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REVIEW

The Effects of Oral Sodium Bicarbonate on Renal Function and Cardiovascular Risk in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Objective: Oral sodium bicarbonate is often used to correct acid-base disturbance in patients with chronic kidney disease (CKD). However, there is little evidence on patient-level benign outcomes to support the practice.

Methods: We conducted a systematic review and meta-analysis to examine the efficacy and safety of oral sodium bicarbonate in CKD patients. A total of 1853 patients with chronic metabolic acidosis or those with low-normal serum bicarbonate (22–24 mEq/L) were performed to compare the efficacy and safety of oral sodium bicarbonate in patients with CKD.

Results: There was a significant increase in serum bicarbonate level (MD 2.37 mEq/L; 95% CI, 1.03 to 3.72) and slowed the decline in estimated glomerular filtration rate (eGFR) (MD −4.44 mL/min per 1.73 m^2, 95% CI, −4.92 to −3.96) compared with the control groups. The sodium bicarbonate lowered T50-time, an indicator of vascular calcification (MD −20.74 min; 95% CI, −49.55 to 8.08); however, there was no significant difference between the two groups. In addition, oral sodium bicarbonate dramatically reduced systolic blood pressure (MD −2.97 mmHg; 95% CI, −5.04 to −0.90) and diastolic blood pressure (MD −1.26 mmHg; 95% CI, −2.33 to −0.19). There were no statistically significant body weight, urine pH and mean mid-arm muscle circumference.

Conclusion: Treatment of metabolic acidosis with sodium bicarbonate may slow the decline rate of kidney function and potentially significantly improve vascular endothelial function in patients with CKD.

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Keywords: chronic kidney disease, metabolic acidosis, sodium bicarbonate, kidney function, cardiovascular risk

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Introduction

Chronic kidney disease (CKD) is a serious public health issue, characterized by kidney structural and functional abnormalities.[1] Diabetes mellitus and hypertension are common underlying diseases associated with CKD. Major complications of CKD include anemia, cardiovascular disease, renal osteodystrophy, and metabolic acidosis (MA).[2,3] These complications are mainly responsible for the increased morbidity and mortality of the disease.

Metabolic acidosis is present in approximately 15% of patients with CKD, due to the inability of the kidney to synthesize ammonia and excrete hydrogen ions, and

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is a well-recognized complication of CKD.[4] MA often brings about a range of adverse effects in CKD patients, such as insulin resistance, increased cardiovascular risk, impaired muscle function, systemic inflammation, lower bone mineral density and increased fracture risk.[5–7] Moreover, the relationship between impaired renal function and increased mortality in the CKD patients is positively related.[8,9] Even though MA is a recognized risk factor for CKD, there is no clinically established protocol for improving the condition of patients with predialysis CKD.

Cardiovascular disease is the main cause of death in CKD patients.[10] In CKD patients, cardiovascular diseases mainly manifest as impaired vascular endothelial function and accelerate the progress of arteriosclerosis.[11] The T50 calcification inhibition test (T50-test) is a comprehensive functional test that analyzes the overall propensity of serum calcification. The in vitro diagnostic test is used to measure the conversion of primary to secondary calciprotein particles into serum. The half-maximum time for this conversion is called "T50", and the unit is minutes (min).[12] Low T50-time was related to progressive aortic stiffening and to all-cause mortality in non-dialysis CKD patients.[13] Interventions to decrease vascular calcification and thus reduce mortality in CKD patients are of great importance. Hypertension is one of the most relevant risk factors for cardiovascular disease and is closely linked to coronary heart disease and stroke. The pathogenesis of the arterial dysfunctions can only be partially explained by conventional cardiovascular risk factors, thus suggesting a mechanism related to renal insufficiency. Furthermore, MA can accelerate progression of cardiovascular disease.[14,15] Low serum bicarbonate levels have been associated with low T50-time, and sodium bicarbonate supplementation appears to be an effective regulator of calcification propensity.

Clinical practice guidelines suggest that treatment with alkalinizing agents (sodium bicarbonate and sodium citrate) improves the renal function of patients with CKD. Oral sodium bicarbonate is more likely to correct acid-base disturbance in CKD patients than sodium citrate to counteract MA in clinical practice.[16,17] There have been reports on the role of oral bicarbonate supplementation in correcting the MA.[18,19] The 2012 Kidney Disease Improving Global Outcomes guideline suggests base administration for CKD patients with serum bicarbonate concentration <22 mEq/L.[20] The National Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends administration

of a base to maintain the value within the normal range, which is 22–29 mEq/L.[21] However, there are few patient-level data to support the practice of using oral bicarbonate supplementation in clinical.[22,23] Moreover, only a few studies have indicated whether sodium bicarbonate can effectively prevent adverse cardiovascular outcomes in advanced CKD, and whether it is safe in the context of increased sodium load, rather than merely increasing circulating sodium bicarbonate concentration.

A previous meta-analysis of small trials suggested a modest beneficial effect of sodium bicarbonate on estimated glomerular filtration rate (eGFR) and serum bicarbonate levels, indicating an uncertain effect on progression of kidney disease.[24] However, the study did not examine its effects on cardiovascular disease. To summarize the latest evidence on this topic, we conducted a systematic review and meta-analysis to examine the safety and efficacy of oral sodium bicarbonate supplementation in patients with CKD.

Patients and Methods

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and a prespecified registered protocol in PROSPERO (CRD42020207185).

Search Strategy

PubMed, Embase and Cochrane CENTRAL databases were searched for relevant full-text studies (published between Jan. 2015 and Aug. 2020) (Supplemental Table S1). We also searched Clinicaltrials.gov and abstracts presented in the American Society of Nephrology annual meetings (2015–2020). The search was limited to randomized controlled trials (RCTs) conducted on human subjects. No language restrictions were applied.

Inclusion and Exclusion Criteria

For inclusion, the studies had to meet the following criteria: (1) include patients with stage 3–5 CKD and chronic MA, or those with low-normal serum bicarbonate (22–24 mEq/L); (2) include oral sodium bicarbonate therapy for the treatment of CKD in the experimental group and no treatment, usual patient care, or placebo therapy in the control group; (3) randomized controlled trial and (4) be available as a full-text publication. The exclusion criteria were as follows: (1) studies on end-stage kidney disease (ESKD) patients, dialysis and kidney transplantation patients, (2) studies evaluating the effect of intravenous

sodium bicarbonate on acute MA, (3) studies with inconsistent outcome indicators, (4) inability to extract the corresponding data, and (5) observational or non-randomized trials.

Measured Outcomes

1. Kidney disease progression end points: change in eGFR decline at the end of the study period; serum bicarbonate; serum creatinine; and change in urinary albumin-to-creatinine ratio (ACR).

2. Cardiovascular risk outcomes: T50-time (an indicator of vascular calcification); systolic and diastolic blood pressure (BP).

3. Adverse effects and electrolyte changes: body weight; 24 h urinary sodium excretion; urine pH; mean mid-arm muscle circumference; changes in electrolyte measurements (eg, serum albumin, serum phosphate, serum potassium, serum calcium).

Data Collection

The initial searches were independently conducted by two authors (Qiang Li and Jinglin Wang) according to the inclusion and exclusion criteria, and disagreements were settled through consensus. Subsequently, the authors further searched for the full text of the relevant studies to determine which among them ultimately satisfied the inclusion criteria and cross-checked. Data were extracted using a standard data extraction sheet, including author names, year of publication, number of participants receiving oral sodium bicarbonate or placebo, study type, baseline eGFR (mL/min per 1.73 m^2), duration of follow-up, and outcomes.

The quality of the studies was independently assessed by two authors (Fang Cheng and Fang Zeng) without blinding to authorship or journal, using the Cochrane risk of bias tool in several domains, viz. blinding of investigators and participants, personnel and outcome assessors, completeness of outcome data, reporting of selected outcomes, random sequence generation, allocation concealment, and other sources of bias.

Patient and Public Involvement

No patients were involved.

Statistical Analysis

Heterogeneity was evaluated by using the Cochrane's Q and I^2 statistic values, where $I^2 < 50\%$ and $P > 0.10$, indicated non-significant heterogeneity, and therefore, the fixed effect models were used to ensure the robustness and sensitivity of the selected models to detect outliers. On the contrary, in case of clinical heterogeneity, the random-effect model should be selected. A sensitivity analysis was performed using the fixed-effect models and reported separately if the result differed from that of the random-effect model. For continuous variables, MD with 95% CIs was used to assess the effects of treatment (such as eGFR decline, serum bicarbonate, etc.). We assessed publication bias using funnel plots to determine the asymmetry when the number of studies was more than 5. Publication bias was determined using Begg's and Egger's tests; $P < 0.05$ indicated statistical significance. Meta-analyses were performed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 13.2 (StataCorp, College Station, TX, USA).
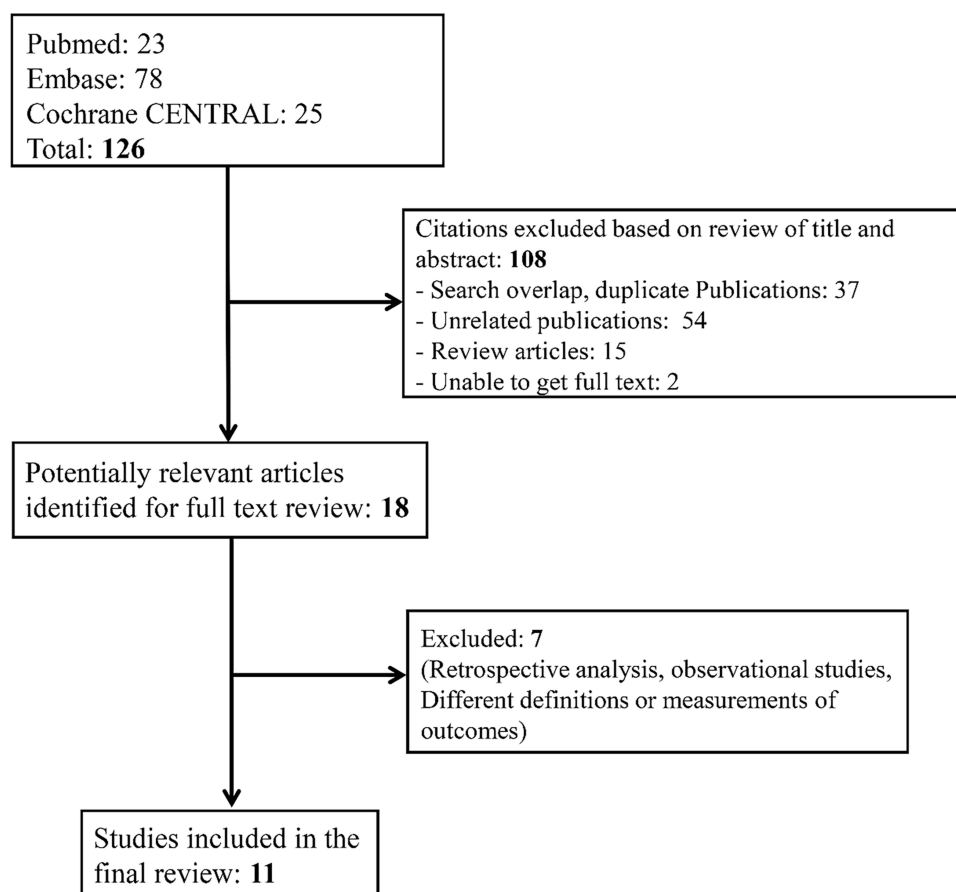
Results

Search Results

Following a comprehensive search of PubMed, Embase, Cochrane CENTRAL databases from 2015 to 2020, a total of 126 publications were identified, of which 108 were excluded because they were review articles, duplicate or unrelated publications, or not able to get full text. Full-text evaluation of 18 potentially relevant articles identified 11 eligible studies involving 1853 participants (Figure 1).

Study Characteristics

In all 11 studies, the effects of oral sodium bicarbonate supplementation were compared with the effects noted in a control group (no treatment, usual care, or placebo), and the extracted information is summarized in Table 1. In most of the included studies, patients with stage 3–5 CKD and MA (serum bicarbonate, 22 mEq/L) were included, except for the studies by Raphael et al.,[25] Melamed et al,[26] and Goraya et al,[27] where patients with low-normal serum bicarbonate levels (22–24 mEq/L). Goraya et al compared both sodium bicarbonate and dietary intervention (fruits and vegetables) with usual care.[27] In the eligible studies, oral bicarbonate supplementation was intended to achieve serum bicarbonate levels between 24 and 28 mmol/L. The starting daily dose was calculated to replace half of the bicarbonate deficit (bicarbonate deficit in mmol=[24-serum bicarbonate in mmol/L]×[total body weight (kg)×0.5]). Depending on the dose required, participants took the

Pubmed: 23
Embase: 78
Cochrane CENTRAL: 25
Total: **126**

Citations excluded based on review of title and
abstract: **108**
- Search overlap, duplicate Publications: 37
- Unrelated publications: 54
- Review articles: 15
- Unable to get full text: 2

Potentially relevant articles
identified for full text review: **18**

Excluded: **7**
(Retrospective analysis, observational studies,
Different definitions or measurements of
outcomes)

Studies included in the
final review: **11**

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

medication two to three times per day. If the serum bicarbonate level was >28 mEq/L, the dose of sodium bicarbonate would be reduced by 50%. Raphael et al assigned participants to three groups: higher-dose (HD-NaHCO$_3$; 0.8 mEq/kg of lean body weight per day), lower-dose (LD-NaHCO$_3$; 0.5 mEq/kg of lean body weight per day) NaHCO$_3$ and placebo groups.[25] The study durations varied from 4 weeks to 5 years.

Study Outcomes

The combined effects of oral sodium bicarbonate supplementation on kidney function (Table 2 and Figure 2), cardiovascular risk (Table 3 and Figure 3) and biochemical measurements (Table 4) are summarized, respectively.

Kidney Function

The results indicated that oral sodium bicarbonate significantly slowed the decline in eGFR (MD −4.44 mL/min per 1.73 m^2, 95% CI, −4.92 to −3.96) compared to that in the control groups: an eGFR increase of 4.44 mL/min per 1.73 m^2 was noted in the sodium bicarbonate group.

There was a significant increase in serum bicarbonate levels (MD, 2.37 mEq/L; 95% CI, 1.03 to 3.72) with treatment. The average serum bicarbonate level was ≥22 mEq/L in the oral sodium bicarbonate groups, except for those in the studies by Alva et al,[28] and Witham et al.[29] Overall, the analyses showed that oral sodium bicarbonate could significantly increase serum bicarbonate levels to the clinically recommended range or the KDOQI stipulations. In addition, oral sodium bicarbonate was significantly reduced in urinary ACR (MD −31.0 mg/g; 95% CI, −36.0 to −26.0) comparing with control group.

Cardiovascular Risk

The sodium bicarbonate intervention lowered the T50-time compared to that in the control group (MD −20.74 min; 95% CI, −49.55 to 8.08); however, there was no significant difference between the two groups. In addition, oral sodium bicarbonate markedly reduced systolic BP (MD −2.97 mmHg; 95% CI, −5.04 to −0.90) and diastolic BP (MD −1.26 mmHg; 95% CI, −2.33 to −0.19).

Table 1 Characteristics of the Authors, 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	Intervention (N)	Outcomes
Bellasi et al;[6] 2016	Randomized, open-label trial	1yr	I: 32±14 C: 35±15	I: Sodium bicarbonate (n=71) C: No treatment (n=74)	HOMA-IR, HOMA %B
Dubey et al;[7] 2018	Randomized, open-label trial	6 mo	I: 29.2 (27.0 to 31.3)[a] C: 31.5 (29.3 to 33.8)[a]	I: Sodium bicarbonate (n=94) C: Standard care (n=94)	Change in MAMC, LBM, eGFR
Gaggl et al;[30] 2018	Randomized, open-label trial	4w	N/A	I: Sodium bicarbonate (n=18) C: No treatment (n=17)	Change in T$_{50}$, eGFR, serum bicarbonate
Kendrick et al;[31] 2018	Open-label, crossover trial	14 wk	I: 25±8 C: 24±8	I: Sodium bicarbonate (n=9) C: No treatment (n=9)	Change in eGFR, PTH, FGF23
Aigner et al;[32] 2019	Randomized, open-label trial	4w	I: 23.64±5.87 C: 27.45±10.05	I: Sodium bicarbonate (n=18) C: No treatment (n=17)	Change in T$_{50}$, eGFR, serum bicarbonate
Di Iorio et al;[33] 2019	Randomized, open-label trial	3y	I: 33.4±12.4 C: 36.9±10.8	I: Sodium bicarbonate (n=376) C: Standard care (n=364)	Change in serum creatinine, All-cause mortality and time to initiation of renal replacement therapy
Goraya et al;[27] 2019	Randomized, open-label trial	5y	I-1: 39.6±6.6 I-2: 39.4±6.4 C: 39.5±6.9	I-1: HCO3 (n = 36) I-2: F + V (n = 36) C: Standard care (n=36)	Change in eGFR, indicators of CVD risk
Melamed et al;[26] 2019	Randomized, open-label trial	2y	I: 36.4±11.4 C: 36.2±11.1	I: Sodium bicarbonate (n=74) C: Placebo (n=75)	Change in muscle function, adverse events
Alva et al;[28] 2020	Randomized, open-label trial	9 mo	I: 22.39±4.08 C: 21.21±4.37	I: Sodium bicarbonate (n=33) C: Standard care (n=34)	Change in eGFR, bicarbonate, muscle mass and serum albumin
Raphael et al;[25] 2020	Double-blind, paralleled trial	28w	I-1: 36±10 I-2: 37±10 C: 35±9	I-1: HD-NaHCO3 (n=90) I-2: LD-NaHCO3 (n=52) C: Placebo (n=52)	The prescribed dose at week 28, change in serum bicarbonate and eGFR, ACR, urinary ammonium excretion, urinary pH
Witham et al;[29] 2020	Double-blind, paralleled trial	2y	I: 19.7±6.5 C: 18.2±6.4	I: Sodium bicarbonate (n=152) C: Placebo (n=148)	SPPB, EuroQoL EQ-5D-3L, renal function, disease-specific health-related quality of life

Note: [a]Median (95% confidence interval).
Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; I, intervention group; C, control group; HOMA-IR, homeostatic model assessment–insulin resistance; HOMA %B, homeostatic model assessment–b pancreatic cell function; T50, half-maximum time of the conversion of primary to secondary calciprotein particles; F+V, fruits and vegetables, MAMC, midarm muscle circumference; LBM, lean-body mass; KRT, kidney replacement therapy; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; N/A, not available; CVD, cardiovascular disease; HD-NaHCO3, high dose NaHCO3; LD-NaHCO3, low dose NaHCO3; ACR, change in urinary albumin to creatinine ratio; SPPB, short physical performance battery; EuroQoL, EQ-5D-3L, generic health-related quality of life.

Biochemical Measurements

Oral sodium bicarbonate significantly increased serum calcium level (MD 0.12 mg/dl; 95% CI, 0.05 to 0.19) and serum phosphate level (MD 0.09 mg/dl; 95% CI, 0.04 to 0.15) compared to those in the control groups. However, there were no significant differences in serum potassium and serum albumin levels.

Adverse Effects

Oral sodium bicarbonate significantly increased the 24-hour urinary sodium excretion (MD 24.31 mEq/24 h;

95% CI, 21.74 to 26.89). In contrast to control group, sodium bicarbonate supplementation led to an increase in body weight (MD 0.25 kg; 95% CI, −1.12 to 1.61), urine pH (MD 0.23; 95% CI, 0.16 to 0.31), and mean mid-arm muscle circumference (0.14 cm; 95% CI, −0.46 to 0.74), although these changes were not statistically significant (Table 5).

Study Quality and Publication Bias

Supplemental Figure S1 outlines the publication bias of the included studies. Publication bias was not determined

Table 2 The Effects of Oral Sodium Bicarbonate on Kidney Disease Progression End Points in Patients with CKD

Outcomes	No. of Studies	No. of Patients	Effect Estimate MD [95% CI]	P-value	I^2%
eGFR decline, mL/min per 1.73 m^2	8	778	−4.44[−4.92 to −3.96]	<0.001	9
Serum bicarbonate, mEq/L	10	1781	2.37 [1.03 to 3.72]	<0.001	98
Creatinine (mg/dL)	1	188	−0.5 [−0.56 to-0.44]	<0.001	N/A
Urinary ACR, mg/g	1	104	−31.0 [−36.0 to −26.0]	<0.001	N/A

Abbreviations: CKD, chronic kidney disease; No, number; eGFR, estimated glomerular filtration rate; MD, mean differences; ACR, change in urinary albumin to creatinine ratio.

for outcomes other than serum bicarbonate levels because of the small number of studies (fewer than 10 studies) (Supplemental Table S2), Bias was determined using the Begg's and Egger's tests, and the results showed that there was publication bias for the outcome of serum bicarbonate levels.

Discussion

MA is a complication of CKD and is associated with bone demineralization, increased protein catabolism, and reduced insulin sensitivity.[30,31] Current guidelines recommend treatment of MA in CKD with sodium (Na$^+$)-based alkali, such as sodium bicarbonate.[32] The association of

MA with CKD progression and poor kidney function has been widely reported.[27,33] An adverse effect of long-term sodium bicarbonate supplementation in patients with CKD is sodium mediated fluid retention, resulting in weight gain, peripheral edema, elevated blood pressure and even heart failure.[34] Although previous studies have demonstrated an improvement in kidney function, differences in study protocol and small sample size prevented from reaching definitive conclusions.[35] To date, there has been no consensus on the effect of oral sodium bicarbonate supplementation on vascular endothelial function. This meta-analysis focused on MA treatment in patients with CKD who received oral sodium bicarbonate versus
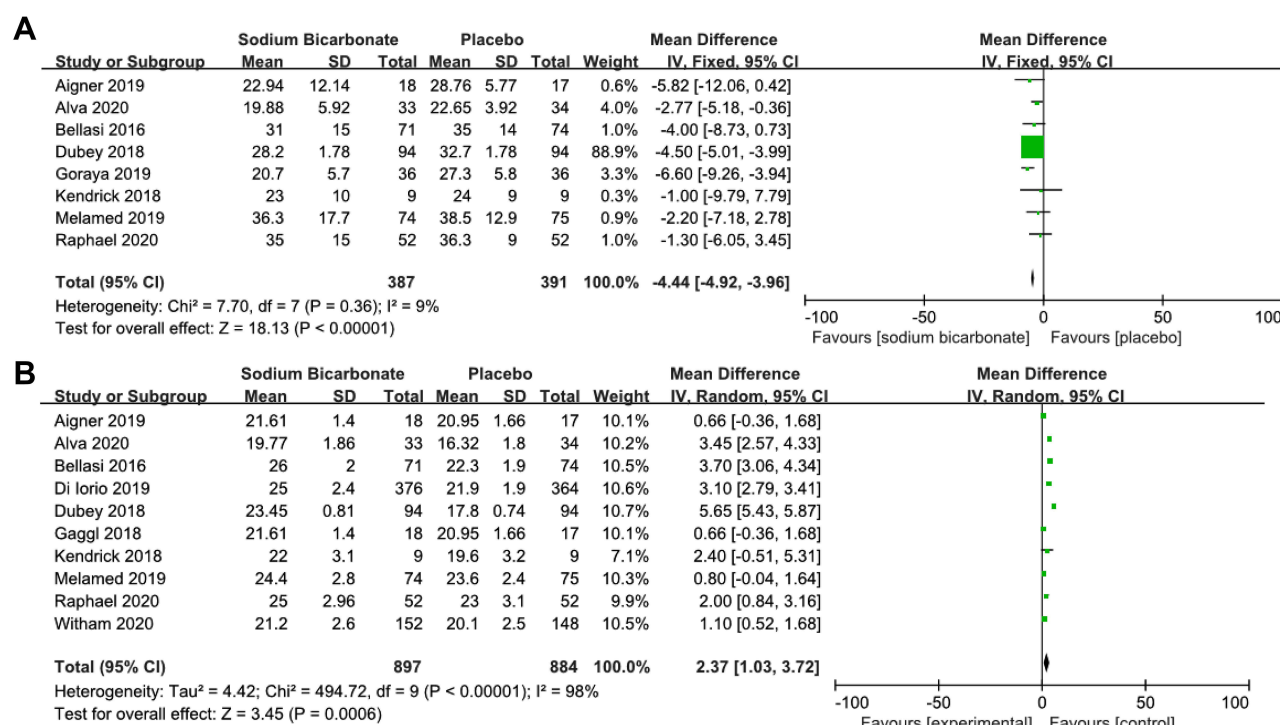
Figure 2 The decline in estimated glomerular filtration rate (eGFR) and serum bicarbonate level at the end of study period with oral sodium bicarbonate. (**A**) Forest plot of decline in eGFR. (**B**) Forest plot of serum bicarbonate level.
Abbreviations: df, degrees of freedom; IV, inverse variance; SD, standard deviation; CI, confidence interval.

Table 3 The Effects of Oral Sodium Bicarbonate on Cardiovascular Risk Outcomes in Patients with CKD

Outcomes	No. of Studies	No. of Patients	Effect Estimate MD [95% CI]	P-value	$I^2\%$
T50-time	3	88	−20.74[−49.55 to 8.08]	0.16	0
Systolic BP, mm Hg	6	1312	−2.97 [−5.04 to −0.90]	0.005	56
Diastolic BP, mm Hg	5	1395	−1.26 [−2.33 to −0.19]	0.02	0

Abbreviations: CKD, chronic kidney disease; No, number; MD, mean differences; T50 time, half-maximum time of the conversion of primary to secondary calciprotein particles; BP, blood pressure.

patients who were untreated, received routine care, or a placebo.

Previous studies have revealed that serum bicarbonate levels were associated with kidney function and mortality in CKD patients.[36] Mortality has been shown to increase at bicarbonate levels <17 and >27 mEq/L.[37] The KDIGO 2012 guidelines recommend alkali therapy when the bicarbonate levels are <22 mEq/L but do not specify any evidence-based target levels. Similarly, the Renal Association of Great Britain and Caring for Australians with Renal Impairment proposal to maintain serum bicarbonate levels >22mEq/L.[38] However, evidence-based optimal therapeutic targets for venous bicarbonate levels to be maintained in pre-dialysis CKD are unknown.

It is well-known that decreased eGFR is very common in patients with CKD. eGFR is an indicator of disease severity used to monitor responses to treatment in clinical practice.[39] Retrospective studies have confirmed that MA is associated with a more rapid decline in kidney function.[40] It is estimated that 30–50% of patients with CKD develop MA, as the eGFR drops to 30–40 (mL/min/1.73m²).[41] Krolewski et al confirmed that an eGFR loss of ≥3.3% per year occurs in CKD.[42] Nonetheless, other studies have found that oral sodium bicarbonate therapy can reduce kidney dysfunction and delay the decline in eGFR.[36] Therefore, the decline in eGFR was chosen as an indicator of the progression in renal function. Our results indicated that oral sodium bicarbonate
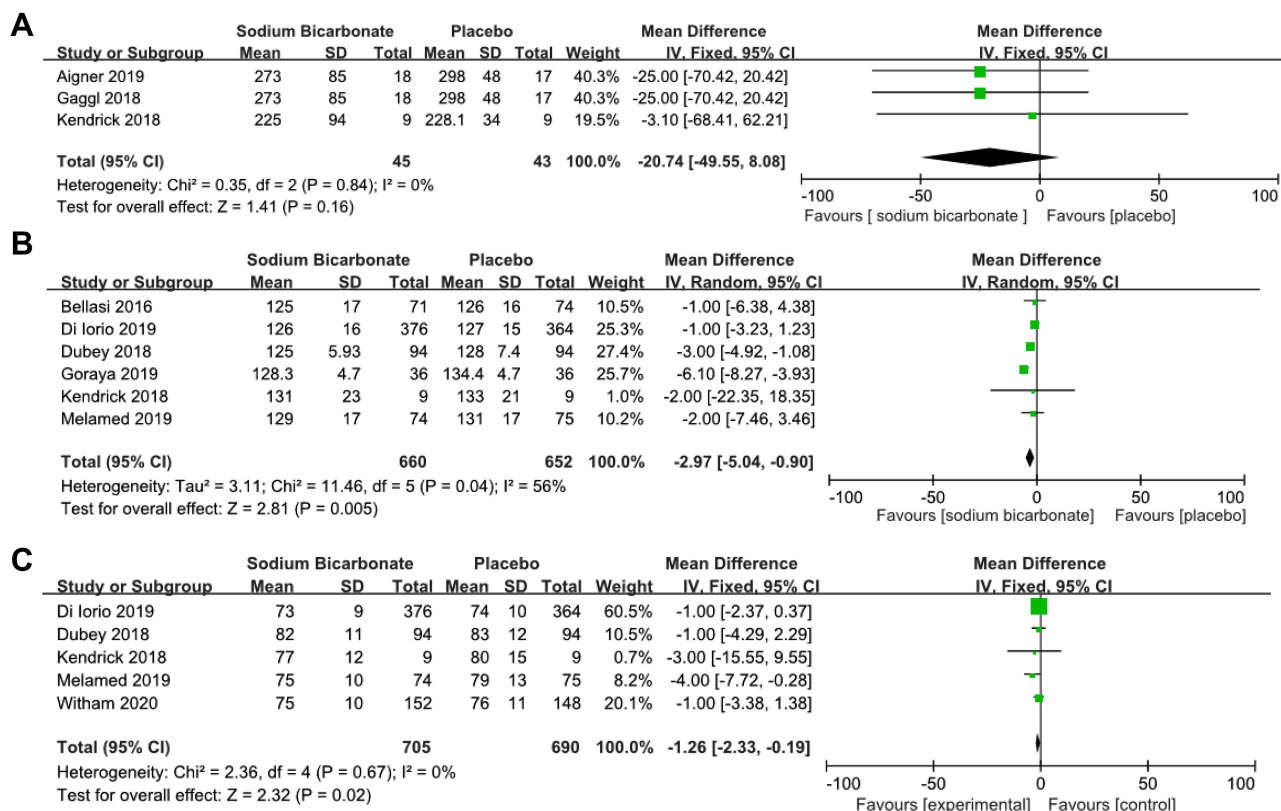
Figure 3 The effects of oral sodium bicarbonate on cardiovascular risk outcomes in patients with chronic kidney disease (CKD). (**A**) Forest plot of half-maximum time of the conversion of primary to secondary calciprotein particles (T50 time). (**B**) Forest plot of systolic blood pressure (BP). (**C**) Forest plot of diastolic BP.
Abbreviations: df, degrees of freedom; IV, inverse variance; SD, standard deviation; CI, confidence interval.

Table 4 The Effects of Oral Sodium Bicarbonate on Change in Biochemical Measurements

Outcomes	No. of Studies	No. of Patients	Effect Estimate MD [95% CI]	P-value	I^2%
Serum potassium, mEq/L	4	1224	0.01 [−0.06 to 0.07]	0.94	0
Serum calcium, mg/dl	3	88	0.12 [0.05 to 0.19]	0.007	0
Serum phosphate, mg/dl	4	276	0.09 [0.04 to 0.15]	0.001	57.4
Serum albumin, g/L	4	1030	0.12 [0.09 to 0.15]	0.18	31.4

Abbreviations: No, number; MD, mean differences.

Table 5 Adverse Effects of Oral Sodium Bicarbonate in Patients with CKD

Outcomes	No. of Studies	No. of Patients	Effect Estimate MD [95% CI]	P-value	I^2%
Body weight, kg	3	1077	0.25 [−1.12 to 1.61]	0.725	0
24 h urinary sodium excretion, mEq/24 h	4	1067	24.31 [21.74 to 26.89]	<0.001	92.8
Urine pH	3	327	0.23 [0.16 to 0.31]	0.062	53.4
Mean mid-arm muscle circumference (cm)	2	488	0.14[−0.46 to 0.74]	0.64	0

Abbreviations: CKD, chronic kidney disease; No, number; MD, mean differences.

supplementation significantly increased serum bicarbonate levels, resulting in a slower decline in eGFR and a reduction in ACR, which is in agreement with an earlier study that also showed a slower decline in eGFR after bicarbonate supplementation.[43]

Reducing vascular calcification can reduce mortality in patients with CKD.[44] MA may contribute to increased inflammation[45,46] and production of angiotensin II, aldosterone, and endothelin-1,[47–49] which resulting in endothelial dysfunction in patients with CKD. Sodium bicarbonate supplementation appears to be an effective regulator of vascular calcification propensity. However, the effects of sodium bicarbonate on long-term cardiovascular function have not yet been clearly elucidated. Results of animal experiments showed that correction of MA could increase vascular calcification.[50] Nevertheless, some studies have shown that the gradual development of MA with decreasing renal function could actually reduce vascular calcification.[14] Observational studies have reported associations between lower serum bicarbonate levels and increased risks of endothelial dysfunction, hypertension, heart failure, and death.[40] A previous study also indicated that correction of MA seems to have favorable effects on vascular function, which was assessed by flow-mediated dilation.[24] In addition, compared with patients with bicarbonate concentrations between 22 and 26 mmol/L, patients with persistently high serum bicarbonate levels (>26 mmol/L) actually had an increased risk of heart failure and mortality.[51]

T50, a novel marker of serum calcification propensity, is used to determine the overall calcification propensity of serum before and after sodium bicarbonate treatment.[13] Studies have shown that low T50-time is related to progressive aortic sclerosis and all-cause mortality in non-dialysis CKD, dialysis, and transplant patients.[52] Our results showed that there was no significant difference in T50 between the sodium bicarbonate group and the control group. However, the positive effects of sodium bicarbonate may have been masked by the parallel increase in phosphate concentrations, which are expected to have an opposing effect on calcification propensity. An earlier study indicated that serum T50 was inversely associated with circulating phosphate, age, eGFR.[53] The results of the study indicated that serum phosphate levels increased significantly, which contributed to explaining the phenomenon mentioned above. Furthermore, the results showed significantly increased serum calcium levels; however, serum calcium concentrations cannot reflect the nature of serum calcification. Due to impaired renal function in regulating calcium and abnormal bone transformation in patients with CKD, vascular calcification occurred in a considerable number of patients before the increase in blood calcium levels.[54] Moreover, our study showed that sodium bicarbonate decreased systolic or diastolic BP. However, this may be attributed to the increased antihypertensive therapy when patients receive sodium bicarbonate in clinical practice.

Potential benefits of oral sodium bicarbonate supplementation on micro-nutritional status such as serum albumin, potassium levels, and mid-arm muscle circumference

were investigated in a limited number of patients, and no significant differences were found in our analysis. A major concern regarding long-term sodium bicarbonate supplementation in patients with CKD is sodium-mediated fluid retention leading to peripheral and pulmonary edema, weight gain, and increased BP.[55] A significant proportion of patients on sodium bicarbonate would require increased diuretic therapy. In addition, the results showed significantly increased urinary sodium excretion in patients with CKD after oral sodium bicarbonate therapy. Some studies have found an association between higher urinary sodium excretion and kidney disease progression and cardiovascular events.[56,57] Diuretic therapy could also partially account for the increased urinary sodium excretion in the sodium bicarbonate group. Although blood pressures were comparable, this might be attributed to a higher dosage of diuretics. However, there was no significant increase in urine pH. Hence, these data indicated that sodium bicarbonate supplementation in patients with CKD was relatively safe.

Strengths and Limitations of This Study

- This is a comprehensive systematic review, including meta-analysis, of the effectiveness and safety of oral sodium bicarbonate in CKD patients.
- Our results show that sodium bicarbonate may slow the decline rate of kidney function and potentially significantly improve vascular endothelial function in patients with CKD.
- The main limitation of our analysis is the lack of long-term follow-ups of oral sodium bicarbonate on patient-centered endpoints, including mortality.
- Most of the included studies were single-center, open-label trials that enrolled only a small number of patients, preventing the analysis of patient-centered endpoints.
- There was significant clinical heterogeneity of the included trials, such as sodium bicarbonate dose, control strategy, baseline eGFR and serum bicarbonate levels, and treatment duration, so it was difficult to obtain an exact conclusion.

Conclusion

In this meta-analysis, the efficacy and safety of oral sodium bicarbonate in patients with CKD were investigated. The results suggested that treatment of MA with sodium bicarbonate may delay the decline of kidney function while maintaining serum calcification propensity in patients with CKD, indicating that treatment of MA with sodium bicarbonate is safe and overall improves kidney function.

Abbreviations

CKD, chronic kidney disease; MA, metabolic acidosis; RCT, randomized controlled trial; MD, mean differences; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ACR, change in urinary albumin-to-creatinine ratio; CPP, calciprotein particles; T50-time, half-maximum time of the conversion of primary to secondary calciprotein particles; BP, blood pressure.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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