

The Role of Bicarbonate in CKD: Evidence Bulks Up

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The metabolic acidosis that commonly accompanies CKD may be the result of several processes. These include decreased nephron mass with decreased ammonia production, decreased proton secretion, and hyperkalemia which suppresses ammoniogenesis; ultimately, all of these involve the production and trapping of ammonia (1). Metabolic acidosis often occurs early in CKD and leads to non-anion gap metabolic acidosis before the accumulation of organic anions that leads to the high anion gap-type acidosis seen in advanced CKD. The general approach to the treatment of this problem has evolved over the years and continues to evolve. For example, textbooks from the 1990s suggested that serum bicarbonate be kept >20 mmol/L to help alleviate the accompanying bone disease. Bone and mineral guidelines from a decade ago and to the present with Kidney Disease Improving Global Outcomes (KDIGO) have suggested that the HCO_3^- be kept at ≥ 22 mmol/L (2). In the past, the concern was primarily about the potential adverse effects on bone, including dissolution of bone to buffer the acid. However, it has also been recognized for many years that muscle and protein catabolism is increased by metabolic acidosis (3). The more recent CKD guidelines also point to evidence showing that acidosis also leads to inflammation, impaired glucose tolerance, cardiac dysfunction, and increased mortality (2). But perhaps most exciting, several studies have suggested that administration of bicarbonate (or other alkali) may slow progression of CKD, presumably by amelioration of acidosis, whether clinically apparent or not.

Although there are much older suggestions that alkali therapy could be beneficial in kidney disease, modern attention to the possibility that correction of metabolic acidosis might slow the progression of CKD was rekindled by studies by Nath *et al.* (4). They showed that correction of acidosis in a rat model of progressive CKD slowed the decline in glomerular filtration rate (4). This was postulated to be secondary to the amelioration of the high ammonia concentrations in the medulla that were compensating for the metabolic acidosis. These authors suggested that complement activation was involved; additional evidence in this direction has since accumulated (5). Multiple other mechanisms, including those involving angiotensin II and aldosterone, are probably involved as well (6). Wesson *et al.* have shown that endothelin levels are increased (7,8). Other studies have suggested that tubule fluid pH may be an important factor in promoting

tubule injury in the presence of proteinuria, with alkalinization, at least *in vitro*, ameliorating tubule cell injury (9). Compensations in CKD, including ammoniogenesis and increased endothelin production, may occur early and before an actual decrease in serum bicarbonate level. In fact, both animal and human studies suggest that subclinical acidosis (an acid state within the kidneys) may be present in CKD even without a low plasma bicarbonate or clinically apparent acidosis and may be associated with detrimental increases in aldosterone and endothelin (10,11).

From a clinical treatment perspective, at this point several studies in the last few years have suggested that the administration of sodium bicarbonate (or other alkali sources, such as citrate or fruits and vegetables) in patients with CKD, even with minimally decreased or even normal serum bicarbonate concentrations, may slow progression (8,12–15). Although all of these studies have been relatively small, they all point to a beneficial effect of alkali administration on progression of CKD. A systematic review concluded that the studies were suggestive but not definitive for a beneficial effect, with little indication of significant adverse effects (16). In addition, some observational studies are consistent with a beneficial effect of a higher bicarbonate (or lower acid intake) on CKD progression (17–20).

The article by Abramowitz *et al.* in this issue of *CJASN* addresses two matters related to the treatment of patients with CKD (21). First, it expands on the previous studies implicating acidosis in muscle catabolism by examining a functional correlate. The decrease in urine urea excretion induced by bicarbonate therapy is consistent with decreased muscle catabolism and corroborates findings previously shown by other investigators of improvements in nutritional and muscle status (22). Similarly, effects on the IGF-1 pathway, strongly implicated (with the glucocorticoid and insulin signaling pathways) in the muscle wasting commonly seen in CKD, are consistent with the thesis that bicarbonate decreases muscle catabolism through this mechanism (22). The study by Abramowitz and colleagues appears to be the first to show that correction of the acidosis improves muscle function, as judged by sitting to standing time. Of note is that the patients' serum bicarbonate levels, which averaged 23 ± 2.4 mmol/L, were already, at least on mean, higher than the target suggested by the KDIGO guidelines. This study strongly supports the idea that correction of acidosis has a positive functional effect on muscle.

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Second, this study addresses the safety of giving sodium bicarbonate to patients with CKD by using an escalating dose strategy. These patients already often have hypertension and a tendency to sodium retention, with some having manifest edema. Previous studies showed that the administration of sodium bicarbonate results in less sodium retention than giving sodium chloride in CKD (23). The present study supports the notion that giving sodium bicarbonate to these patients is safe. The patients did not have worsening edema or worsening of hypertension. However, in this regard, the study is a small, with only 20 patients, and excluded patients with systolic BP >160 mmHg, or those who had more than moderate edema.

Certainly, larger studies are needed to confirm the safety and examine the limits of the types of patients in whom bicarbonate (or bicarbonate equivalent) is safe. However, we now have other studies, including those cited above, looking at the efficacy and safety of bicarbonate in CKD that also support the relative safety of sodium bicarbonate. Abramowitz and colleagues' study also showed that administration of sodium bicarbonate had the added benefit of lowering the potassium by a modest but statistically significant amount. This was accomplished with no increase in gastrointestinal adverse effects, which is another concern in giving sodium bicarbonate. Sodium citrate has been used effectively by others (8) to correct the acidosis of CKD, but it is more expensive and promotes aluminum absorption from the gut when given with aluminum-containing antacids; citrate would be an alternative if sodium bicarbonate was unacceptable.

Thus, the recent studies on the progression of CKD and the results reported here on muscle strength suggest that our threshold for treating patients who have CKD with bicarbonate may be too conservative: Minimal decreases in serum bicarbonate or, likely, even normal serum bicarbonates may warrant treatment. The result of this might be the amelioration of bone disease, improvement in muscle strength, improvement of hyperkalemia, and retardation of progression of CKD. Larger studies are needed to define the level of CKD and/or acidosis that should trigger bicarbonate treatment, along with a more comprehensive picture of the effects, mechanisms, and potential adverse effects of bicarbonate treatment in all patients with CKD. Although the reported benefits of bicarbonate treatment seem to be too good to be true for such an inexpensive treatment, the evidence is mounting that they are indeed true. It will be up to the nephrology community and national resources to verify and expand these studies because there is little pharmaceutical industry interest in such a treatment.

Disclosures

None

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See related article, “Effects of Oral Sodium Bicarbonate in Patients with CKD,” on pages 714–720.