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## A basic approach to CKD

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**Metabolic acidosis often complicates chronic kidney disease (CKD) and adversely affects bone, nutrition, and metabolism. Phisitkul *et al.* demonstrate that sodium citrate may ameliorate kidney injury in CKD patients not on dialysis. Further, they provide evidence in humans that treatment lowers urinary endothelin levels, and hence increased endothelin may be part of the mechanism whereby acidosis hastens CKD progression.**

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Metabolic acidosis commonly complicates chronic kidney disease (CKD) and has adverse effects on bone, nutrition, and metabolism. For patients treated with dialysis, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend maintaining serum bicarbonate levels  $\geq 22$  mM to help prevent these complications.<sup>1</sup> Phisitkul *et al.*<sup>2</sup> (this issue) now demonstrate that sodium citrate (as an alkalinizing agent) may ameliorate kidney injury in CKD patients not on dialysis. Further, they provide evidence in humans that bicarbonate lowers urinary endothelin levels, and hence increased endothelin may be part of the mechanism whereby acidosis hastens CKD progression.

Metabolic acidosis is a predictable accompaniment of CKD.<sup>3</sup> Adaptations in kidney acid excretion may initially prevent a fall in serum bicarbonate levels, but as glomerular filtration rate (GFR) declines to the 20- to 40-ml/min range, metabolic acidosis commonly develops. Initially this acidosis is typically a hyperchloremic variety, but in later stages of CKD it may be a high-anion-gap acidosis. Hydrogen ion excretion is relatively intact, so urine pH generally remains appropriately low.

When factored for GFR, titratable acid excretion is augmented. However, the ability to excrete more phosphate during acidosis is limited, so adaptation in titratable acidic excretion is limited. As in all metabolic acidoses, the major adaptation to net urinary acid excretion is an increase in ammonium excretion. In metabolic acidosis, ammonium excretion may increase manyfold; in CKD, when factored for GFR, ammonium excretion is augmented. However, even when factored for GFR, ammonium excretion in CKD is lower than is seen in metabolic acidosis of other etiologies. In absolute terms, total urinary ammonium excretion is markedly impaired. Several mechanisms contribute to the failure of ammonium excretion to keep pace with the decline in GFR. Proximal tubule ammoniogenesis is increased but may be insufficient because of a decline in total nephron mass and possibly because of a defect in glutamine uptake (the major source of renal ammonium). Furthermore, ammonium produced in the proximal tubule may not be transported into the collecting duct, predominantly because of a decrease in interstitial ammonium concentration (see below). Whether other mechanisms exist to limit ammonium excretion is unknown, but some data suggest that the specific ammonia transporter Rhcg does increase in the 5/6 nephrectomy model of reduced renal mass.<sup>4</sup>

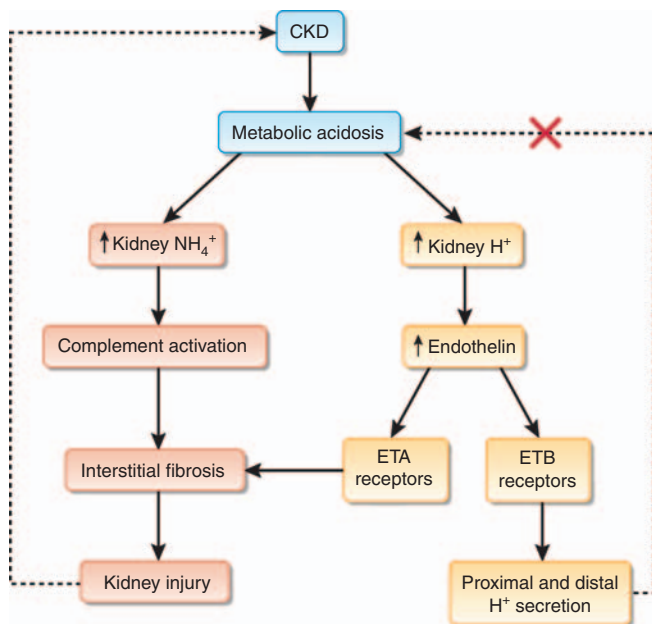
A few previous studies have suggested that alkali therapy slows progression of CKD. In 1985, Nath *et al.* reported that

correction of metabolic acidosis in the rat remnant kidney model ameliorates the decline in renal function.<sup>5</sup> Tubulointerstitial injury is a powerful predictor of progression in kidney failure, and the study by Nath *et al.* showed that bicarbonate treatment led to less severe interstitial injury and higher GFRs. Nath *et al.* presented data in support of the postulation that increased ammonia levels in the kidney led to increased complement cleavage, which in turn mediated tubulointerstitial injury. Although complement cleavage may well play an important role in progression of kidney failure, it was not convincingly shown to be paramount. Notably, in the same rat remnant kidney model, ammonia levels in the cortex are about twice those of controls, but levels in the medulla are actually lower.<sup>6</sup> Also, some subsequent experimental studies failed to support the beneficial effects of alkali on progression of renal disease.

In more recent years, our understanding of the mechanisms of progression of CKD has markedly expanded. However, few laboratories have addressed how bicarbonate might ameliorate CKD progression. But Wesson's group has explored the effects of acidosis on endothelin and the subsequent effects on kidney injury.<sup>7–9</sup> Studies in rats showed that dietary protein via acid production induces endothelin production.<sup>8</sup> Endothelin stimulated collecting duct acid secretion via endothelin B receptors and tubulointerstitial injury via endothelin A receptors<sup>7,8</sup> (Figure 1). Bicarbonate ameliorated the injury induced by protein.<sup>7</sup> Wesson's group further showed that dietary protein induced a lower cortical interstitial pH and, by manipulating the diet, showed that injury correlated with pH.<sup>9</sup> Other laboratories have demonstrated that endothelin mediates in part the response of the proximal tubule to acidosis (see, for example, Laghmani *et al.*<sup>10</sup>). Clinical studies examining the mechanisms of the effects of correction of acidosis have been even more limited. Thus, the observation by Phisitkul *et al.*<sup>2</sup> (this issue) that sodium citrate may exert a beneficial effect on endothelin-mediated progression is important. The clinical studies by Phisitkul *et al.*<sup>2</sup> also demonstrated a decrease in *N*-acetyl- $\beta$ -

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**Figure 1 | Mechanisms linking acidosis and CKD.** CKD leads to metabolic acidosis, which may promote interstitial fibrosis due to adaptations in ammonia handling. Additionally, the acidic milieu may stimulate endothelin (ET) production, which may promote interstitial fibrosis. However, endothelin may have a salutatory effect of promoting acid secretion, which would ameliorate the acidosis (X). Bicarbonate therapy would directly ameliorate the acidosis (X). ETA, endothelin A; ETB, endothelin B.

D-glucosaminidase, a marker of tubulointerstitial injury, urinary albumin, and urinary transforming growth factor- $\beta$ 1. Additional effects of bicarbonate or citrate may yet be identified.

The study by Phisitkul *et al.*<sup>2</sup> also shows that over a 2-year period, treatment with sodium citrate (equivalent to sodium bicarbonate but more palatable) slowed progression of CKD to severe CKD. (The effects on serum creatinine and estimated GFR were not statistically significant with citrate therapy, but other measures of kidney disease progression were significant.) This study addressed only patients with CKD presumably secondary to hypertension. A similar recent study in a larger group of patients with more varied etiology and more severe initial disease by de Brito-Ashurst *et al.*<sup>11</sup> showed a beneficial effect of sodium bicarbonate on progression of CKD. The latter study also showed a beneficial effect of sodium bicarbonate on nutritional parameters. Both recent clinical studies were remarkably similar in the effects of alkali treatment on progression of CKD. In both studies there was a group of control patients, representing 25–45% of the controls, who had a dramatic decline in kidney function over 12–30 months. In

both studies, bicarbonate treatment decreased this number by about 80%. Thus, this simple maneuver had powerful effects particularly in a subset of patients.

A potential concern regarding treatment of patients with CKD with sodium bicarbonate or sodium citrate is the possible increase in extracellular fluid volume and hypertension. Such concerns were addressed more than 30 years ago by Husted *et al.*<sup>12</sup> They examined patients with advanced CKD with average GFRs of about 10 ml/min. Patients were placed on an extremely low-sodium diet of 10 mequiv. per day and supplemented with either sodium chloride or sodium bicarbonate. Sodium chloride but not sodium bicarbonate produced an increase in weight and blood pressure. The two recent clinical studies<sup>2,11</sup> suggest that sodium bicarbonate or citrate supplementation is indeed safe even when added to a more normal-sodium diet; blood pressures, clinical edema, and heart failure were not worsened by sodium alkali supplementation. The amount of sodium citrate prescribed in the study by Phisitkul *et al.*<sup>2</sup> was 1 mequiv./kg/d. This amount of bicarbonate would be sufficient to neutralize the entire acid load present in the usual Western diet. It seems likely that the

amount of citrate ingested was less than prescribed (as judged by the reduction in net acid excretion). The amount of sodium bicarbonate used by Brito-Ashurst *et al.*<sup>11</sup> was 1800 mg in divided doses (about 21 mequiv.), titrated up as needed to normalize plasma bicarbonate; the amount actually used averaged 1820 mg/d. Thus, it appears that relatively modest doses of alkali are sufficient to exert a beneficial effect. Theoretical concerns about possible detrimental effects of alkali on calcium phosphate deposition in the kidney have not been borne out in these clinical studies. Another theoretical aspect that may not be clinically significant, and which could be addressed in future studies, is that citrate (and not bicarbonate) has been shown to increase aluminum absorption in the gastrointestinal tract.<sup>13</sup>

Thus, alkali supplementation as bicarbonate or citrate appears to be a promising and inexpensive approach to retarding progression of renal insufficiency and improving nutritional status. Several unanswered questions remain. Will the results hold up to larger blinded studies in patients with diverse causes of kidney disease? What is the level of acidosis or plasma bicarbonate that warrants treatment? If patients are not acidotic, will sodium bicarbonate or citrate be effective and safe? What amount of sodium bicarbonate is actually needed to see the beneficial effect? Finally, further studies on mechanisms are needed. In the era of cost-benefit analysis, alkali supplementation appears to be a promising low-cost, high-benefit adjunct treatment for patients with CKD.

#### DISCLOSURE

The authors declared no competing interests.

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## Sugar-sweetened beverages and chronic disease

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**Sugar-sweetened beverages, a major source of fructose, raise serum uric acid levels and are associated with an increased risk of gout, hypertension, and diabetes. However, it is unclear whether the associations with hypertension and diabetes are caused by fructose *per se*, or through some other mechanism. Nevertheless, given their demonstrated adverse health associations and the lack of any health benefit, the evidence favors minimization of sugar-sweetened beverage intake.**

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It is certain that a higher serum uric acid level increases the risk of gout. Many dietary factors raise the serum uric acid level, such as alcohol, seafood, and meat, whereas dairy intake reduces it. There is now substantial evidence that higher fructose intake also increases the serum uric acid level and increases the risk of gout.<sup>1,2</sup> However, it is unclear whether fructose, the predominant sweetener in sugar-sweetened beverages such as sodas, has other important health consequences.

Much of the debate around the role of fructose involves the potential impact of serum uric acid on blood pressure. A higher serum uric acid level is associated with an increased risk of hypertension in younger individuals, but it is unclear whether the uric acid is causal or simply a marker. There are persuasive animal data about the potential harmful effect of uric acid on vascular function and blood pressure, but the importance in humans remains to be determined. In fact, several lines of evidence suggest that uric acid may be only a marker for hypertension risk in humans. For example, reducing uric acid levels in humans either with recombinant uricase or with probenecid does not improve vascular function, in contrast to animal studies.<sup>3,4</sup> Furthermore, the prospective association between fructose

intake and gout and that between fructose intake and hypertension are greatly dissimilar (Figure 1). This was demonstrated by the strong association between fructose intake and risk of gout in a large male cohort. However, a prospective study in this same male cohort and two large female cohorts, involving more than 200,000 individuals and over 57,000 incident cases of hypertension, found no association between fructose intake and risk of incident hypertension.<sup>5</sup> In addition, a significant association between soda consumption and hypertension was found for both sugar-sweetened and artificially sweetened beverages,<sup>6</sup> suggesting a mechanism not related to the sweetener. Thus, at present, it does not seem likely that fructose intake influences the risk of hypertension in humans.

The inverse cross-sectional relation between serum uric acid and renal function has been known for decades, but recent studies also suggest that higher uric acid levels may predict the subsequent loss of renal function, though not necessarily with chronic kidney disease.<sup>7</sup> Although animal data suggest a potential causal relation, the human data to date support only a possible association.

Bombback and colleagues<sup>8</sup> (this issue) now report on a study examining the relation between sugar-sweetened soda consumption and hyperuricemia and chronic kidney disease (CKD). They believed that hyperuricemia was ‘a causal intermediate in the association of sugar-sweetened soda consumption and CKD,’ so they analyzed these outcomes separately. They used the well-known and high-quality Atherosclerosis Risk in Communities study (ARIC), involving more than 15,000 white and black adults in the United States. As expected, the baseline cross-sectional study found that individuals with higher sugar-sweetened soda consumption were significantly more likely to meet the criteria for hyperuricemia. The findings are consistent with previous reports, including those from the National Health and Nutrition Examination Survey (NHANES).<sup>2</sup> Bombback *et al.*<sup>8</sup> also found a marginal association between higher soda consumption and prevalent CKD (estimated glomerular filtration rate < 60 ml/min per 1.73 m<sup>2</sup>). However, in the longitudinal

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