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Article

# Effects of Treatment of Metabolic Acidosis in CKD
## A Systematic Review and Meta-Analysis

*Sankar D. Navaneethan,[1] Jun Shao,[2] Jerry Buysse,[2] and David A. Bushinsky[3]*

### Abstract

**Background and objectives** Metabolic acidosis is associated with progression of CKD and has significant adverse effects on muscle and bone. A systematic review and meta-analysis was conducted to evaluate the benefits and risks of metabolic acidosis treatment with oral alkali supplementation or a reduction of dietary acid intake in those with CKD.

**Design, setting, participants, & measurements** MEDLINE, Embase, and Cochrane CENTRAL were searched for relevant trials in patients with stage 3–5 CKD and metabolic acidosis (<22 mEq/L) or low-normal serum bicarbonate (22–24 mEq/L). Data were pooled in a meta-analysis with results expressed as weighted mean difference for continuous outcomes and relative risk for categorical outcomes with 95% confidence intervals (95% CIs), using a random effects model. Study quality and strength of evidence were assessed using Cochrane risk of bias and the Grading of Recommendations Assessment, Development and Evaluation criteria.

**Results** Fourteen clinical trials were included ($n$=1394 participants). Treatment of metabolic acidosis with oral alkali supplementation or a reduction of dietary acid intake increased serum bicarbonate levels (14 studies, 1378 patients, mean difference 3.33 mEq/L, 95% CI, 2.37 to 4.29) and resulted in a slower decline in eGFR (13 studies, 1329 patients, mean difference −3.28 ml/min per 1.73 $m^2$, 95% CI, −4.42 to −2.14; moderate certainty) and a reduction in urinary albumin excretion (very-low certainty), along with a reduction in the risk of progression to ESKD (relative risk, 0.32; 95% CI, 0.18 to 0.56; low certainty). Oral alkali supplementation was associated with worsening hypertension or the requirement for increased antihypertensive therapy (very-low certainty).

**Conclusions** Low-to-moderate certainty evidence suggest that oral alkali supplementation or a reduction in dietary acid intake may slow the rate of kidney function decline and potentially reduce the risk of ESKD in patients with CKD and metabolic acidosis.

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[1]Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas; [2]Tricida, Inc., South San Francisco, CA; and [3]Division of Nephrology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

**Correspondence:** Dr. Sankar D. Navaneethan, Selzman Institute for Kidney Health, Section of Nephrology, Baylor College of Medicine, 1 Baylor Plaza, Suite 100.37D, Houston, TX 77030. Email: Sankar.navaneethan@bcm.edu

## Introduction

Patients with CKD often develop chronic metabolic acidosis due to a progressive reduction in kidney acid excretion with continued metabolic acid production, resulting in acid retention. The retained acid mobilizes buffer from muscle and bone and eventually depletes the principal extracellular buffer, bicarbonate, to a level below the normal lower limit of 22 mEq/L in blood. The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative guidelines recommend administration of base when serum bicarbonate levels are <22 mEq/L, to maintain a level ≥22 mEq/L (1). The Kidney Disease: Improving Global Outcomes guidelines also recommend administering base when serum bicarbonate is <22 mEq/L, to maintain the value within the normal range, generally regarded as 22–29 mEq/L (2).

Observational data demonstrate an independent association between lower serum bicarbonate levels and kidney disease progression (3–6). Findings of these analyses have been supported by interventional studies with oral alkali supplementation (7,8). A previous systematic review of the effect of alkali therapy suggested a potential benefit of alkali therapy on preservation of GFR in patients with CKD (9). The small number of included trials ($n$=6) in this earlier report, along with a limited number of patients, precluded definitive conclusions regarding the risks and benefits of oral alkali supplementation. Subsequently, longer-term prospective trials have examined the effect of intervention with oral alkali supplementation (*e.g.*, sodium bicarbonate or sodium citrate) (10–15) or dietary intervention (*e.g.*, diets enriched with fruits and vegetables or very-low-protein diets supplemented with ketoanalogues, both designed to reduce the intake of dietary acids) (11–14,16) on kidney disease progression and other surrogate outcome measures. To summarize the current evidence on this topic, we performed a systematic review and meta-analysis examining the effect of oral alkali supplementation or dietary intervention compared with no treatment, usual care, or placebo, in patients with stage 3–5 CKD and metabolic acidosis and low-normal serum bicarbonate levels.

## Materials and Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of systematic reviews of interventions and a prespecified registered protocol in PROSPERO (17).

### Search Strategy

MEDLINE, Embase and Cochrane CENTRAL databases were searched for relevant studies (published up to October 2018) (Supplemental Appendix 1). We also searched Clinicaltrials.gov and abstracts presented in the American Society of Nephrology annual meetings (2014–2017). The references of relevant studies and review articles were manually searched.

### Study Selection

All clinical trials of oral alkali supplementation, dietary intervention, or any combination used to treat nondialysis-dependent patients with CKD with chronic metabolic acidosis (defined as serum bicarbonate <22 mEq/L) or those with low-normal serum bicarbonate (22–24 mEq/L) and stage 3–5 CKD for at least 4 weeks were considered for inclusion. We planned to include studies that enrolled patients with stage 1–5 CKD and those with low serum bicarbonate (<22 mEq/L), but restricted the analyses to those with stage 3–5 CKD given its clinical relevance to this population. We also extended it to those with low-normal bicarbonate levels, on the basis of the mean serum bicarbonate levels reported in study tables, and so patients with normal serum bicarbonate levels might have been included in these studies. Studies enrolling patients with ESKD and assessing acute metabolic acidosis interventions with intravenous bicarbonate were excluded. All eligible studies had a comparison of oral alkali supplementation or dietary intervention with no treatment, usual care, placebo, or a defined control group.

### Outcome Measures

We planned to analyze the following outcome measures:

1. Kidney disease progression end points: change in eGFR decline at the end of study period, eGFR decline per year (details outlined in the Supplemental Appendix 1), eGFR decline of >30%, >40%, and/or >50%; doubling of serum creatinine or serum cystatin C; change in urinary albumin-to-creatinine ratio (ACR); and progression to ESKD or initiation of kidney replacement therapy.
2. Patient-centered outcomes: mortality; hospitalization; occurrence of cardiovascular events; and measurements relating to nutritional status, muscle strength and coordination, bone density and bone fracture occurrence, and sleep quality.
3. Adverse effects and electrolyte changes: the incidence of electrolyte disturbances (*e.g.*, hyperkalemia, hyperphosphatemia, hypercalcemia), new or worsening of edema or fluid status, increased or worsening calcification in tissues or vasculature, changes in antihypertensive therapy or diuretic dosing, and changes in hypertensive status.

### Data Extraction

Data extraction was carried out by the authors using a standard data extraction sheet (18). The titles and abstracts identified in the initial search were screened by two authors independently (S.D.N. and J.S.), discarding studies that were not applicable before assembling a reconciled list of citations that included relevant data for the review. The authors retrieved the full-text articles of the initial studies to determine which studies satisfied the inclusion criteria. Authors of the studies (except the study by Williams *et al.* [19]) that tested dietary interventions were contacted to obtain baseline bicarbonate levels of whom four responded (14,16,20,21).

### Assessment of Risk of Bias and Strength of Evidence

The risk of bias in the studies was assessed independently by two authors (S.D.N. and J.B.) without blinding to authorship or journal using the Cochrane risk of bias tool (18). Discrepancies were resolved by discussion. Two authors (S.D.N. and J.B.) assessed the strength of the overall evidence (as high, moderate, low, or very low) related to kidney outcome measures using the Grading of Recommendations Assessment, Development, and Evaluation approach (22), on the basis of the five domains: risk of bias, consistency, directness, precision, and publication bias (Supplemental Table 1).

### Data Synthesis and Analyses

Data were pooled using the random effects model, but the fixed effects model was also used in the analysis to ensure robustness of the model chosen and susceptibility to outliers. For dichotomous outcomes (*e.g.*, progression to ESKD, changes in antihypertensive therapy, *etc.*), results were expressed as relative risks (RRs) with 95% confidence intervals (95% CIs). Mean differences with 95% CIs were used where continuous scales of measurement were used to assess the effects of treatment (*e.g.*, eGFR decline, serum electrolytes, *etc.*). Both separate and combined analyses were conducted for oral alkali supplementation and dietary intervention. We planned to conduct subgroup analyses according to age, stage of kidney disease, cause of kidney disease, amount of proteinuria, and severity of metabolic acidosis; however, these subgroup analyses were not conducted because of the limited number of studies. We conducted sensitivity analysis by (*1*) excluding studies that enrolled patients with low-normal serum bicarbonate levels, and (*2*) excluding studies that compared low-protein diet with usual diet group (data presented in the Supplemental Appendix 1). Publication bias was assessed by examining the funnel plot for outcomes for which more than ten studies provided data. Heterogeneity was analyzed using a chi-squared test on N-1 degrees of freedom, with an $\alpha$ of 0.05 used for statistical significance, to assess whether observed differences in results were from chance alone. A low $P$ value provides evidence of heterogeneity of intervention effects. An $I^2$ test (23) along with 95% CIs was also used to assess levels of heterogeneity in the data with 0%–30% indicating mild, 30%–60% indicating moderate, and >60% suggesting substantial heterogeneity between the included studies. We also explored the reasons for heterogeneity for eGFR decline by (*1*) excluding studies of low quality and (*2*) restricting the analysis only to those

with 1-year follow-up. Meta-analyses were performed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and 95% CIs for the $I^2$ values were obtained from StatsDirect software (StatsDirect Ltd., Cambridge, UK).

## Results

### Search Results

The combined search of MEDLINE, Embase, Cochrane CENTRAL. and other databases identified a total of 5330 citations, of which 5277 were excluded because they were review articles, duplicate publications, or studies irrelevant to this review. Full-text assessment of 53 potentially relevant articles identified 14 eligible studies involving 1394 participants (Figure 1).

### Study Characteristics

Eight of the 14 studies compared oral alkali supplementation (seven studies, sodium bicarbonate; one study, sodium citrate) with a control (no treatment, usual care, or placebo) (7,10,15,24–28); five studies compared dietary intervention (ketoanalogue-supplemented very-low-protein diet, very-low-protein diets, low-protein diet, or six-point diet) with control diets (usual diet or low-protein diets) (16,19–21,29), whereas one study compared both sodium bicarbonate and dietary intervention (fruits and vegetables) with usual care (Table 1) (14). All trials used a parallel-group design except for the study by Kendrick *et al*. (28), which used a crossover design. Study duration varied from 8 weeks to 5 years. Most studies included patients with metabolic acidosis, except for those in the studies by Goraya *et al*. (14), Gennari *et al*. (20), Pisani *et al*. (29), and Williams *et al.* (19), which included patients with low-normal serum bicarbonate levels (22–24 mEq/L). Inclusion and exclusion criteria of these trials are outlined in Supplemental Table 2.

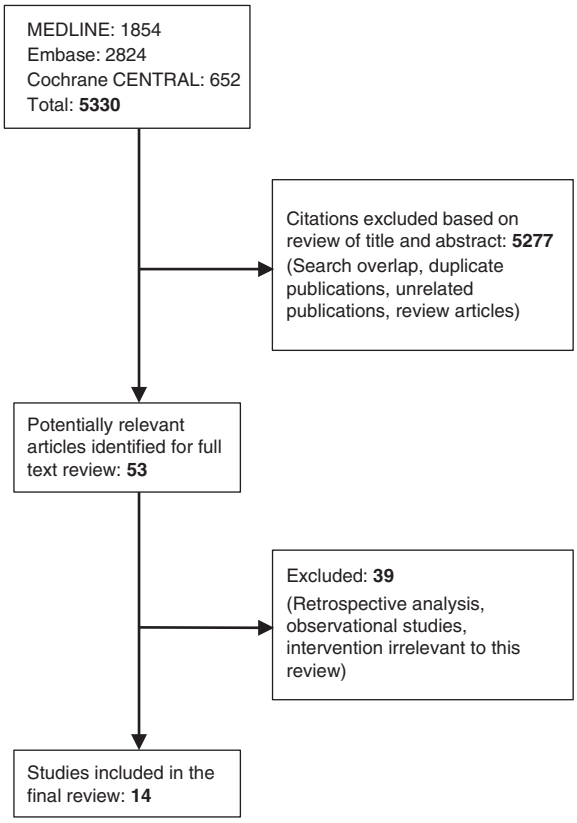


**Figure 1. | Flow chart showing number of citations retrieved by individual searches and number of trials included in the systematic review.**

### Study Outcomes

The combined effects of oral alkali supplementation and dietary intervention on kidney disease progression end points and biochemical measurements are summarized in Table 2, Figures 2 and 3, and Table 3, respectively. The effects of individual treatments are summarized in Supplemental Tables 3–6. Results using the fixed-effects model are outlined in the Supplemental Tables 7 and 8. Included studies did not report all-cause mortality and hospitalization data consistently to be pooled in a meta-analysis.

### Kidney Outcomes

Moderate quality evidence indicated that oral alkali supplementation and dietary intervention (both individually and when pooled together) significantly slowed the decline in eGFR (Figure 2, Table 2) and eGFR decline per year (Figure 3, Table 2, moderate certainty) compared with the control groups. There was moderate heterogeneity noted (Figure 2) that attenuated substantially when the analysis was restricted to only studies with >1 year follow-up (Figure 3). Sensitivity analysis conducted by excluding studies with low-normal serum bicarbonate levels are presented in Supplemental Figures 1 and 2. There was a significant reduction in urinary ACR (two trials, 167 patients; mean difference −51.55 mg/g; 95% CI, −75.73 to −27.38; $I^2$=0%; 95% CI, 0% to 73%; Table 2) with treatment (very low certainty). In addition, on the basis of low certainty, oral alkali supplementation or dietary intervention significantly reduced the risk of progression to ESKD (four trials, 434 patients; RR, 0.32; 95% CI, 0.18 to 0.56; $I^2$=17%; 95% CI, 0% to 73%; Figure 4) with no heterogeneity between these two types of interventions.

### Biochemical Measurements

Oral alkali supplementation or dietary intervention significantly increased the serum bicarbonate level compared with the control groups (Table 3). There were no significant differences in serum potassium, calcium, phosphate, albumin, and parathyroid hormone levels, and midarm muscle circumference between the groups (Table 3).

### Adverse Effects

**Oral Alkali Supplementation.** One trial reported that oral alkali supplementation significantly increased 24-hour urinary sodium excretion ($n$=134) (7), and urinary sodium-to-creatinine ratio ($n$=59) (15). Pooled analyses also showed worsening edema requiring increased diuretic therapy and worsening hypertension or the requirement for increased antihypertensive therapy in the treatment (sodium bicarbonate or sodium citrate) group (Table 4, very-low certainty). Table 4 outlines other adverse events.

**Dietary Intervention.** In contrast to oral alkali supplementation, treatment of metabolic acidosis with dietary

**Table 1. Characteristics of the population, interventions, and outcomes of included trials**

| Reference | Study Design | Study Duration | Baseline eGFR or CrCl, ml/min or ml/min per 1.73 $m^2$; Mean±SD | Baseline Serum Bicarbonate, mEq/L; Mean±SD | Intervention(s) (*N*) | Outcomes |
|---|---|---|---|---|---|---|
| **Oral alkali supplementation** | | | | | | |
| Bellasi *et al.*, 2016 (24) | Randomized, open-label trial | 1 yr | I: 32±14<br>C: 35±15 | I: 21.2±1.9<br>C: 21.6±2.0 | I: Sodium bicarbonate (*n*=71)<br>C: No treatment (*n*=74) | HOMA−IR, HOMA %B |
| de Brito-Ashurst *et al.*, 2009 (7) | Randomized, open-label trial | 2 yr | I: 20.12±6.47<br>C: 20.70±5.55 | I: 19.8±2.2<br>C: 19.9±1.5 | I: Sodium bicarbonate (*n*=67)<br>C: Standard care (*n*=67) | Change in CrCl, ESKD, nutritional status |
| Disthabanchong and Treeruttanawanich, 2010 (25) | Randomized, paralleled trial | 8–12 wk | I: 18.9±7.8<br>C: 18.7±7.6 | I: 20.5±1.6<br>C: 21.4±1.7 | I: High-dose sodium bicarbonate (*n*=21)<br>C: No treatment or low-dose sodium bicarbonate (*n*=20) | Thyroid function |
| Dubey *et al.*, 2018 (10) | Randomized, open-label trial | 6 mo | I: 29.2 (27.0 to 31.3)[a]<br>C: 31.5 (29.3 to 33.8)[a] | I: 18.1 (17.7 to 18.6)[a]<br>C: 18.1 (17.6 to 18.6)[a] | I: Sodium bicarbonate (*n*=94)<br>C: Standard care (*n*=94) | Change in MAMC, LBM, eGFR |
| Jeong *et al.*, 2014 (26) | Randomized, paralleled trial | 1 yr | I: 16.7±6.1<br>C: 17.7±6.4 | I: 18.5±3.9<br>C: 18.9±4.1 | I: Sodium bicarbonate (*n*=40)<br>C: Standard care (*n*=40) | Change in eGFR, KRT, nutritional status |
| Kendrick *et al.*, 2018 (28) | Open-label, crossover trial | 14 wk | I: 25±8<br>C: 24±8 | I: 19.3±2.9<br>C: 19.7±2.3 | *n*=19<br>I: Sodium bicarbonate<br>C: No treatment | Change in GFR, PTH, FGF23 |
| Mathur *et al.*, 2006 (27) | Single-blind, paralleled trial | 3 mo | N/A | I: 19.49±5.51<br>C: 19.35±3.74 | I: Sodium bicarbonate (*n*=20)<br>C: Placebo (*n*=20) | Serum creatinine, blood urea, PTH |
| Phisitkul *et al.*, 2010 (15) | Open-label, paralleled trial | 2 yr | I: 31.4±8.2<br>C: 31.7±7.9 | I: 20.5±1.1<br>C: 20.5±0.8 | I: Sodium citrate (*n*=30)<br>C: No treatment (*n*=29) | Change in eGFR, urine biomarkers of kidney injury |
| **Dietary intervention** | | | | | | |
| Garneata *et al.*, 2016 (16) | Randomized, open-label trial | 15 mo | I: 18.0 (15.5 to 20.1)[a]<br>C: 17.9 (14.3 to 19.3)[a] | I: 16.7 (15.8 to 17.6)[a]<br>C: 16.8 (15.9 to 17.8)[a] | I: Keto-VLPD (*n*=104)<br>C: LPD (*n*=103) | Change in eGFR, KRT, nutritional status |
| Gennari *et al.*, 2006 (20) | Randomized, open-label trial | 1 yr | Study B<br>I: 20.4±4.8<br>C: 20.2±3.9 | Study B<br>I: 21.6±3.6<br>C: 22.3±3.7 | Study B<br>I: VLPD (*n*=99)<br>C: LPD (*n*=107) | Change in eGFR |
| Mircescu *et al.*, 2007 (21) | Randomized, open-label trial | 48 wk | I: 17.9±4.8<br>C: 16.1±4.8 | I: 18.1±1.5<br>C: 18.3±1.3 | I: Keto-VLPD (*n*=27)<br>C: LPD (*n*=26) | Blood urea, eGFR, nutritional status |
| Pisani *et al.*, 2016 (29) | Randomized, open-label trial | 6 mo | I: 21.2±7.4<br>C: 21.0±8.3 | I: 23.4±2.4<br>C: 24.1±3.5 | I: Six-point diet (*n*=27)<br>C: LPD (*n*=27) | Serum urea nitrogen, eGFR, nutritional status |
| Williams *et al.*, 1991 (19) | Randomized, paralleled trial | 1 yr | I: 23.4±15.6<br>C: 28.3±16.7 | I: 23.1±4.5<br>C: 22.0±3.8 | I: LPD (*n*=31)<br>C: Usual diet (*n*=29) | Change in CrCl, KRT |
| **Oral alkali supplementation and dietary intervention** | | | | | | |
| Goraya *et al.*, 2014 (14) | Randomized, open-label trial | 3 yr | I-1: 39.6±6.6<br>I-2: 39.4±6.4<br>C: 39.5±6.8 | I-1: 23.1±0.6<br>I-2: 23.0±0.6<br>C: 23.0±0.5 | I-1: Sodium bicarbonate (*n*=36)<br>I-2: Fruits/vegetables (*n*=36)<br>C: Usual care (*n*=36) | Change in eGFR, urine biomarkers of kidney injury |

CrCl, creatinine clearance; I, intervention; C, control; HOMA-IR, homeostatic model assessment– insulin resistance; HOMA %B, homeostatic model assessment–$\beta$ pancreatic cell function; MAMC, midarm muscle circumference; LBM, lean body mass; KRT, kidney replacement therapy; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; N/A, not available; Keto-VLPD, ketoanalogue-supplemented very-low-protein diet; LPD, low-protein diet; VLPD, very-low-protein diet.
[a]Median (95% confidence interval).

**Table 2. Effects of oral alkali supplementation or reduction of dietary acid intake on kidney disease progression end points in patients with CKD with metabolic acidosis**

| Outcomes | No. of Studies/ Comparisons | No. of Patients | Effect Estimate [95% CI] | *P* Value | $I^2$ (95% CI), % | Certainty of Evidence, GRADE | Comments Regarding the Quality of Evidence |
|---|---|---|---|---|---|---|---|
| eGFR decline, ml/min per 1.73 $m^2$ | 13/14 | 1329 | MD −3.3 [−4.4 to −2.1] | <0.001 | 39 (0 to 66) | [1] Moderate | [1] Lack of blinding |
| eGFR decline per year, ml/min per 1.73 $m^2$/yr | 9/10 | 1284 | MD −2.1 [−2.8 to −1.4] | <0.001 | 0 (0 to 53) | [1] Moderate | [1] Lack of blinding |
| Progression to ESKD | 4 | 434 | RR 0.3 [0.2 to 0.6] | <0.001 | 17 (0 to 73) | [1,2] Low | [1] Lack of blinding<br>[2] Imprecision: risk estimate includes null effect |
| Urinary ACR, mg/g | 2/3 | 167 | MD −52 [−76 to −27] | <0.001 | 0 (0 to 73) | [1,2,3] Very low | [1] Lack of blinding<br>[2] Indirectness: data derived from small no. of studies<br>[3] Imprecision: data derived from small sample size |

95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; RR, risk ratio; ACR, albumin-to-creatinine ratio. For the effect estimates, "−" indicates reduction in decline in kidney function measures.

intervention significantly reduced systolic BP. There was also a trend toward decreased body weight and diastolic BP, although these were not statistically significant (Table 4).

**Study Quality and Publication Bias.** Supplemental Figure 3 outlines the risk of bias of the included studies. Publication bias was not tested for outcomes other than eGFR decline and serum bicarbonate because of the smaller number of studies (fewer than ten studies) (Supplemental Figures 4 and 5). There was no evidence of publication bias for these outcome measures.

## Discussion

This meta-analysis of clinical trials using oral alkali supplementation or reduction in dietary acid intake, compared with no treatment, usual care, or placebo, for the treatment of metabolic acidosis in patients with stage 3–5 CKD found that these treatments significantly increased serum bicarbonate and resulted in a slower decline in eGFR and a reduction in ACR, along with a reduction in the risk of progression to ESKD. Oral alkali supplementation, however, was associated with worsening edema requiring increased diuretic therapy and worsening hypertension or the requirement for increased antihypertensive therapy. Dietary intervention was associated with a significant reduction in systolic BP. In general, the strength of evidence for reported outcomes varied from very low to moderate certainty evidence using the Grading of Recommendations, Assessment, Development and Evaluations criteria (22).

Retrospective studies in humans have found that serum bicarbonate levels below the normal range were associated with more rapid decline in kidney function (3–6). Experimental studies in animals with reduced nephron mass also have shown that acid-inducing diets cause a progressive decline in GFR that is mediated by metabolic acidosis (30,31). Proposed mechanisms through which acidosis accelerates the progression of CKD include increased production of hormones (*e.g.*, endothelin, angiotensin II, and aldosterone) and proinflammatory cytokines, and activation of complement induced by increased ammonia production per nephron, each of which promotes acute acid excretion but chronically results in kidney inflammation and fibrosis through enhanced complement and renin-angiotensin system activation (32). Studies using oral alkali therapy in animals and humans with reduced kidney function have demonstrated a slower decline in eGFR (7,33,34). A previous meta-analysis included six studies (two short-term, <7 days; four long-term, >2 months) on the effects of alkali therapy. In aggregate, they demonstrated improvement in kidney function but differences in study protocol and small sample size precluded the authors from reaching definitive conclusions (9). Dietary interventions were not included in this earlier review.

Our analyses of pooled data from the existing clinical trials note that treatment of metabolic acidosis, using either oral alkali or dietary interventions, significantly increased serum bicarbonate levels, and offered kidney benefits in patients with stage 3–5 CKD and metabolic acidosis. These data also indicate that there may be a potentially higher effect eGFR decline at the end of study period with oral alkali (mean difference −4.00 [95% CI, −5.07 to −2.93] ml/min slower decline) than dietary interventions (mean difference −2.70 [95% CI, −4.71 to −0.70] ml/min slower decline), but

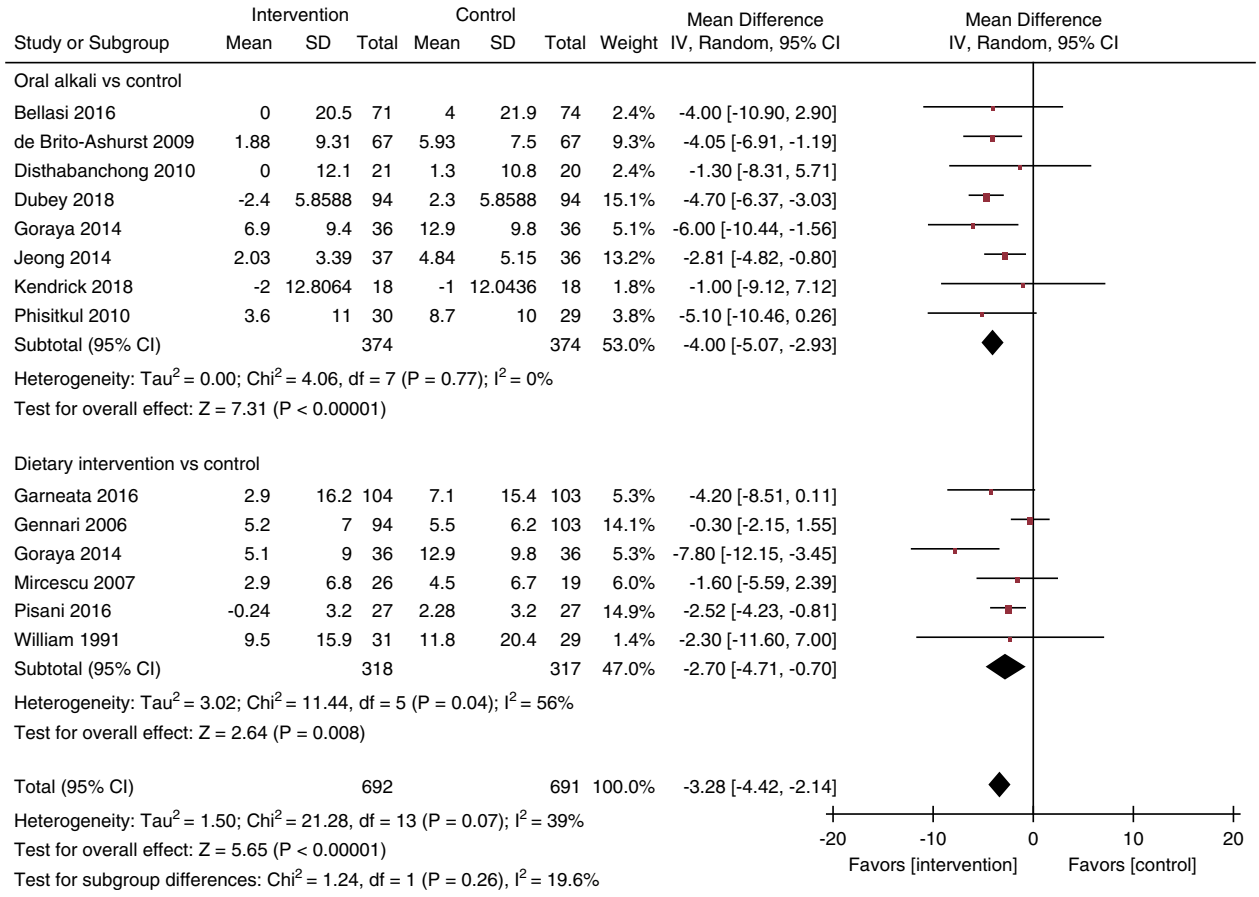


**Figure 2.** | **Forest plot shows slower decline in eGFR at the end of study period with oral akali supplementation or reduction of dietary acid intake.** $I^2$ for the combined effect estimate: 39% (95% CI, 0% to 66%). df, degrees of freedom; IV, inverse variance.

the test of subgroup difference was not significant ($P$=0.26) (Figure 2). As expected, interventions testing oral alkali or dietary interventions had several differences in their characteristics (study population, interventions, follow-up, *etc.*). Effects of oral alkali on albuminuria were assessed only in two trials, limiting the reliability of ascertaining the benefits of treatment of metabolic acidosis on this parameter. Although it is encouraging to see potential benefits, it is important to note that data for kidney disease progression to ESKD were derived from only four trials, two each for oral alkali supplementation and dietary intervention, with significant reduction for ESKD using dietary intervention but not with oral alkali supplementation (Figure 4). Given the lack of trials comparing oral alkali and dietary interventions head to head, superiority of one over the other is unclear. Additional adequately powered trials are needed to derive definitive conclusions regarding the effect of treatment of metabolic acidosis on the risk of kidney disease progression to ESKD with these different types of interventions.

Higher consumption of acid-producing animal protein contributes to metabolic acidosis in patients with CKD. Dietary interventions have been shown to provide an effective means of raising serum bicarbonate in patients with CKD who have metabolic acidosis or low-normal bicarbonate levels. Our summary data from the dietary intervention studies showed smaller but significantly slower reduction in kidney function, although with significant heterogeneity between the included studies that could be attributed to the differences among the dietary intervention protocols. These data should be interpreted with caution since these studies were not primarily designed to address the metabolic effect of these diets and included different levels of protein restriction. Base-providing diets tend to have a high potassium content and hence participants in these studies were carefully selected to be at very low risk to develop hyperkalemia (11,13,14). Further, willingness to adhere to a restrictive diet is a challenging factor in dietary intervention studies in patients with CKD. In one study, only 14% of screened patients who met all eligibility criteria agreed to adhere to the dietary requirements and were randomized (16). Other dietary interventions that could alter acid-base status in patients with CKD were not included in this analysis because of a lack of bicarbonate data. Further, some patients with normal serum bicarbonate levels could have been included these studies; future individual patient-level (rather than study-level) meta-analysis could provide additional insights. Further, it is possible that the observed benefits with dietary interventions could be ascribed to effects apart from the noted improvement in metabolic acidosis. Despite these limitations, the potential benefits of dietary intervention merit carefully designed larger studies.

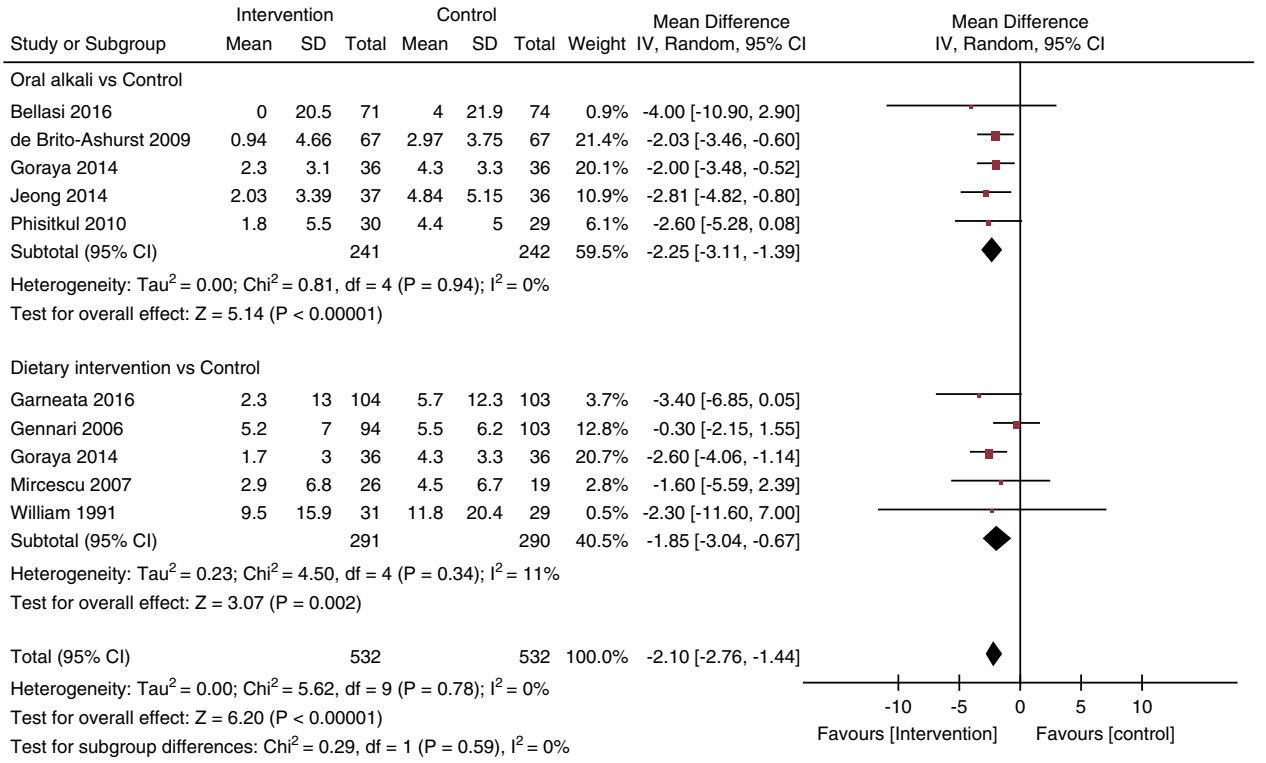


**Figure 3.** | **Forest plot shows slower decline in eGFR per year with oral akali supplementation or reduction of dietary acid intake.** $I^2$ for the combined effect estimate: (95% CI, 0% to 53%). df, degrees of freedom; IV, inverse variance.

Potential benefits of oral alkali supplementation on nutritional assessments such as serum albumin and potassium, midarm muscle circumference, and handgrip strength were suggested in a few single-center studies with a limited number of patients (7,35), but no significant differences were noted in our analysis. Ongoing trials could provide additional details about the effects of bicarbonate supplementation on physical function and quality of life (36). We also did not find outcome data for several prespecified outcomes (outlined in the Materials and Methods), and thus, a meta-analysis could not be conducted for these outcomes. In this analysis, there was a significant increase in worsening edema requiring increased diuretic therapy and worsening hypertension or the requirement for increased antihypertensive therapy associated with oral alkali supplementation in patients with CKD. Further, two trials reported a significantly increased urinary sodium excretion associated with oral alkali supplementation in those with CKD. Observational data associate higher urinary sodium excretion with kidney disease progression and cardiovascular events (37,38). It is important to note that the prospective studies included in this analysis were designed to exclude patients with CKD and comorbidities including uncontrolled hypertension, decompensated congestive heart failure, morbid obesity, volume overload, or hyperkalemia (39). Hence, the generalizability of these data to patients with CKD and multiple comorbidities is unclear.

This review has several strengths and limitations. Strengths include a systematic search of all major medical

**Table 3. Effects of oral alkali supplementation or reduction of dietary acid intake on change in biochemical measurements**

| Outcomes | No. of Studies/ Comparisons | No. of Patients | Effect Estimate MD [95% CI] | *P* Value | $I^2$ (95% CI), % |
|---|---|---|---|---|---|
| Serum bicarbonate, mEq/L | 14/15 | 1378 | 3.3 [2.4 to 4.3] | <0.001 | 93 (91 to 95) |
| Serum potassium, mEq/L | 4/5 | 522 | −0.15 [−0.38 to 0.07] | 0.17 | 88 (73 to 93) |
| Serum calcium, mg/dl | 8 | 764 | 0.04 [−0.26 to 0.35] | 0.79 | 82 (64 to 89) |
| Serum phosphate, mg/dl | 9 | 818 | −0.30 [−0.62 to 0.02] | 0.06 | 59 (0 to 78) |
| Serum albumin, g/L | 7 | 741 | 0.43 [−0.54 to 1.41] | 0.39 | 68 (0 to 84) |
| Serum PTH, pg/ml | 2 | 58 | −22 [−126 to 81] | 0.67 | 42 (N/A) |
| Midarm muscle circumference, cm | 5 | 647 | 0.2 [−0.2 to 0.6] | 0.29 | 0 (0 to 64) |

MD, mean difference; 95% CI, 95% confidence interval; PTH, parathyroid hormone; N/A, not available or not applicable. For the effect estimates, "−" indicates reduction in reduction in the reported outcome measures.

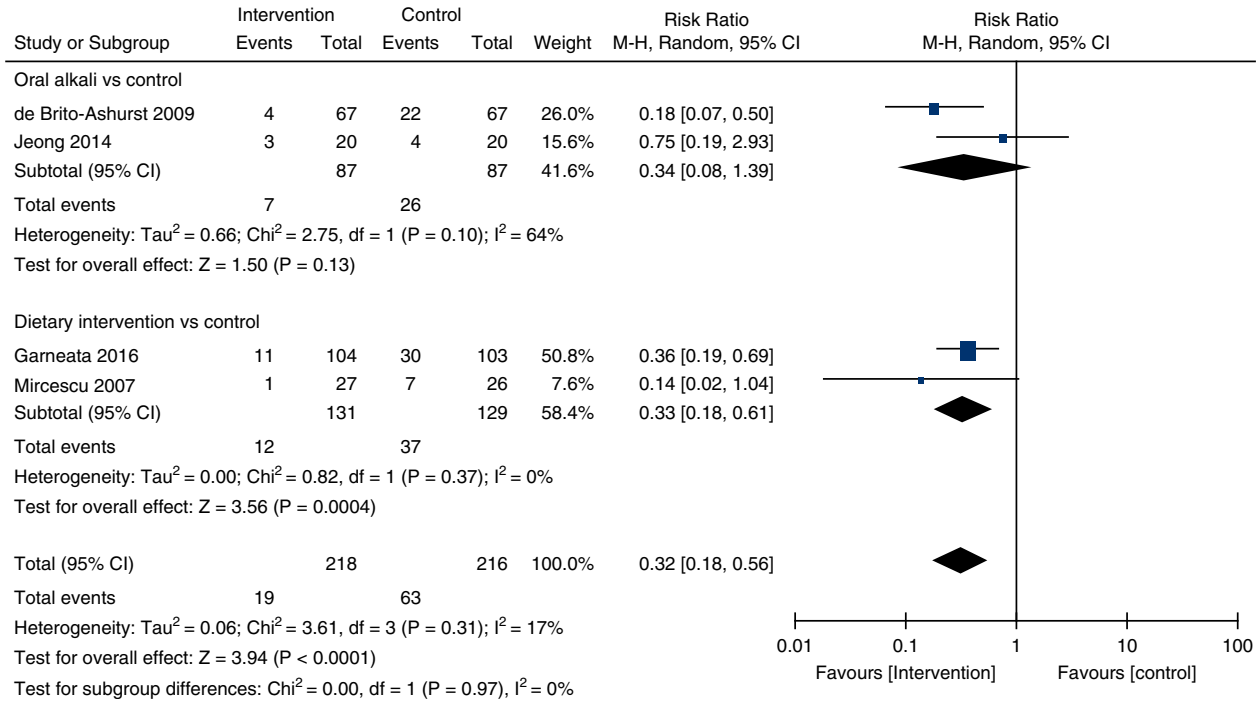


**Figure 4.** | **Forest plot shows potentially reduced risk of end stage kidney disease with oral alkali supplementation or reduction of dietary acid intake.** $I^2$ for the combined effect estimate: (95% CI, 0% to 73%). df, degrees of freedom; M-H, Mantel-Haenszel.

databases, data extraction and analysis, and trial quality assessment according to a prespecified protocol (17). Most included studies enrolled patients with stage 3–5 CKD and metabolic acidosis (serum bicarbonate <22 mEq/L) or low-normal serum bicarbonate (22–24 mEq/L), but few likely included patients with normal serum bicarbonate levels. A sensitivity analysis that excluded studies that enrolled patients with low-normal serum bicarbonate showed findings similar to those of the main analysis. The major limitation of our analysis is the lack of long-term outcome studies analyzing the effect of oral alkali supplementation or dietary intervention on patient-centered end points, including mortality. Most of the included studies were single-center, open-label trials that enrolled a small

**Table 4. Adverse effects of oral alkali supplementation or reduction of dietary acid intake in patients with CKD with metabolic acidosis**

| Outcomes | No. of Comparisons | No. of Participants | Effect Estimate [95% CI] | *P* Value | $I^2$ (95% CI) |
|---|---|---|---|---|---|
| **Oral alkali supplementation** | | | | | |
| Body weight, kg | 5 | 518 | MD 0.2 [−0.6 to 0.9] | 0.67 | 0 (0 to 64) |
| Systolic BP, mm Hg | 7 | 711 | MD −0.1 [−1.9 to 1.7] | 0.93 | 23 (0 to 67) |
| Diastolic BP, mm Hg | 5 | 580 | MD 1.6 [−0.4 to 3.5] | 0.12 | 49 (0 to 79) |
| Worsening hypertension or requiring increase in antihypertensive therapy | 3 | 362 | RR 1.38 [1.07 to 1.79] | 0.01 | 0 (0 to 73) |
| Worsening edema or requiring increase in loop diuretics | 5 | 420 | RR 1.39 [1.02 to 1.89] | 0.04 | 25 (0 to 73) |
| Achieving goal of systolic BP <130 mm Hg | 1 | 72 | RR 0.60 [0.24 to 1.48] | 0.27 | N/A |
| 24 h urinary sodium excretion, mEq/24 h | 1 | 134 | MD 24.6 [19.8 to 29.4] | <0.001 | N/A |
| Urinary sodium-to-creatinine ratio, mEq/g | 1 | 59 | MD 13 [7.3 to 18.7] | <0.001 | N/A |
| **Dietary intervention** | | | | | |
| Body weight, kg | 2 | 126 | MD −1.9 [−5.5 to 1.8] | 0.31 | 0 (N/A) |
| Systolic BP, mm Hg | 2 | 117 | MD −11.3 [−16.8 to −5.9] | <0.001 | 0 (N/A) |
| Diastolic BP, mm Hg | 1 | 45 | MD −3.4 [−14.3 to 7.5] | 0.54 | N/A |

95% CI, 95% confidence interval; MD, mean difference; RR, risk ratio; N/A, not applicable or available. For the effect estimates, "−" indicates reduction in outcome measures.

population of patients, excluded patients with multiple comorbidities, and were not powered to analyze patient-centered end points. In addition, for some outcomes, significant clinical heterogeneity existed among included trials, including differences in the types and doses of intervention, strategies of the control group, baseline eGFR and serum bicarbonate levels, and treatment duration. We were not able to explore the acute versus long-term effect of bicarbonate supplementation and the potential dose response on the basis of available trial evidence. Finally, most included studies with oral alkali supplementation did not report data on changes in BP status or antihypertensive and loop diuretic therapy, precluding definitive conclusions on the potential adverse effects associated with treatment with oral alkali therapy. We were not able to conduct several analyses planned *a priori* (such as 30% or 40% decline in eGFR, doubling of serum creatinine, hospitalization, and mortality) as these data were not reported in the included studies. Ongoing trials (Clincialtrials.gov identifiers: NCT01452412, NCT02915601) (40,41) could provide additional evidence on the effects of sodium bicarbonate supplementation in CKD populations.

In summary, current clinical trial evidence suggests that oral alkali supplementation or a reduction of dietary acid load improved serum bicarbonate levels and may slow the progression of kidney disease, on the basis of very-low- to moderate-certainty clinical evidence. Further larger, long-term studies of better quality are warranted to establish the benefits (such as delaying initiation of kidney replacement therapy or slowing progression to ESKD) and risks of treatment with oral alkali and/or a reduction in dietary acid load in patients with CKD.

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**Disclosures**

Dr. Navaneethan served as a consultant for Tricida for the work under consideration. Outside the submitted work, Dr. Navaneethan has served on an independent event adjudication committee for clinical trials sponsored by Bayer and Boehringer Ingelheim and has received investigator-initiated research support from Keryx Pharmaceuticals. Dr. Bushinsky is a consultant and member of the Scientific Advisory Board for Tricida and reports consulting fees and owns stock and stock options in Tricida. Dr. Bushinsky reports additional consulting fees from Amgen, Sanofi/Genzyme, Fresenius/Relypsa/Vifor, Novo Nordisk/Covance/Quintiles, speaker fees from Sanofi/Genzyme and stock ownership in Amgen and past stock ownership in Relypsa, all outside of the submitted work. Dr. Bushinsky also receives grant support from the National Institutes of Health and Renal Research Institute, both outside of the submitted work. Dr. Buysse and Dr. Shao are employees of Tricida and have a stock ownership interest in Tricida. In addition, Dr. Buysse reports personal fees and other from Tricida, Inc., during the conduct of the study and personal fees and other from Tricida,Inc., outside the submitted work. Dr. Buysse has a patent US9,205,107 issued, a patent US9,925,214 issued, a patent US9,993,500 issued, a patent EP3003327 issued, a patent WO2014/197725 pending, a patent WO2017193050 pending, a patent WO2017193064 pending, a patent WO2017193024 pending, a patent (Treatment of Eubicarbonatemic Metabolic Acidosis) pending, and a patent (Treatment of Metabolic Acidosis) pending. Dr. Shao reports personal fees and other from Tricida, Inc., during the conduct of the study and personal fees and other from Tricida, Inc., outside the submitted work.

**Supplemental Material**

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.13091118/-/DCSupplemental.

Supplemental Appendix 1. Search strategy.

Supplemental Table 1. GRADE quality of evidence.

Supplemental Table 2. Key inclusion and exclusion criteria of the included studies.

Supplemental Table 3. Effects of oral alkali supplementation on kidney disease progression end points in patients with CKD.

Supplemental Table 4. Effects of dietary intervention on kidney disease progression end points in patients with CKD.

Supplemental Table 5. Effects of oral alkali supplementation on change in biochemical measurements.

Supplemental Table 6. Effects of dietary intervention on change in biochemical measurements and midarm muscle circumference.

Supplemental Table 7. Effects of oral alkali supplementation/dietary intervention on kidney disease progression end points in patients with CKD using fixed effects method.

Supplemental Table 8. Effects of oral alkali supplementation/dietary intervention on change in biochemical measurements using fixed effects method.

Supplemental Figure 1. Effects of oral alkali supplementation or dietary intervention on kidney disease progression at the end of study period in patients with CKD.

Supplemental Figure 2. Effects of oral alkali supplementation or dietary intervention on eGFR slope (eGFR decline per year).

Supplemental Figure 3. Assessment of risk of bias using Cochrane Collaboration tool.

Supplemental Figure 4. Funnel plot for publication bias on end of-study eGFR decline.

Supplemental Figure 5. Funnel plot for publication bias on change in serum bicarbonate.

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