Current Status of Bicarbonate in CKD

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Abstract

Metabolic acidosis was one of the earliest complications to be recognized and explained pathologically in patients with CKD. Despite the accumulated evidence of deleterious effects of acidosis, treatment of acidosis has been tested very little, especially with respect to standard clinical outcomes. On the basis of fundamental research and small alkali supplementation trials, correcting metabolic acidosis has a strikingly broad array of potential benefits. This review summarizes the published evidence on the association between serum bicarbonate and clinical outcomes. We discuss the role of alkali supplementation in CKD as it relates to retarding kidney disease progression, improving metabolic and musculoskeletal complications.

Keywords: progression of renal failure, acidosis, metabolism

Patients with CKD experience a multitude of abnormalities and disabilities, among which metabolic acidosis was one of the earliest complications to be recognized and explained pathologically. In typical CKD, there is a direct correlation between the decline in GFR and the reduction in serum bicarbonate thought to be due primarily to the inability of the kidney to synthesize ammonia, regenerate bicarbonate, and excrete hydrogen ions. In some instances, acid excretion is diminished earlier than usual in the course of GFR decline. Diseases in which this may be seen include obstructive nephropathy, sickle cell nephropathy, and occasionally in diabetic CKD.

Epidemiologic studies have shown an independent association between serum bicarbonate and adverse renal outcomes and mortality. Limited data from small interventional trials of alkali therapy supplementation and dietary interventions have confirmed the benefits of raising serum bicarbonate.

New evidence has emerged on the benefit of dietary acid reduction earlier in the course of CKD, even before the diagnosis of metabolic acidosis becomes evident. However, the optimal range for serum bicarbonate in patients with CKD is yet to be established, because metabolic alkalosis also portends poor outcomes.

In this review, we summarize the published evidence on the association between serum bicarbonate and clinical outcomes and discuss the role of alkali supplementation in CKD.

Metabolic Acidosis in CKD

As renal function declines, the kidneys progressively lose the capacity to synthesize ammonia and excrete hydrogen ions. Consequently, low bicarbonate levels are more common in patients with lower eGFR;
approximately 19% of patients with CKD stages 4–5 have a serum bicarbonate <22 mmol/L. In the presence of additional defects in tubular acid excretion, such as in hyporeninemic hypoaldosteronism, metabolic acidosis can appear early in the course of CKD. Furthermore, there is an inverse correlation with age: Serum bicarbonate decreases steadily after age 60 years. Therefore, the exact prevalence of metabolic acidosis caused solely by CKD remains to be determined.

The extrarenal generation of acid by metabolism, known as net acid production, is another player in the acid base balance. Western diets are notorious for being high in acid and are prevalent in the United States, both in people with normal or impaired kidney function and significantly above the recommended dosage of 0.8 g/kg per day in patients with advanced CKD. Maintenance of acid base balance requires the kidney to reclaim most of the filtered bicarbonate and to excrete additional H⁺ ions equivalent in amount to net acid production and any excreted bicarbonate. A high net endogenous acid production was shown to be associated with a faster decline in GFR in patients with CKD.

**Renal Effects of Metabolic Acidosis**

Experimental evidence suggests that metabolic acidosis contributes to progression of CKD. Observational studies in animal models and in humans have proven the association between metabolic acidosis and worsening renal disease. A very small number of interventional trials with varying patient types have shown that bicarbonate supplementation slows the rate of kidney disease progression.

Although acidosis of CKD results from decreased renal ammoniagenesis, ammonia production per residual nephron actually rises as CKD progresses. In animal models, metabolic acidosis was shown to lead to renal hypertrophy and hyperplasia, and administration of sodium bicarbonate led to decreased tubular injury and slowed the decline in kidney function. In addition, sodium bicarbonate/calcium citrate administered to 5/6 nephrectomized rats attenuated tubular interstitial disease and the decline in GFR.

Several mechanisms of action are postulated. Nath et al proposed that the increase in renal cortical ammonia resulting from the stimulation of increased ammonia production in residual nephrons by metabolic acidosis activates the alternative complement pathway and leads to progressive tubular injury. The group lead by Wesson using both human and animal models with metabolic acidosis showed that increased endothelin production may mediate the tubular interstitial injury and decline in GFR. Finally, it was proposed that the new renal bicarbonate synthesis in response to metabolic acidosis leads to calcium precipitation in the kidney. Table 1 summarizes the available literature in humans on the association between serum bicarbonate and adverse renal outcomes.

**Alkali Supplementation in CKD**

The effects of alkali supplementation on the progression of renal disease have been tested only in small studies, with less than optimal design. A single-center randomized controlled but unblinded study in patients with late stage CKD and established acidosis demonstrated that correction of metabolic acidosis with alkali supplements slowed progression of CKD to ESRD. Two other small studies support the above findings. These and the prior animal studies raise the strong possibility that such treatment could retard progression. The sodium load given at the time of alkali supplementation has not been associated with an increase in BP, edema, or episodes of heart failure, likely owing to the fact that sodium excreted after sodium bicarbonate supplementation is greater compared with sodium chloride administration. The results of ongoing alkali supplementation trials are eagerly expected (Table 2).

A couple of studies using dietary interventions with fruits and vegetables, which lower the net dietary acid load, showed a similar role in improving markers of kidney injury expressed as urinary albumin, N-acetyl-β-D-glucosaminidase, TGF-β, and endothelin 1. GFR was preserved in patients with hypertension-associated kidney disease who reduced their intake of dietary acid by consuming base-inducing fruits and
vegetables or bicarbonate.\textsuperscript{18}

Markers of tubular injury have been a major focus of studies in AKI in recent years. However, as noted above, similar markers for chronic kidney injury have not been so well developed. Urinary albumin is the best-studied index of chronic kidney injury. However, prior small-scale studies have not shown effects of bicarbonate therapy on proteinuria.\textsuperscript{29,39} Indeed, earlier animal studies suggested that the benefit of bicarbonate is to preserve the tubulointerstitial compartment.\textsuperscript{29,40} Hence, glomerular leakage of albumin might not be expected to change. However, tubular reabsorption of small molecular weight proteins does appear to improve.\textsuperscript{29} Because the glomerular sieving of large proteins such as albumin is difficult to assess in human studies, reabsorption of freely filtered small peptides such as cystatin is likely a better index of this proximal tubular function. Other tubular functions such as secretion tend to decline with GFR in most CKD. However, measurement of the secretion of exogenous substances such as phenolphthalein was used as an index of renal function in the early days of nephrology, and measurement of secretion of endogenous compounds is now analytically feasible and might be a better index than GFR for assessing a therapy that may selectively preserve the tubules such as bicarbonate.\textsuperscript{41} Table 3 summarizes the interventional trials of alkali therapy supplementation aiming to slow the progression of kidney disease. Large interventional trials of alkali therapy in CKD are lacking. Small available trials favor a beneficial effect of bicarbonate on renal outcomes.

**Nonrenal Effects of Metabolic Acidosis in CKD**

**Cardiovascular Effects of Metabolic Acidosis in CKD**

The large cardiovascular disease burden experienced by patients with CKD remains poorly understood and data from both human and animal studies are lacking.

The role of acidosis on cardiac muscle is not completely understood and relatively limited literature exists in the field. Animal models showed that mild renal insufficiency in rats results in early cardiac fibrosis and impaired diastolic function, which progresses to more global left ventricular remodeling and dysfunction.\textsuperscript{42} Acidosis has been associated with the reduction of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in myocardial cells,\textsuperscript{43} which could lead to reduced myocardial contractility and congestive heart failure.\textsuperscript{44} In addition, acidosis regulates endothelial cell adhesion and may play a role in the inflammatory response of vascular endothelial cells.\textsuperscript{45} A potential link between the high concentration of hydrogen ions present in metabolic acidosis and the impaired heart function in CKD could be mediated through inflammatory processes. However, a direct link between metabolic acidosis in CKD and atherosclerotic heart disease remains to be proven. Acidosis is associated with inflammation in CKD.\textsuperscript{46} Chronic inflammation commonly seen in patients with CKD\textsuperscript{47} may predispose to an increased rate of atherosclerosis.\textsuperscript{48} Acidosis is associated with increased endothelin and aldosterone levels.\textsuperscript{49} A high aldosterone level was shown to be related to increased cardiovascular disease risk.\textsuperscript{50} It is reasonable to speculate that the metabolic acidosis results in increased inflammation, atherosclerosis, and elevated endothelin and aldosterone levels that could contribute to a change in left ventricular geometry.

Our previous work showed an association between high and low bicarbonate levels and heart failure events, and we hypothesized the pathophysiologic mechanism to be due to increased cardiac fibrosis.\textsuperscript{20}

**Metabolic and Musculoskeletal Effects of Acidosis**

Nonspecific symptoms such as malaise and fatigue may attend metabolic acidosis. The strongest evidence that alkali therapy can ameliorate these derives from a study of patients receiving acetazolamide for glaucoma. Blinded administration of sodium acetate with the carbonic anhydrase inhibitor reduced this complex of symptoms.\textsuperscript{51} Whether the treatment of the acidosis of CKD would mitigate such complaints is unknown.
Muscle Effects

Loss of skeletal muscle and weakness are well known accompaniments of ESRD. Functional evidence of disability occurs before ESRD is reached. For example, patients with lower eGFR or higher serum cystatin were more likely to report diminished activity and develop functional impairment than those with better renal function even after adjustments for relevant variables. In the third National Health and Nutrition Examination Survey (NHANES), the fraction of people who reported that walking one-quarter mile would be very difficult or impossible rose from 8% for those with an eGFR of 60 ml/min per 1.73 m² to 30% at an eGFR of 15 ml/min per 1.73 m². Young adults from the same cohort, with low bicarbonate and high anion gap, had lower cardiorespiratory fitness, assumed to be mediated by differences in lean body mass. Direct measurements of exercise capacity, including VO₂ max in patients with a mean eGFR of 30 ml/min per 1.73 m², have demonstrated reduced performance compared with age norms. Animal studies conclusively demonstrate that uremia and acidosis, in particular, cause proteolysis of muscle tissue. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance. Acidosis activates skeletal muscle breakdown by stimulating proteolysis by the ubiquitin-proteasome system and the caspase-3 protease. Correction of acidosis in humans with ESRD decreased protein degradation and improved muscle mass. However, functional benefits of bicarbonate therapy have not been tested even in ESRD, and there are limited data on functional or biochemical effects of such therapy in pre-ESRD. A single-blinded pilot study on patients with CKD with mild acidosis showed improved sit-to-stand time after a short time intervention.

Insulin Sensitivity

Insulin resistance appears very early in the course of progressive renal disease and has been associated with the degree of acidosis. As with bone and muscle complications of CKD, several pathways likely contribute to this problem. Angiotensin II–induced inflammation and/or the production of a tyrosine phosphatase (SIRP-a) stimulated by inflammation might result in insulin resistance in CKD. However, acidosis not only correlates with insulin resistance in CKD, but acidosis alone can also cause insulin resistance. For example, DeFronzo and Beckles induced insulin resistance in normal patients by acidification with ammonium chloride. More recently, Farwell and Taylor examined the 1999–2000 and 2001–2002 NHANES and reported a link between lower serum bicarbonate and insulin resistance, a link that persisted with multivariable adjustment. Attempts to treat insulin resistance by reducing acidosis are very limited. Mak treated eight young patients receiving maintenance hemodialysis with oral sodium bicarbonate for 2 weeks and found an improvement in their insulin sensitivity. Whether such an effect would persist is unknown and base treatment has not been examined at all in earlier stages of CKD.

Insulin resistance is a well recognized cardiovascular disease risk factor in the general population. The risk for cardiovascular disease in people with CKD has also been well documented. Perhaps some of that risk for cardiovascular disease in CKD is mediated through the effects of acidosis on insulin resistance.

Bone Effects

Bone disease appears in CKD well before ESRD supervenes. Fracture rates are increased in people with eGFRs even in the range of 30–60 ml/min per 1.73 m² and tend to increase with yet lower eGFR. The underlying pathophysiology is complex but acidosis is an often-cited contributor. Acidosis causes increased bone resorption and decreased bone formation. This effect is not simply due to chemical buffering by the calcium phosphate and carbonate content of bone; rather, it is an active cellular process involving at least upregulation of parathyroid hormone receptors in osteoblasts, increased osteoclastic activity, and reduced activity of the osteoblasts.

Correction of acidosis promotes growth in children and improves bone parameters including bone mineral density in adults with renal tubular acidosis. A study that tested differing dialysate bicarbonate
concentrations in ESRD concluded that “…correction of acidosis could decrease progression of hyperparathyroidism in patients with high bone turnover, and stimulate bone turnover in patients with low bone turnover.” (pp 1112, ref 83)

Frassetto et al. called attention to the possibility that even in the general population, bone loss may occur due to acid retention imposed by the typical modern Western diet. 85 These investigators showed that relatively large dosages (60–120 mmol/d) of potassium bicarbonate improved calcium balance and markers of bone resorption and formation in postmenopausal women. 85 These authors more recently described the additional exacerbating effects caused by diets high in sodium chloride and age-related declines in acid excretory capacity. 86 To our knowledge, there have been no attempts to test alkali therapy for its effects on bone in patients with CKD before ESRD.

**Effects on Mortality**

Acidosis seems to have a different effect on mortality in patients with ESRD compared with patients with CKD. Table 4. Patients undergoing maintenance hemodialysis have low mortality at predialysis serum bicarbonate >22 mEq/L. 65 Patients with CKD seem to have a high risk of death with both high and low serum bicarbonate (U-shaped association), although this was not confirmed in other large well defined CKD cohorts such as the Chronic Renal Insufficiency Cohort (CRIC) and the Modification of Diet in Renal Disease cohort, pointing toward other more significant contributors to the death risk in the CKD population (e.g., cardiovascular disease). 7,66

**Effects on Accumulation of β2-Microglobulin**

It is known that accumulation of β2-microglobulin and the development of amyloid contribute to carpal tunnel syndrome, cysts in bone, and cardiomyopathy in ESRD. 89 Metabolic acidosis may enhance cellular β2-microglobulin generation and release in patients with ESRD, as one study found an inverse correlation between plasma bicarbonate and β2-microglobulin levels. 89

**Metabolic Alkalosis and Cardiovascular Outcomes**

Metabolic alkalosis is less studied in the setting of CKD but overtreatment of metabolic acidosis might have adverse effects. For example, an alkaline pH augments calcification of rat aortas in cell cultures 90 and alkalization increases vascular calcification in cultured cells and uremic rats. 91

Our previous work 20 using the CRIC data showed a 14% increased risk of heart failure events with each 1-mmol/L increase in serum bicarbonate >24 mmol/L. The high risk of cardiovascular events observed at high serum bicarbonate could potentially be explained by the effect of alkalosis on regulatory proteins.

The optimal desired serum bicarbonate level, dose, and time of initiation of alkali-based therapy in CKD is yet to be determined. It seems that a level between 24 and 26 mEq/L correlates with the best clinical outcomes, but this requires proper validation. The range of potential benefits including not only mitigation of renal injury but also protection of other organ systems routinely damaged in the course of CKD support efforts to test alkalinization in clinical trials. Several clinical trials are underway to further test the value of bicarbonate supplementation.

**Disclosures**

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**Footnotes**

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References


48. Recio-Mayoral A, Banerjee D, Streather C, Kaski JC.: Endothelial dysfunction, inflammation and


64. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH.: Effects of oral sodium bicarbonate in


**Figures and Tables**

**Table 1.**

Epidemiologic studies of serum bicarbonate and progression of CKD

<table>
<thead>
<tr>
<th>First Author</th>
<th>Population</th>
<th>Participants (N)</th>
<th>Outcomes</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
</table>

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341479/?report=printable
HR, hazard ratio; 95% CI, 95% confidence interval.

Table 2.
Ongoing clinical trials of sodium bicarbonate supplementation in CKD

<table>
<thead>
<tr>
<th>Title (Study Identifier)</th>
<th>Principal Investigators</th>
<th>Study Design</th>
<th>Estimated Enrollment (N)</th>
<th>Eligibility Criteria</th>
<th>Assigned Intervention</th>
<th>Primary Outcomes (Time Frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-Controlled Randomized Clinical Trial of Alkali Therapy in Patients with Chronic Kidney Disease (NCT01452412)</td>
<td>T. Hostetter and M. Melamed</td>
<td>Randomized double-blind placebo controlled trial</td>
<td>150</td>
<td>Adult patients with CKD stages 3B and 4</td>
<td>Sodium bicarbonate versus placebo</td>
<td>Sit to stand to sit speed; HOMA-IR; DEXA of wrist; urinary NGAL and KIM-1 (1 yr)</td>
</tr>
<tr>
<td>Effect of Treatment of Metabolic Acidosis on Vascular Function in Patients with Chronic Kidney Disease: A Pilot Study (NCT02031770)</td>
<td>Jessica B. Kendrick</td>
<td>Randomized open-label crossover trial</td>
<td>20</td>
<td>Patients aged 40–70 yr with CKD stage 4</td>
<td>Sodium bicarbonate versus control (no treatment)</td>
<td>Brachial artery flow mediated dilation (14 wk)</td>
</tr>
<tr>
<td>A Prospective, Controlled, Randomized, Multicentric Study: Correction of Metabolic Acidosis with Use of Bicarbonate in Chronic Renal</td>
<td>Biagio Di Iorio</td>
<td>Randomized open-label trial</td>
<td>600</td>
<td>Adult patients with CKD stage 3B and 4</td>
<td>Sodium bicarbonate versus usual treatment (no bicarbonate)</td>
<td>Doubling of creatinine (3 yr)</td>
</tr>
</tbody>
</table>
Insufficiency (CKD3b-4) (NCT01640119)

**Effect of Oral Sodium Bicarbonate Supplementation on Progression of Chronic Kidney Disease in Patients with Chronic Metabolic Acidosis:** Study Protocol for a Randomized Controlled Trial (SoBic-Study) (EUDRACT no. 2012-001824-36)

- **Martina Gaggl**
  - Randomized, controlled, open-label clinical phase IV study
  - Treatment groups: 200 CKD stage 3 or 4 high-dose versus low-dose sodium bicarbonate

- **Investigations of the Optimum Serum Bicarbonate Level in Renal Disease (NCT01574157)**
  - **Kalani L. Raphael**
  - Randomized double-blind placebo controlled trial
  - Treatment groups: 74 adult patients with diabetes, proteinuria, and CKD stages 2–4

- **Alkali Therapy in Subjects with Sickle Cell Disease (SCD)–Evaluation of Efficacy, Safety, and Beneficial Effects (NCT01894594)**
  - **Jane Little**
  - Nonrandomized open-label single group assignment
  - Treatment groups: 20 sickle cell adult patients with eGFR<90 ml/min per 1.73 m²

HOMA-IR, homeostasis model assessment–estimated insulin resistance; DEXA, dual-energy X-ray absorptiometry; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; MDRD, Modification of Diet in Renal Disease study equation.

**Table 3.**

Interventional trials of alkali supplementation aimed to slow progression of kidney disease

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Population</th>
<th>Treatment Groups</th>
<th>Outcomes</th>
<th>Results</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Brito-Ashurst 13 (2009)</td>
<td>CKD stages 4 and 5</td>
<td>134 patients randomized to sodium bicarbonate versus standard care (24-mo follow-up)</td>
<td>Rate of CrCl decline</td>
<td>Slower (1.88 [-0.39 to 4.15] versus 5.93 [4.19 to 7.76] ml/min per 1.73 m²)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fall in CrCl&gt;3ml/min per year</td>
<td>Less likely (9% versus 45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Development of ESRD requiring dialysis (CrCl&lt;10 ml/min)</td>
<td>Less likely (6.5% versus 33%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Mahajan (2010) | CKD stage 2 hypertensive nephropathy | 120 patients randomized to sodium bicarbonate versus placebo versus sodium chloride (5-yr follow-up) | Rate of eGFR decline | Slower decline in eGFR in sodium bicarbonate group of −1.47±0.19 ml/min per yr versus −2.13±0.19 ml/min per yr versus −2.05±0.19 ml/min per yr 0.01 0.03

CrCl, creatinine clearance.

**Table 4.**

Epidemiologic studies of serum bicarbonate and all-cause mortality in CKD

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Population</th>
<th>Participants (N)</th>
<th>Referent (mEq/L)</th>
<th>Hazard Ratio (95% CI) for All-Cause Mortality</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovesdy (2009)</td>
<td>CKD stages 1–5</td>
<td>1240</td>
<td>26–29</td>
<td>1.43 (1.10 to 1.87) for bicarbonate &lt;22 mEq/L 1.11 (0.95 to 1.35) for bicarbonate 22–25 mEq/L 1.24 (0.94 to 1.64) for bicarbonate &gt;29 mEq/L</td>
<td>NR</td>
</tr>
<tr>
<td>Menon (2010)</td>
<td>Nondiabetic CKD</td>
<td>1781</td>
<td>26–40</td>
<td>0.99 (0.75 to 1.13) for bicarbonate 11–20 mEq/L 0.85 (0.65 to 1.11) for bicarbonate 21–23 mEq/L 0.77 (0.58 to 1.03) for bicarbonate 24–25 mEq/L</td>
<td>0.4</td>
</tr>
<tr>
<td>Navaneethan (2011)</td>
<td>CKD stages 3 and 4</td>
<td>41,749</td>
<td>23–32</td>
<td>1.23 (1.16 to 1.31) for bicarbonate &lt;23 mEq/L 1.74 (1.52 to 2.00) for bicarbonate &gt;32 mEq/L</td>
<td>NR</td>
</tr>
<tr>
<td>Raphael (2013)</td>
<td>General adult population (only 8% with CKD)</td>
<td>15,836</td>
<td>26–30</td>
<td>All: 1.75 (1.12 to 2.74) for bicarbonate &lt;22 mEq/L CKD only: 2.56 (1.49 to 4.38) for bicarbonate &lt;22 mEq/L</td>
<td>NR</td>
</tr>
<tr>
<td>Dobre (2013)</td>
<td>CKD stages 2–4</td>
<td>3939</td>
<td>NA</td>
<td>0.98 (0.95 to 1.02) per 1-mEq/L increase in serum bicarbonate</td>
<td>0.3</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval; NR, not reported; NA, not applicable.

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