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.

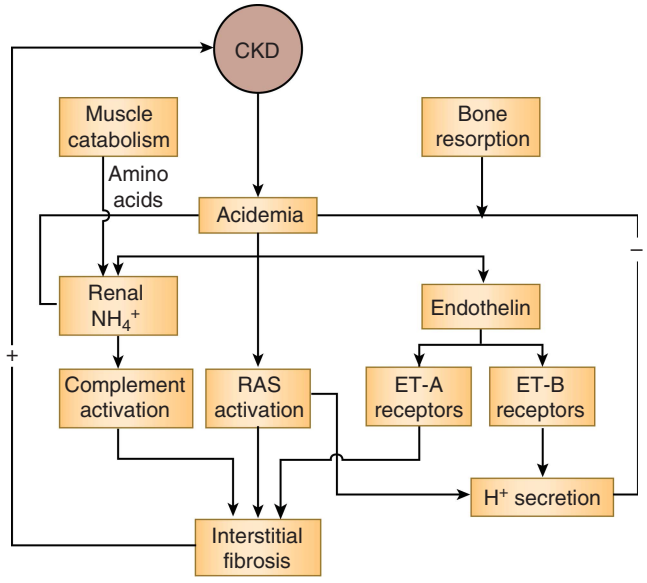

Figure 1 | To maintain isohydria, nephrons show an increase in the production of ammonia, which induces nonenzymatic activation of alternative complement pathway and synthesis of inflammatory mediators. Another nephrotoxic agent is endothelin-1 (ET-1), which induces vasoconstriction, inflammation, and 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

Table 1 | Favorable effect of $NaHCO_3$ and alkali supplementation in different CKD animal models

Study	Model	Result
Nath *et al.*[12]	$1\frac{3}{4}$ Nephrectomized rats	↓Impairment of tubular function, ↓histological evidence of tubulo interstitial damage, ↓deposition of the complement components C3 and C5b-9, ↓renal vein total ammonia concentration
Phisitkul *et al.*[2]	5/6 Nx rats and protein acidification	$NaHCO_3$ in combination with anti-hypertensive therapy ameliorated metabolic acidosis and delayed GFR decline
Wesson *et al.*[11]	2/3 Nx rats	$CaHCO_3$ caused ↓H^+ retention, ↓distal nephron acidification, ↓plasma and kidney levels of AII, ET-1, and aldosterone

Abbreviations: AII, angiotensin II; CKD, chronic kidney disease; ET-1, endothelin-1; GFR, glomerular filtration rate.

but is ameliorated by dietary alkali. This proposed acid retention associated with reduced GFR without metabolic acidosis increases kidney levels of endothelin, aldosterone, and angiotensin II in animals[11] and plasma endothelin and aldosterone levels in humans.[14] The signal(s) leading to these changes in the absence of frank metabolic acidosis are not known but might include pH 'sensors'[19] located in extra plasma compartments such as the kidney interstitium.[10] Consequently, dietary $NaHCO_3$ might be protective in patients with reduced GFR without metabolic acidosis through the reduction of associated acid retention. The potential kidney-protective effects in patients with reduced GFR but no metabolic acidosis raises consideration as to whether it should be recommended kidney protection earlier in the course of CKD progression. Additional studies are necessary to establish precise criteria for indications concerning such therapy in CKD patients.

SAFETY

Side effects

In clinical studies to date, $NaHCO_3$ has had few notable side effects when given to CKD patients.[13,16,18] Most of the common side effects were caused by CO_2 released through a reaction in the stomach, as shown in Figure 2, and included belching, gastric distension, and flatulence. Practitioners must be aware that higher alkali doses might cause fluid retention and worse blood pressure control in patients treated with very low GFR.

Short-term[15] and long-term[14] studies also show that $NaHCO_3$ therapy can reduce serum potassium, an outcome that can be beneficial in CKD patients who are at increased risk of hyperkalemia, particularly in the later stages of CKD and in such patients taking angiotensin-converting enzyme inhibitors.[18]

COMPLICATIONS

Metabolic alkalosis with exogenous HCO_3

Exogenous $NaHCO_3$ rarely causes metabolic alkalosis in patients with normal GFR and normal extracellular fluid volume,[20] and it did not increase serum [HCO_3] above normal when given for 1 year at 1 mEq/kg b.w./day (5.9 g /day for 70 kg b.w.) to CKD stage 4 patients with metabolic acidosis.[17] Therefore, $NaHCO_3$ at doses mostly used in CKD patients (2–3 g/day) is unlikely to cause this complication. However, practitioners and patients must be mindful of all circumstances that can cause metabolic alkalosis (e.g., vomiting, diarrhea, and hypokalemia), and in such cases $NaHCO_3$ should be temporarily discontinued. The recent study by Dobre *et al.*[7] revealed that even a slight increase of serum bicarbonate over 24 mmol/l is associated with increased heart failure risk. Results of this study should increase vigilance when long-term alkali treatment is being considered.

A special situation that can cause metabolic alkalosis is simultaneous ingestion of $NaHCO_3$ and non-absorbable antacids (aluminum and magnesium carbonate) in combination with cation-exchange resins.[20] This situation causes the formation of water-soluble and easily absorbable $NaHCO_3$ in the small intestine.[20] In this case, metabolic alkalosis can occur when base excretion from the extracellular fluid is limited.

Another possible complication of $NaHCO_3$ therapy is milk alkali syndrome that occurs only when $NaHCO_3$ is administered with calcium. This syndrome occurs in patients who ingest large quantities of milk and antacids (to treat peptic ulcer disease), or, recently, in patients using calcium alkali salts to treat osteoporosis or individuals habitually chewing betel nuts in Asia.[21] Therefore, caution is required during simultaneous use of $NaHCO_3$ and calcium carbonate. Calcium carbonate has a lower alkalizing potential than $NaHCO_3$,[22] and it can cause milk alkali syndrome and vessel calcification. Therefore, calcium carbonate should not be used as the primary alkalinization agent for CKD patients.

Spontaneous rupture of the stomach

Taking into account that $NaHCO_3$ is quite commonly used, the very few reported cases support that this fatal complication is extremely rare. The ingestion of ½ teaspoon of $NaHCO_3$, i.e., 2.5 g, resulted in only small amounts of sudden gas release that were not sufficient to cause spontaneous rupture.[23] To avoid the risk of stomach rupture, patients should take $NaHCO_3$ between meals not at a high dose and never after a large meal.[23]

Sodium (volume) overload

In short-term and long-term studies (maximum of 5 years), $NaHCO_3$ supplementation did not elevate blood pressure or require increased dose of anti-hypertensive agents.[15,17] In a small study of patients with advanced CKD, Husted *et al.*[24] observed that short-term $NaHCO_3$ supplementation at a dose

Table 2 | Clinical studies of $NaHCO_3$ supplementation in CKD patients

Study	Population	Intervention	Results
de Brito-Ashurst *et al.*[13] randomized open label Duration: 2 years	$n = 134$, CrCl 15–30 ml/min per 1.73 m^2, plasma HCO_3^-, 16–20 mmol/l	Control group—standard care Test group—$NaHCO_3$ 3×600 mg/day modified to achieve a serum bicarbonate level ⩾23 mml/l. The average dose of $NaHCO_3$ was 1.82 ± 0.80 g/day	In the $NaHCO_3$ group: ↓extent of decrease in CrCl (1.88 ± 0.38 vs. 5.93 ± 0.39; $P < 0.0001$). ↓dialysis requirement 6.5 vs. 33% ($P < 0.001$). ↓probability of progression to ESRD within 2 years after the study (8 vs. 33% (Kaplan–Meier analysis), $P < 0.001$). ↑dietary protein intake ↑muscle mass
Wesson *et al.*[9] placebo-controlled double blind Duration: 30 days	$n = 106$, 26 CKD1 (eGFR 100.8 ± 8.5 ml/min per 1.73 m^2), 80 CKD2 (eGFR 75.68 ± 6.2 ml/min per 1.73 m^2)	Control group: NaCl Test group: $NaHCO_3$ 0.5 mEq/kg lean b.w.	↓ H^+ retention in CKD2. ↓ plasma ET and aldosterone, but level of these parameters was higher in the CKD2 group
Phisitkul *et al*[3] open label Duration: 24 months.	$n = 59$, eGFR 20–60 ml/min per 1.73 m^2, serum HCO_3^- <22 mEq/l	All patients were offered oral sodium citrate at a dose equivalent to 1 mEq $NaHCO_3$/kg b.w. daily. Thirty patients who accepted formed the test arm	In the alkali group: eGFR was higher. Urine ET-1 and marker of tubular injury were decreased
Mahajan *et al.*[14] randomized, placebo-controlled, double blind Duration: 5 years	$n = 120$, eGFR 60–90 ml/min per 1.73 m^2 and macroalbuminuria; serum bicarbonate ⩾24.5 mEq/l	Three groups (40 subjects each) were administered $NaHCO_3$ (0.5 mEq/kg b.w. daily), or sodium chloride, or placebo	In the $NaHCO_3$ group: significantly delayed the decline of eGFR. ↓ albuminuria ↓ urine ET-1, and N-acetyl-β-D-glucosaminidase excretion
Goraya *et al.*[15] open-label study Duration: 30 days	$n = 199$, (79 CKD1 (eGFR > 90 ml/per min per 1.73 m^2) and 120 CKD2 (eGFR 60–90 ml/min per 1.73 m^2), $TCO_2 > 22$ mmol/l)	Three groups (control, or $NaHCO_3$—0.5 mEq/kg b.w. daily, or fruit + vegetable diet (F + V)).	CKD2 patients $NaHCO_3$ and F + V:↓ albuminuria, ↓ excretion of ET-1, transforming growth factor β (TGF-β), and N-acetyl-β-D-glucosaminidase. In CKD1 and CKD2 F + V groups: a greater reduction of blood pressure and diminished renal excretion of sodium, increased excretion of potassium. In CKD1 and CKD2 $NaHCO_3$ groups: a greater reduction of serum aldosterone concentration
Abramowitz *et al.*[16] single-blinded, placebo controlled Duration: 8 weeks	$N = 20$, eGFR 15-45 ml/min per 1.73 m^2, serum $NaHCO_3$ 20–24 mEq/l	Participants received during successive 2-week periods placebo and 0.3, 0.6, and 1.0 mEq/kg escalating oral $NaHCO_3$ doses	Each 0.1 mEq/kg of $NaHCO_3$ per day increase in dose caused an increase of serum bicarbonate level by 0.33 mEq/l. $NaHCO_3$: slight↓serum potassium level, small↑weight increase,↑muscle strength
Goraya *et al.*[17] randomized open label Duration: 1 year	$n = 76$, eGFR, 15-29 ml/min per 1.73 m^2, $PTCO_2$ <22 mmol/l	One group ($n = 35$) received during 1 year oral $NaHCO_3$ in a dose of 1.0 meEq/kg/day and the second ($n = 36$) F + V to reduce daily acid by half	Similar effect of both interventions on eGFR. In $NaHCO_3$ group: higher increased $PTCO_2$ (21.2 ± 1.3 vs. 19.9 ± 1.7 mmol/l) and decreased net acid excretion. The same influence on eGFR and transforming growth factor β (TGF-β), and N-acetyl-β-D-glucosaminidase excretion. In $NaHCO_3$ group: ↑ urine K^+ excretion ↓ plasma [K^+] ↓ urine aldosterone excretion ↓ ratio of active to inactive urine cortisol metabolites
Susantitaphong *et al.*[18] meta-analysis	Short term (⩽7days) two studies, $n = 17$; and long term (⩾2 months) four studies, $n = 295$	21–180 mEq/day	In long-term studies, mean net changes in GFR, serum creatinine level, and serum urea nitrogen level occurred, that were beneficial for CKD patients. Increased serum bicarbonate and decreased serum potassium and chloride concentrations were also observed. Systolic and diastolic blood pressure were not affected by long-term $NaHCO_3$ administration. The meta-analysis revealed that $NaHCO_3$ therapy produced a net improvement in GFR of 3.2 ml/min per 1.73 m^2 and a 79% reduction in the incidence of dialysis requirement

Abbreviations: b.w., body weight; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ET-1, endothelin-1.

of 200 mEq/day caused Na excretion that was higher than the amount excreted with equivalent NaCl supplementation. Furthermore, $NaHCO_3$ did not increase blood pressure in contrast to NaCl. The dose of $NaHCO_3$ in these studies was much higher (200 mEq/day vs. 24–36 mEq/day) than that typically used in CKD treatment. A more typical daily dose of $NaHCO_3$ used to treat metabolic acidosis in CKD (2–3 g) is 0.54–0.81 g (23.22–44.83 mmol) of sodium, i.e., less than the recommended daily dietary sodium for hypertension and CKD (<2 g/day). In addition, whether excessive sodium restriction is actually healthy for CKD patients will be determined in future studies. In CKD patients with and without congestive heart failure, lower and higher sodium levels are both associated with higher mortality.[25] Accordingly, $NaHCO_3$, compared with NaCl, might be considered as a comparatively safe sodium source for CKD patients, especially for those whose hypertension is treated with hypotensive agents, such as angiotensin-converting enzyme inhibitors.

F + V contain largely base-producing proteins and therefore might be considered as a strategy to reduce dietary acid.[17] Thirty days of added F + V attenuated kidney injury similarly to $NaHCO_3$,[15] reduced systolic blood pressure and b.w.,[15,17] and provided antioxidants that are helpful for CKD patients. Although added F + V was associated with the potential benefit of reduced urinary sodium excretion, it was

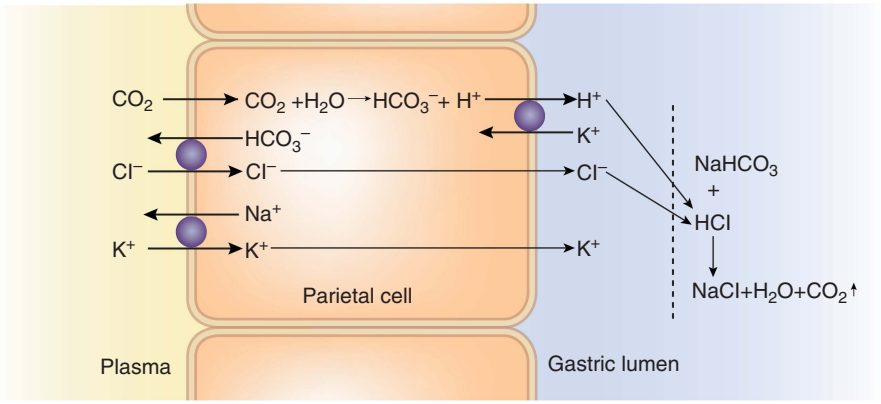

Figure 2 | HCO_3^- regeneration in the parietal cell of the stomach.

also associated with increased potassium excretion due to the concomitant higher potassium intake associated with F + V. The latter could be problematic in CKD patients whose potassium excretory capacity is lower owing to their reduced GFR.[15,17] Dietary alkalinization with $NaHCO_3$ avoids concomitant potassium ingestion inherent with F + V, more effectively reduces the aldosterone levels associated with decreased GFR,[9] and is possibly associated with better compliance than F + V. Therefore, oral $NaHCO_3$ appears to be a safer, more accessible, and less expensive dietary alkalization strategy for CKD patients.

INTERACTIONS

By changing the stomach and urinary tract pH, $NaHCO_3$ can affect the absorption and excretion of various substances. Table 3 shows the most important interactions of $NaHCO_3$ and different popular drugs (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~cjQKuV:1). To avoid interactions in the pharmaceutical phase (i.e., chemical reactions in the stomach), $NaHCO_3$ should not be simultaneously taken with other medications (a 1- to 2-h interval is recommended). Importantly, $NaHCO_3$ does not interact with anti-hypertensive drugs.

DOSAGE

The optimal daily dose of $NaHCO_3$ that provides kidney protection and yet minimizes side effects remains to be determined. The National Kidney Foundation recommends 0.5–1.0 mEq of $NaHCO_3$/kg b.w. in patients with HCO_3 <22 mmol/l. The quantity of base required to increase serum HCO_3^- by a given amount can be calculated according to the following formula: (desired HCO_3^- level) − (measured HCO_3^- level) × (HCO_3^- space = 50% b.w. (kg)).[26] Because metabolic acidosis increases the space of distribution of administered HCO_3,[27] CKD patients with metabolic acidosis might require slightly more administered HCO_3 than suggested by this formula. In studies in patients with CKD and HCO_3 <22 mmol/l, the usual dose was 1 mEq/kg b.w. such that a 70-kg patient received approximately 5.9 g of $NaHCO_3$ daily. In the study by de Brito-Ashurst *et al.*,[13] patients started therapy under a dosing regimen of 3 × 600 mg, and the average dose of $NaHCO_3$ was 1.82 ± 0.80 g/day. The serum HCO_3^- level was monitored every 2 months. In CKD patients without acidosis, $NaHCO_3$ was administered at a dose of 0.5 mEq, i.e., 42 mg/kg b.w. daily (patients weighing 70 kg received approximately 3 g of $NaHCO_3$ divided in three doses).[14] Susantitaphong *et al.*[18] recommended 0.5 mEq /kg b.w. daily in their meta-analysis. Rutkowski and Ciechanowski[22] in their review recommended the use of $NaHCO_3$ when serum HCO_3 is <22 mmol/l or eGFR is <60 ml/min per 1.73 m^2 (usually, the serum HCO_3^- concentration in such case is lower by 2 mmol/l relative to patients with GFR >80 ml//min).

GALENIC FORMS

The tolerance and compliance of patients using $NaHCO_3$ depends on the galenic form of this substance (Table 4) (from reference Krapf *et al.*[28]). Tablets and capsules are well tolerated by patients, and the dose can be better controlled. Some manufacturers add flavors to improve the taste of tablets. The official status of $NaHCO_3$ depends on local regulations. In some countries, $NaHCO_3$ is registered as a drug, whereas it is registered in other countries as a food supplement. It can also be registered as both a food supplement and a drug.

Regulations regarding medical use of $NaHCO_3$ are confusing for patients and for medical practitioners. People often do not trust food supplements or products available outside of pharmacies. Nevertheless, there is no chemical difference between baking soda bought in the supermarket and $NaHCO_3$ powder or tablets bought in pharmacies. Only in the pharmacy, however, can patients be professionally advised regarding interactions, side effects, and warnings. Dosing with powder is less precise than with tablets. In addition, its temperature sensitivity makes storage of $NaHCO_3$ challenging. Consequently, the better recommendation for CKD patients is $NaHCO_3$ prescribed and purchased as tablets or capsules from a pharmacy rather than from a supermarket. Other alkali products are also available (e.g., Na citrate, K citrate, Ca citrate, Ca acetate, Ca carbonate), but only $NaHCO_3$ and Na citrate were the subject of clinical

Table 3 | Possible interactions of $NaHCO_3$ with other drugs (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~cjQKuV:1)

Drug	Type of interaction $NaHCO_3$—drug	Procedure
Urinary acidifiers (ammonium chloride, ascorbic acid, and potassium or sodium phosphates)	Counteracts the effect	Avoid concurrent use
Quinidine	Decreases urine elimination, increases toxicity	Avoid concurrent use. Dose of quinidine should be reduced
Anticholinergic drugs	Decreases absorption from gastrointestinal tract, and reduces urine elimination	Use 1 h after or before. Side-effect monitoring is recommended
Ciprofloxacin, norfloxacin, and ofloxacin	Reduces the solubility in urine. Possibility of crystalluria and nephrotoxicity	Avoid concurrent use
Drugs in enteral capsules	Capsule can be dissolved in stomach, which causes inactivation of the active substance or stomach irritation	Use 1 h after or before
Ephedrine	Increases $T_{1/2}$ and time of activity	Ephedrine dose should be corrected
H_2 receptor antagonists	Decreases gastrointestinal absorption	Use 1 h after or before
	Use 2 h after or 1 h before	Use 2 h after or 1 h before
	Use 2 h before	Use 2 h before
Iron products		
Ketoconazole and itraconazole		
Lithium salts	Increases elimination	Avoid concurrent use
Mexiletine	Prolongs elimination	
Salicylates	Enhances elimination (especially high doses)	Dose of salicylates should be increased
Sucralfate	Decreases binding to the gastric mucosa	Use 0.5–1 h after
Tetracyclines	Reduces absorption	Use 1–2 h after or before

Table 4 | Oral $NaHCO_3$ products and bicarbonate precursors[28]

Product	Content of $NaHCO_3$
$NaHCO_3$ tablets or capsules or pharmacopeial powder	11.9 mEq/1000 mg
Baking soda	60 mEq/teaspoon
Shohl's solution:Bicitra	
Na citrate	1 mEq/ml
Citric acid	1 mEq/ml
Polycitra	
Na citrate	1 mEq/ml
K citrate	1 mEq/ml
Citric acid	1 mEq/ml

Table 5 | Comparison of different alkali products

Product	Advantages	Disadvantages
$NaHCO_3$	Most number of clinical trials proving alkali efficacy in CKD patients	Sodium content: volume overload, risk of the blood pressure increase
	Low price	
	Very popular and easily available	
Na citrate	Low number of clinical trials proving alkali efficacy in CKD patients	Sodium content: volume overload, risk of the blood pressure increase
	Good tolerance	Increases aluminum absorption from the gut when used with aluminum-containing antacids
		Higher price
K citrate	Unknown, due to lack of clinical trials proving alkali efficacy in CKD patients	Potassium content: risk of hyperkaliemia
Ca citrate, Ca acetate, and Ca carbonate	Unknown, due to lack of clinical trials proving alkali efficacy in CKD patients	Calcium content: increased risk of vessel calcification

Abbreviation: CKD, chronic kidney disease.

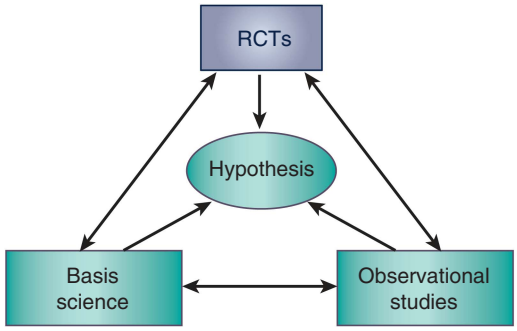

Figure 3 | Suggested alternative ranking paradigm of scientific investigations. RCT, randomized controlled trial.

studies concerning CKD progress prevention. $NaHCO_3$ has some advantages, including its reduced cost, not being associated with increased gastric aluminum absorption, and not providing exogenous calcium with the recent concern that the latter might further increase the already increased cardiovascular risk of CKD. In Table 5 is shown a comparison of different alkali products, which can help individualize the therapy.

CONTRAINDICATIONS

$NaHCO_3$ is contraindicated in patients with metabolic or respiratory alkalosis and in those with hypocalcemia in whom alkalosis may induce tetany, hypochloremia, and hypokalemia. It should also be used with caution in patients with chronic obstructive pulmonary disease, because alkalization can reduce the sensitivity of the respiratory regulatory center.

CONCLUSION

Kovesdy and Kalantar-Zadeh[29] specified a ranking paradigm for scientific investigations based on elements such as basic science, observational studies, randomized controlled studies, and hypothesis, as illustrated in Figure 3. This idea seems to be relevant for $NaHCO_3$ treatment of CKD patients. Current guidelines recommend its use when HCO_3^- is <22 mmol/l. Nevertheless, $NaHCO_3$ is safe, and further multicenter studies performed in large numbers of patients according to the requirements of evidence-based medicine are necessary to establish a precise strategy for using this substance in early stages of CKD.

DISCLOSURE

Ł receives a salary from the pharmaceutical distributor that offers i.a. different alkali products. The other author declared no competing interests.

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