Bicarbonate therapy for prevention of chronic kidney disease progression

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Kidney injury in chronic kidney disease (CKD) is likely multifactorial, but recent data support that a component is mediated by mechanisms used by the kidney to increase acidification in response to an acid challenge to systemic acid–base status. If so, systemic alkalization might attenuate this acid-induced component of kidney injury. An acid challenge to systemic acid–base status increases nephron acidification through increased production of endothelin, aldosterone, and angiotensin II, each of which can contribute to kidney inflammation and fibrosis that characterizes CKD. Systemic alkalization that ameliorates an acid challenge might attenuate the contributions of angiotensin II, endothelin, and aldosterone to kidney injury. Some small clinical studies support the efficacy of alkalization in attenuating kidney injury and slowing glomerular filtration rate decline in CKD. This review focuses on the potential that orally administered $NaHCO_3$ prevents CKD progression and additionally addresses its mechanism of action, side effects, possible complications, dosage, interaction, galenic form description, and contraindications. Current National Kidney Foundation guidelines recommend oral alkali, including $NaHCO_3^-$, in CKD patients with serum $HCO_3^- < 22$ mmol/l. Although oral alkali can be provided by other medications and by base-inducing dietary constituents, oral $NaHCO_3$ will be the focus of this review because of its relative safety and apparent efficacy, and its comparatively low cost.

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Chronic kidney disease (CKD) is a disease of industrialized societies, and it affects approximately 11% of the population in developed countries. Some small-scale studies support that the acid-producing diets typical of industrialized societies contribute to CKD progression. In the USA alone, 11.2 million people are estimated to have Stage 1 and 2 CKD, and continuation of their acid-producing diets without alkali intervention might increase their risk for progression. The social and economic costs of CKD are high, and its prevalence and high treatment costs indicate a need for effective, safe, easily available, and inexpensive prevention. Currently recommended kidney-protective strategies fail to stop CKD in all patients, suggesting a need for complimentary or adjunctive therapies. Important acid–base-related factors that might contribute to the pathology and prevention of CKD include the following:

1. Individuals with CKD have a reduced number of functioning nephrons, obligating more acid excretion per remaining nephron in response to the acid-producing diet typical of industrialized societies.
2. Kidney mechanisms used to augment nephron acid excretion accomplish the short-term physiological goal of increased acid excretion, but these mechanisms might have pathological long-term consequences, including mediating progressive nephropathy.
3. One approach to CKD prevention or progression includes reducing the dietary acid load that must be excreted by the kidney through ingestion of a less-acid-producing diet or adding a base, such as $NaHCO_3$.
4. Consequently, in addition to being effective, CKD prevention must be widely available, well tolerated, and inexpensive.

$NAHCO_3$ IN NEPHROLOGY

Sodium bicarbonate ($NaHCO_3$) is used in the treatment of a wide variety of metabolic acidoses, including renal tubular acidosis, and such treatment has been the topic of many textbooks of nephrology and reviews. It is also used to alkalize urine in patients with cystitis to provide symptomatic relief and prevent the formation of uric acid stones in the kidney. More recently, consideration for the therapeutic use of $NaHCO_3$ has broadened to include its wider use in CKD management and/or prevention.

PATHOPHYSIOLOGICAL BACKGROUND

The typical diet of individuals living in industrialized societies is high in acid-producing animal protein and comparatively low in base-producing proteins derived from fruits and vegetables (F + V). This diet produces about 1 mEq of hydrogen ions (protons)/kilogram body weight (b.w.)/day.[1] Elimination of protons and regeneration of alkali is done primarily by the kidney, but a detailed description of these processes is beyond the scope of this review.

The proposed mechanisms by which acidosis in CKD can worsen the progression of the disease and that are responsible for complications are shown in Figure 1.[1]

Metabolic acidosis due to CKD has been associated with progressive deterioration of kidney function in experimental animals[2] and patients.[3] On the other hand, a U-shaped association was found between serum bicarbonate concentration ($[HCO_3]$) and all-cause mortality in CKD patients.[4] Depending on the study, the optimal serum $[HCO_3]$ in CKD varies widely, ranging from 22 to 32 mEq/l.[5] Kanda *et al.*[6] found that low (<25th percentile) serum bicarbonate level is associated with CKD progression, and a 1-mEq/l increase in serum bicarbonate level (in normal range) was associated with low risk of CKD progression Dobre *et al.*[7] showed that low serum bicarbonate was an independent risk factor for CKD progression. On the other hand, the risk of heart failure in CKD patients was increased by 14% per 1-mEq/l increase in serum bicarbonate level over 24 mEq/l, i.e., in normal range.[7] Other studies showed a direct and positive association between net endogenous acid production and progression of kidney disease.[8] Because humans with reduced glomerular filtration rate (GFR),[9] similar to experimental animals with reduced GFR,[10] might have acid retention without reduced serum HCO_3, reduced GFR without metabolic acidosis might also increase the risk for kidney disease. These observations led to interventional studies to help establish an alkalization strategy in CKD patients.

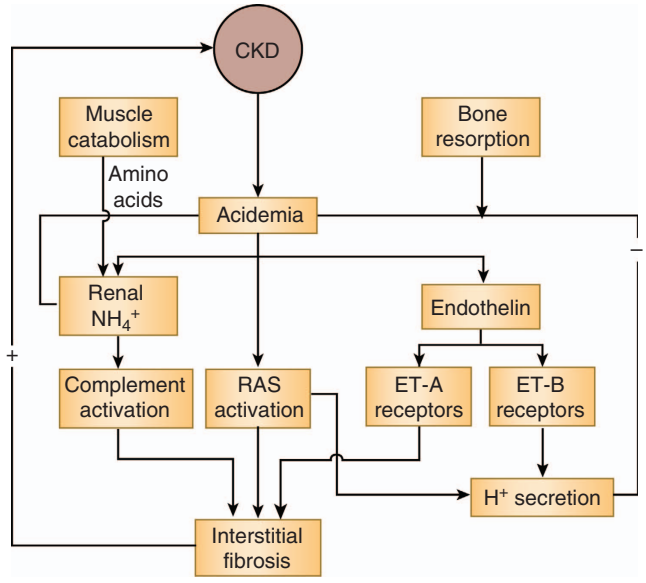

Figure 1 | To maintain isohydria, nephrons show an increase in the production of ammonia, which induces nonenzymatic activation of alternative complement pathway and synthesis of inflammatory mediators. Another nephrotoxic agent is endothelin-1 (ET-1), which induces vasoconstriction, inflammation, and fibrosis, as well as renal acidification. This activity is associated with angiotensin II and free-radical reactions. Increased ET-1 synthesis is caused by acid retention concomitant with decreased glomerular filtration rate, which also causes increased serum aldosterone concentration. Further consequences of acidosis include disturbances of muscle and bone metabolism, leading to renal osteodystrophy. CKD, chronic kidney disease; RAS, renin–angiotensin system.

EXPERIMENTAL STUDIES

Laboratory studies of CKD have typically used the 5/6 nephrectomy (Nx) model with metabolic acidosis[2,10] and the 2/3 Nx model that has greater GFR preservation but has acid retention (determined by kidney and skeletal muscle microdialysis) and no metabolic acidosis.[11] The favorable effect of $NaHCO_3$ and other alkali supplementation in different CKD animal models is shown in Table 1.

CLINICAL STUDIES

Small-scale studies that show a beneficial effect of oral $NaHCO_3$ supplementation in CKD patients are presented in Table 2. Nevertheless, nephrologists appropriately await results of larger, long-term clinical studies before altering currently recommended CKD treatment strategies.

MECHANISMS OF ACTION

$NaHCO_3$ given orally supplies bicarbonate ions indirectly (exchange of one HCO_3^- ion for each H^+ ion used in the reaction in the gastric lumen; Figure 2) and directly (absorption from gastrointestinal tract, especially important in case of enteric capsules). There are several hypotheses explaining the apparent benefit of $NaHCO_3$ in CKD patients. The acid environment of metabolic acidosis and/or acid retention might itself induce kidney injury, and alkalinization might reduce this injury directly by ameliorating this acid environment. On the other hand, dietary acid intake might cause kidney injury indirectly. Dietary acid augments kidney acidification through increased production of endothelin, aldosterone, and angiotensin II.[11] These agents augment distal nephron acidification in the short term, but might increase kidney inflammation and fibrosis over the longer term if increased dietary acid intake is sustained.[2] Therefore, alkalization that reduces acid retention[9] might be equivalent to drug therapies that reduce kidney levels of and/or effects of angiotensin II, endothelin, and aldosterone[11] and might thereby provide kidney protection with a better safety profile than pharmacological antagonists of angiotensin II, endothelin, and aldosterone.

Some animal[10,11] and human[14] studies suggest that dietary acid augments progressive nephropathy in the setting of reduced GFR in the absence of metabolic acidosis. Animals[10] and humans[9] with reduced GFR appear to have acid retention that is not reflected by plasma acid–base parameters