calculated eGFR did not differ between baseline and 1 year or between groups. One-year PTCO₂ was higher than baseline in both the NaHCO₃ (21.2 ± 1.3 versus 19.5 ± 1.5 mM; $P<0.01$) and F+V (19.9 ± 1.7 versus 19.3 ± 1.9 mM; $P<0.01$) groups, consistent with improved MA, and was higher in the NaHCO₃ group than in the F+V group ($P<0.001$). One-year urine indices of kidney injury were lower than baseline in both groups. Plasma [K⁺] did not increase in either group. The investigators concluded that 1 year of F+V group or NaHCO₃ in individuals with stage 4 CKD yielded eGFR that was not different, was associated with higher-than-baseline PTCO₂, and with lower-than-baseline urine indices of kidney injury. They claimed that their data support that F+V improve MA and reduce kidney injury in stage 4 CKD and can do so without producing hyperkalemia.

The results of this study are very interesting. However, a number of points are worthy of remark. The size, duration, and absence of an untreated control group are the main limitations of this study. Moreover, a high proportion of contemporary CKD patients receiving angiotensin blockade have potassium levels >4.6 mEq/L. Such patients were excluded from this study, which therefore limits its generalizability. In addition, patients with advanced CKD are predisposed to AKI, which may unmask a relatively high dietary potassium load manifest as hyperkalemia during these acute episodes. The results of this small but interesting study should be interpreted with caution. This study is likely to have a limited effect on clinical practice. A small group of highly motivated patients wishing to reduce their pill burden through dietary modification may benefit from the results of this study. However, many patients find it difficult to follow a diet high in fruits and vegetables and might therefore be more adherent to a supplement. The efficacy of correcting MA on the progression of CKD remains to be definitively established; a large, multicenter, randomized controlled trial examining the effect of supplemental bicarbonate, with and without dietary intervention, in moderately severe CKD is urgently needed.

Disclosures

None.

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See related article, “A Comparison of Treating Metabolic Acidosis in CKD Stage 4 Hypertensive Kidney Disease with Fruits and Vegetables or Sodium Bicarbonate,” on pages 371–381.