scientific reports

Check for updates

OPEN

Effect of oral sodium bicarbonate supplementation on urine TGF-β in normal serum bicarbonate CKD, a randomized controlled trial

Nipon Ngupis, Bancha Satirapoj, Theerasak Tangwonglert, Ouppatham Supasyndh, Paramat Thimachai & Narongrit Siriwattanasit✉

The consequences of chronic subclinical metabolic acidosis, characterized by an increase in single nephron ammonium generation, contribute to the progression of chronic kidney disease (CKD). Therefore, sodium bicarbonate ($NaHCO_3$) supplementation in CKD with normal serum bicarbonate patients may reduce kidney fibrosis and slow CKD progression. This study aimed to evaluate the impact of high-dose $NaHCO_3$ supplementation on urinary transforming growth factor-beta (TGF-β), a biomarker of kidney fibrosis, in non-diabetic CKD patients with normal serum bicarbonate levels. We conducted a single-center, randomized, open-label controlled trial in patients with non-diabetic CKD stage 3–4 and normal serum bicarbonate (22–26 mEq/L). Participants were randomized to receive high-dose $NaHCO_3$ (0.8 mEq/kg/day) or standard care for 12 weeks. The primary outcome was the change in urinary TGF-β-to-creatinine ratio from baseline. Secondary outcomes included changes in urinary albumin-to-creatinine ratio (UACR), urine pH, serum electrolytes, blood pressure, and adverse events. A total of 64 participants were randomized ($NaHCO_3$ group: n = 32; control group: n = 32). There was no significant difference in the percentage change of urinary TGF-β ($NaHCO_3$: −1.86% vs. control: 5.75%; p = 0.477). However, the $NaHCO_3$ group demonstrated a significant increase in urine pH mean difference (0.56; 95% CI: 0.3,0.82 vs. 0,95% CI −0.24,0.24; p = 0.002) compared to the control group. Similarly, no significant differences were observed in UACR, serum electrolytes, blood pressure, or body weight between groups. No serious adverse events were reported. High-dose $NaHCO_3$ supplementation in non-diabetic CKD patients with normal serum bicarbonate levels did not significantly reduce urinary TGF-β over 12 weeks but effectively increased urine pH without adverse effects. These findings suggest that $NaHCO_3$ is safe; however, its role in modulating profibrotic biomarkers in CKD requires further investigation. Longer-term studies and alternative alkali therapies should be explored to determine the optimal strategies for preserving kidney function in this population.

Clinical trial registration: TCTR20240817007 (17/08/2024).

Keywords Subclinical metabolic acidosis, Chronic kidney disease, Urinary TGF-β

Background

Chronic kidney disease (CKD) represents a worldwide health problem because studies suggest its prevalence reaches 8–16%. In Thailand, it is a significant public health issue. The Thai Society of Nephrology conducted the Screening and Early Evaluation of Kidney Disease (SEEK) study from 2007 to 2008 which demonstrated that the prevalence of CKD was 17.5%[1]. One of the key pathophysiological mechanisms contributing to CKD progression is metabolic acidosis, which is associated with increased renal ammoniagenesis and tubulointerstitial fibrosis, leading to accelerate kidney function decline[2].

The diagnosis of metabolic acidosis in patients with CKD is made when serum bicarbonate levels fall below 22 mEq/L[3]. Among CKD patients, some individuals demonstrate normal serum bicarbonate concentrations

Division of Nephrology, Department of Medicine, Phramongkutklao Hospital, College of Medicine, Bangkok 10400, Thailand. ✉email: nsiriwattanasit@gmail.com

despite evidence of subclinical acid retention. This condition, termed eubicarbonatemic metabolic acidosis, is characterized by elevated renal ammonium production. Increased renal ammoneogenesis activatates profibrotic pathways via transforming growth factor-beta (TGF-β)[4]. TGF-β is considered a biomarker of tubulointerstitial fibrosis in CKD progression and a potential therapeutic target[2,5].

Patients with moderate to severe chronic kidney disease (CKD stage 3–4) may exhibit normal serum bicarbonate levels[6], which can be explained by eubicarbonatemic metabolic acidosis or subclinical metabolic acidosis. Therefore, oral bicarbonate supplementation in patients with moderate to severe CKD and normal serum bicarbonate levels may reduce urine transforming growth factor-beta (TGF-β) and slow CKD progression.

A study on the early stages of CKD found that supplementation with oral sodium bicarbonate ($NaHCO_3$) or alkali sources from fruits and vegetables decreased urinary ammonia and profibrotic biomarkers and may have preserved the eGFR[7,8]. However, in the advanced-stage diabetic CKD with normal bicarbonate levels[9], a low dose of 0.5 mEq/kg/day sodium bicarbonate did not significantly reduce urinary TGF-β over six months. The modest effect of sodium bicarbonate on urinary ammonium excretion may explain this result. A higher dose of 0.8 mEq/kg/day was examined for its efficacy in lowering urinary ammonium excretion more effectively than the low dose while not increasing adverse events[10–12].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines in 2024 recommend the use of sodium bicarbonate orally to normalize blood bicarbonate levels when serum bicarbonate level less than 18 mEq/L[13]. However, the supplementation of oral $NaHCO_3$ in CKD patients with normal serum bicarbonate levels remains uncertain.

This study aims to investigate the effects of high-dose $NaHCO_3$ supplementation (0.8 mEq/kg/day) on urinary TGF-β in non-diabetic CKD patients with normal serum bicarbonate levels. By evaluating both biochemical and clinical outcomes, this study seeks to provide a clearer understanding of whether alkali therapy offers protective benefits beyond traditional indications for metabolic acidosis correction. The findings may help refine clinical guidelines and inform the development of targeted interventions for CKD management.

Objectives

The primary objective of this study is to evaluate the impact of high-dose oral NaHCO3 supplementation on urinary TGF-β levels and, secondarily, on serum electrolyte levels and urinary indices in patients with CKD.

Methods

Study designs

This study was a single-center, randomized, open-label controlled trial evaluating oral $NaHCO_3$ supplementation at 0.8 mEq per kg of lean body weight in non-diabetic CKD stage 3–4 patients with normal serum bicarbonate concentrations. The trial was conducted at Phramongkutklao Hospital over a 12-week follow-up period from October 2023 to March 2024. The Institutional Review Board (IRB) Ethics Committee of the Royal Thai Army Medical Department (IRBTS) approved the trial protocol on October 8, 2023, with an amendment approved on December 12, 2023, under the code R113 h/66."

Study populations

The inclusion criteria were age >18 years, non-diabetic CKD stage 3–4 (eGFR by CKD-EPI of 15–59 mL/min/1.73 m^2), and serum bicarbonate levels of 22–26 mEq/L. Key exclusion criteria included the use of chronic daily oral alkali (such as sodium bicarbonate, sodium citrate, potassium citrate, etc.), serum potassium levels <3.3 or >5.5 mEq/L, self-reported vegetarianism, Symptomatic heart failure classified as NYHA Class 3 or 4, history of staghorn calculi, active glomerular disease requiring immunosuppressive agents, kidney transplant recipients, pregnancy.

Randomization, treatment, and follow-up

As shown in Fig. 1, participants were randomized in blocks of four to receive oral sodium bicarbonate for 12 weeks or to the control group. The daily dose of sodium bicarbonate was 0.8 mEq/Kg of lean body weight. This dose selection was based on findings from the BASE Pilot Trial[10], which demonstrated that this dose lowered urinary ammonium excretion. The high-dose sodium bicarbonate was well tolerated, with no significant difference in adverse events compared to the placebo. Each $NaHCO_3$ tablet contained 300 mg of sodium bicarbonate, equivalent to 3.6 mEq per tablet. Lean body weight was calculated for each patient. Outpatient department visits occurred at baseline and 12 weeks after randomization. Patients' demographic data, comorbidities, and medication information were collected. Blood pressure and body weight were measured at each study visit. Blood samples were collected for BUN, creatinine, serum electrolytes, calcium, magnesium, phosphate, albumin. Random, spot urine samples were examined for urinary TGF-β, urine pH, urinary electrolyte, and urine albumin-creatinine ratio. Urinary TGF-β was measured using the Quantikine® ELISA Human TGF-β1 Immunoassay Kit (R&D Systems, Catalog No. DB100B, Minneapolis, MN, USA), according to the manufacturer's instructions.

Outcomes

The primary outcome was percentage change in urinary TGF-β-to-creatinine ratio and mean difference in TGF-β-to-creatinine ratio from baseline between groups.

The secondary outcome was the mean change in urine albumin-to-creatinine ratio, serum electrolytes, calcium, magnesium, phosphate, blood pressure, and body weight from baseline between groups.

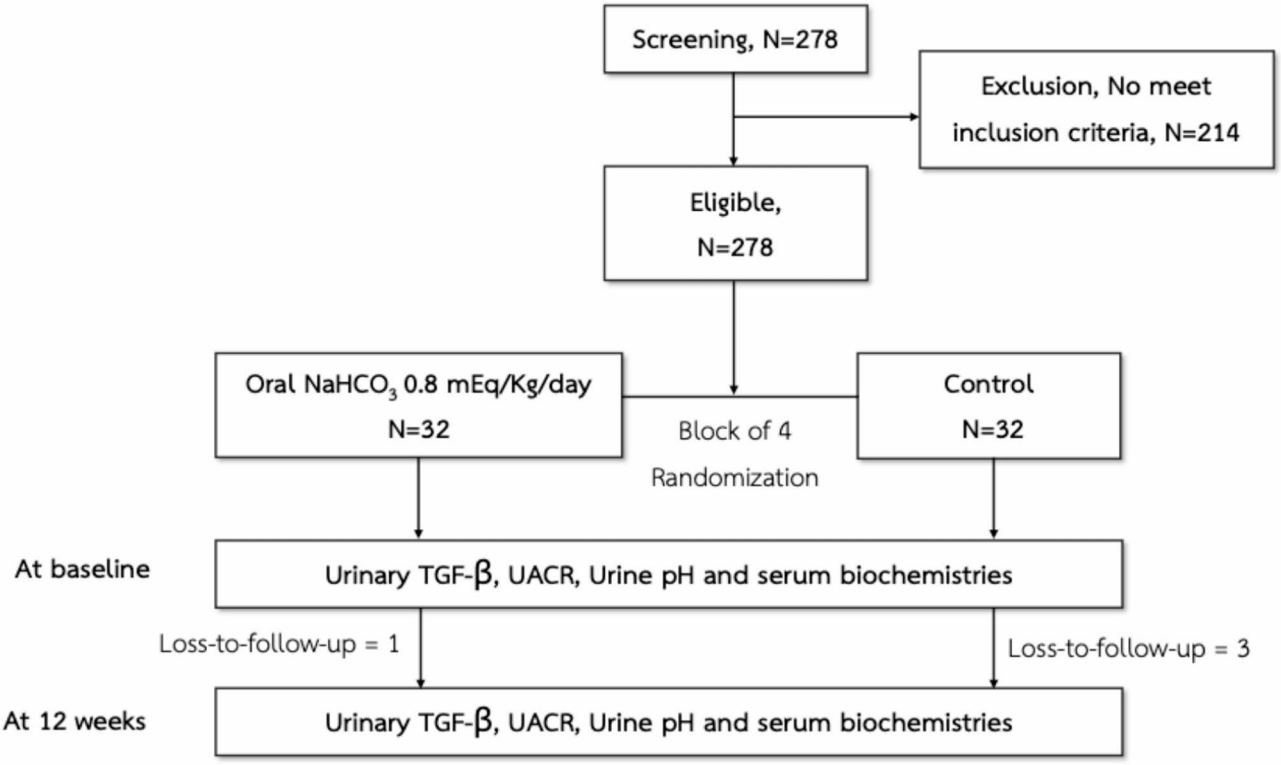

Fig. 1. Flow chart of study.

Sample size

The sample size was calculated based on a randomized trial comparing the Safety, adherence, and pharmacodynamics profile of two doses of sodium bicarbonate in CKD: the BASE Pilot study[10], which provided 90% power. A total of 64 participants were enrolled in this study.

Statistical analyses

Baseline characteristics were expressed as means ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and as frequencies for categorical variables. Normality was assessed using Shapiro-Wilk tests. Comparisons between groups were performed using the Chi-square test or Fisher's exact test for categorical variables, independent t-test for normally distributed continuous variables, and Mann-Whitney U test for non-normally distributed continuous variables. This study was analyzed using an intent-to-treat approach, with the significance level set at $P < 0.05$.

Results

Participants and follow-up

A total of 64 participants were enrolled and randomized into the $NaHCO_3$ group ($n = 32$) and the control group ($n = 32$). The baseline characteristics of all participants are shown in Table 1. Age, sex, eGFR, UACR, and serum bicarbonate levels were generally comparable between the two groups. However, the $NaHCO_3$ group had a slightly lower mean age and higher baseline UACR.

Primary outcome

Changes in urinary TGF-β-to-creatinine levels due to oral sodium bicarbonate supplementation are shown in Table 2; Fig. 2. At week 12, the median urinary TGF-β-to-creatinine difference in the $NaHCO_3$ group was −103.21 pg/g (95% CI: −1080.16, 2285.62), compared to 418.6 pg/g (95% CI: 0, 4142.82) in the control group. This resulted in a median urinary TGF-β-to-creatinine difference of −521.81 (95% CI: −5222.98, 2285.62; $p = 0.405$) between the two groups. The percentage change in urinary TGF-β-to-creatinine was −1.86% (95% CI: −9.78, 21.95) in the $NaHCO_3$ group and 5.75% (95% CI: 0, 46.67) in the control group, resulting in a difference of −7.61% (95% CI: −56.45, 21.95; $p = 0.477$). There was no statistically significant difference in the percentage change or mean difference in urinary TGF-β-to-creatinine levels between the $NaHCO_3$ and control groups.

Secondary outcomes

Table 3; Fig. 3 present the secondary outcomes for each group. The median urine-albumin to creatinine ratio (UACR) difference in the $NaHCO_3$ group was 5.9 (95% CI: −4.4, 89), compared to 0.15 (95% CI: −0.6, 8.7) in the control group. The median UACR difference between groups was 5.75 (95% CI: −13.1, 89.6; $p = 0.941$).

Characteristics	$NaHCO_3$ ($N = 32$)	Control ($N = 32$)	*p*-value
Age (year)	67.47 ± 17.22	76.06 ± 11.64	0.023
Male, N (%)	26 (81.3%)	21 (65.6%)	0.157
Comorbidities, No. of patients (%) • Hypertension	26 (81.3%)	26 (81.3%)	1
• Coronary artery disease	2 (6.3%)	4 (12.5%)	0.391
• Heart failure	3 (9.4%)	2 (6.3%)	0.641
• Atrial fibrillation	1 (3.1%)	1 (3.1%)	1
• Stroke	2 (6.3%)	1 (3.1%)	0.554
• Cancer	2 (6.3%)	4 (12.5%)	0.391
• Glomerulonephritis	1 (3.1%)	2 (6.3%)	0.554
• Gout	9 (28.1%)	4 (12.5%)	0.120
Drugs use, No. of patients (%) • ACEIs/ARBs	20 (62.5%)	11 (34.4%)	0.024
• Beta-blockers	10 (31.3%)	10 (31.3%)	1
• Calcium channel blockers	19 (59.4%)	20 (62.5%)	0.798
• Alpha blockers	8 (25%)	11 (34.4%)	0.412
• SGLT2is	1 (3.1%)	1 (3.1%)	1
• Statin	28 (87.5%)	28 (87.5%)	1
• Aspirin	3 (9.4%)	10 (31.3%)	0.03
• Spironolactone	1 (3.1%)	1 (3.1%)	1
• Diuretics	1 (3.1%)	3 (9.4%)	0.302
Body weight (kilogram)	63 ± 12.2	65.15 ± 11.05	0.464
Body mass index (kg/m^2)	23.41 ± 3.41	25.59 ± 4.23	0.027
Systolic blood pressure (mmHg)	135.09 ± 15.24	133.19 ± 16.81	0.636
Diastolic blood pressure (mmHg)	72.34 ± 12.09	67.81 ± 12.29	0.142
Fasting blood sugar (mg/dL)	97.18 ± 10.86	100.22 ± 8.79	0.223
BUN (mg/dL)	26.73 ± 8.81	21.72 ± 6.78	0.013
Creatinine (mg/dL)	1.92 ± 0.62	1.67 ± 0.36	0.054
eGFR ($mL/min/1.73\ m^2$)	36.41 ± 10.27	37.75 ± 9.64	0.594
• eGFR 45–60, N (%)	8 (25%)	8 (25%)	0.957
• eGFR 30–44, N (%)	14 (43.8%)	15 (46.9%)	
• eGFR 15–29 (%)	10 (31.3%)	9 (28.1%)	
Serum biochemistry • Serum uric acid (mg/dL)	7.27 ± 1.58	7.19 ± 1.7	0.844
• Albumin (g/dL)	4.27 ± 0.39	4.27 ± 0.41	0.955
• Serum sodium (mEq/L)	139.89 ± 1.91	139.91 ± 2.41	0.982
• Serum potassium (mEq/L)	4.57 ± 0.42	4.32 ± 0.46	0.026
• Serum chloride (mEq/L)	105.08 ± 2.09	104.62 ± 2.22	0.397
• Serum bicarbonate (mEq/L)	24.28 ± 1.24	24.74 ± 1.31	0.155
• Serum calcium (mg/dL)	9.44 ± 0.36	9.45 ± 0.5	0.961
• Serum phosphate (mg/dL)	3.32 ± 0.61	3.37 ± 0.68	0.757
• Serum magnesium (mg/dL)	2.07 ± 0.26	2.19 ± 0.18	0.042
Urine biochemistry • Urine albumin-to-creatinine ratio (UACR)	665.78 ± 471.76	91.79 ± 172.74	0.036
• UACR < 30 N, (%)	13 (40.6%)	21 (65.6%)	0.035
• UACR 31–300 N, (%)	6 (18.8%)	7 (21.9%)	
• UACR > 301 N, (%)	13 (40.6%)	4 (12.5%)	
• Urine pH	5.61 ± 0.72	5.8 ± 0.82	0.334
• Urine anion gap	47.85 ± 30.04	46.08 ± 22.86	0.791
• Urine osmolar gap	29.04 ± 21.73	40.18 ± 52.43	0.273
• Urine TGF-β/Cr (pg/gCr)	12,611.42 ± 13,573.2	13,765.09 ± 15,938.22	0.756

Table 1. Characteristics of the patients at baseline. Data presents as mean ± SD.

Change of Outcome	$NaHCO_3$ ($N = 32$)	Control ($N = 32$)	*p*-value
TGF-β/Cr	−103.21 (−1080.16, 2285.62)	418.6 (0, 4142.82)	0.405
TGF-β/Cr change (%)	−1.86 (−9.78, 21.95)	5.75 (0, 46.67)	0.477

Table 2. Primary outcomes. Data presents as median (95%CI). Abbreviation: TGF- β; tumor growth factor-beta.

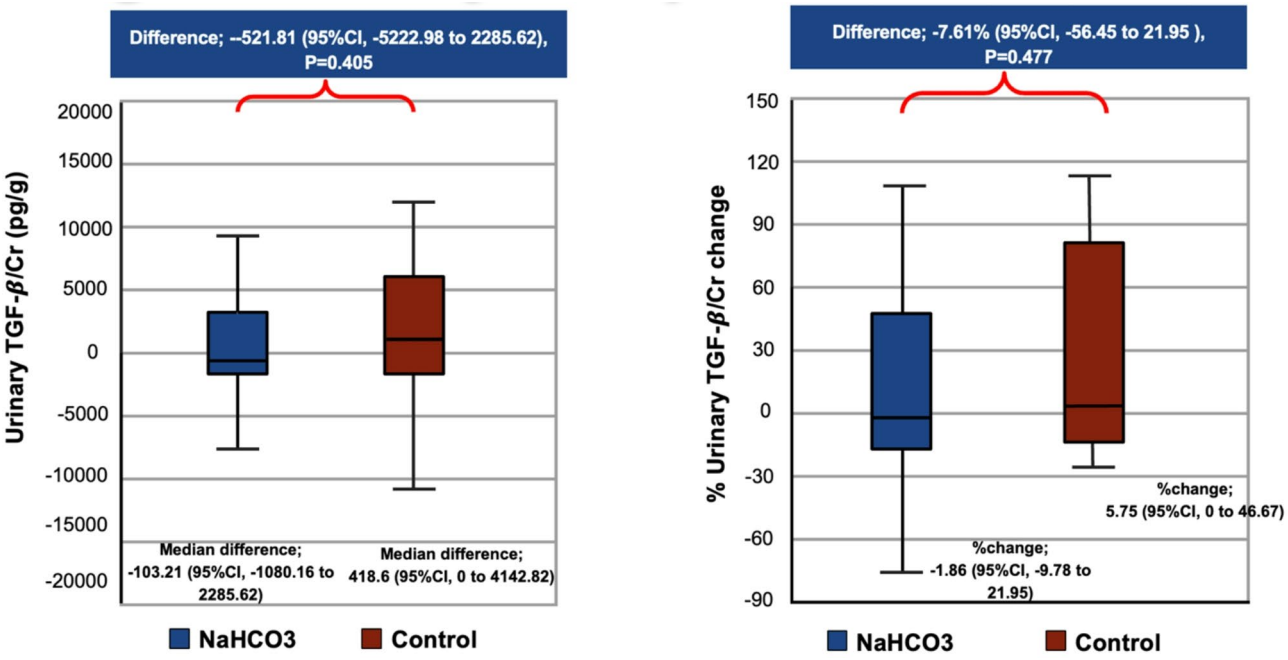

Fig. 2. Change of urinary TGF-β from baseline.

Change of the outcomes	$NaHCO_3$ ($N = 32$) Median (95%CI)	Control ($N = 32$) Median (95%CI)	*p*-value
UACR	5.9 (−4.4, 89)	0.15 (−0.6, 8.7)	0.941
UACR (%)	3.31 (−22.32, 64.29)	7.14 (−5, 32)	0.872
eGFR (mL/min/1.73 m^2)	−0.12 (−1.95, 2.72)	0.94 (0, 2.55	0.493
eGFR change (%)	−0.3 (−6.67, 9.16	2.29 (0, 7.49)	0.420
Serum sodium (mEq/L)	−0.65 (−1.4, 0.3)	0.05 (−0.4, 1)	0.193
Serum potassium (mEq/L)	−0.01 (−0.16, 0.41)	0 (−0.06, 0.25)	0.909
Serum calcium (mg/dL)	0.12 (−0.04, 0.27)	0.08 (0, 0.3)	0.877
Serum phosphate (mg/dL)	0 (−0.11, 0.15)	−0.11 (−0.29, 0.1)	0.307
Serum magnesium (mg/dL)	0.06 (−0.04, 0.15)	0 (0, 0.04)	0.061

Table 3. Secondary outcomes. Data presents as median (95%CI). Abbreviation: UACR; Urine albumin-creatinine ratio.

Regarding the percentage change in UACR, it was 3.31 (95% CI: −22.32, 64.29) in the $NaHCO_3$ group and 7.14 (95% CI: −5, 32) in the control group, resulting in a median percentage change difference of −3.83% (95% CI: −54.32, 69.29; $p = 0.872$) between groups. Other median serum electrolyte differences were also similar between the groups.

Effect of oral sodium bicarbonate

Thirty-two participants received oral sodium bicarbonate supplementation, which increased the mean serum bicarbonate concentration by 0.05 mEq/L and urine pH by 0.56, compared to the control group, which showed no change in urine pH (Table 4).

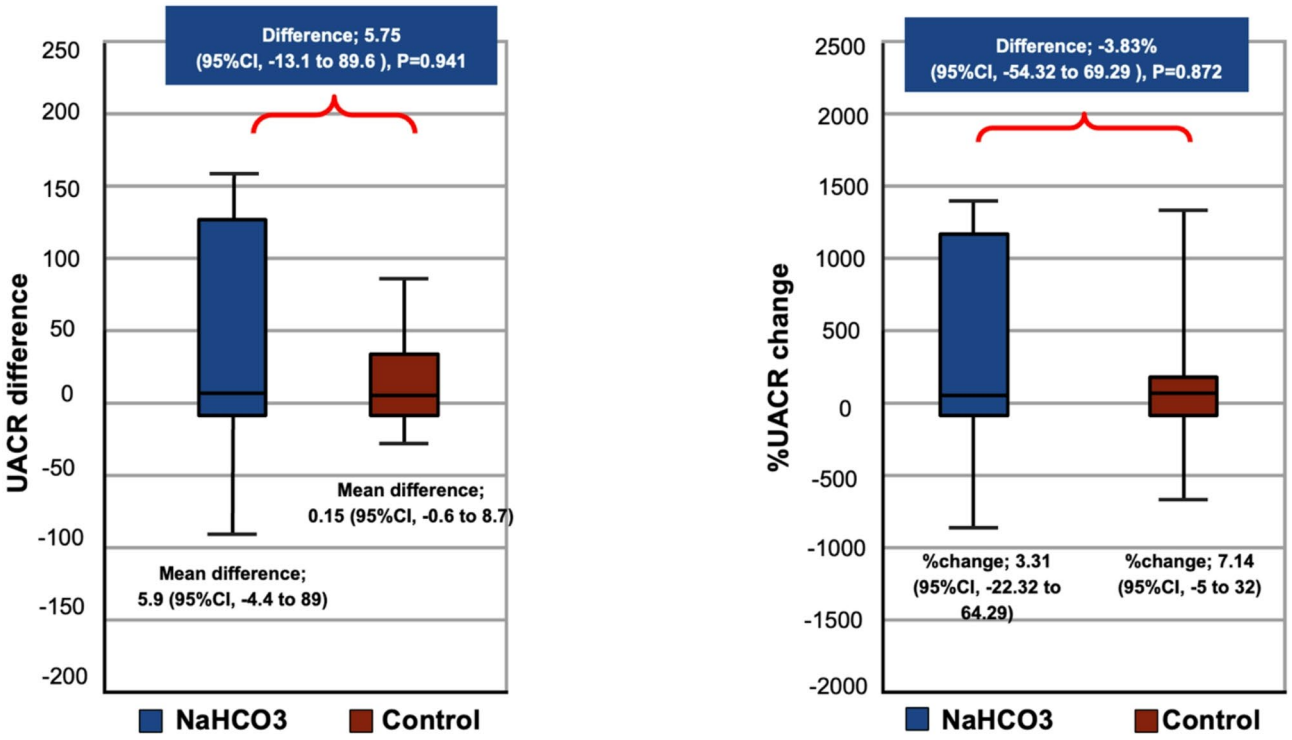

Fig. 3. Change of UACR from baseline.

Change of the outcomes	$NaHCO_3$ ($N = 32$)	Control ($N = 32$)	*p*-value
Serum bicarbonate (mEq/L)	0.05 (−0.83, 0.94)	−0.07 (−0.61, 0.46)	0.802
Urine pH after NaHCO3	6.17 ± 0.75	5.8 ± 0.71	0.043
Mean Urine pH difference	0.56 (0.3, 0.82)	0 (−0.24, 0.24)	0.002
Body weight change (%)	0.17 (−2.4, 2.73)	0.42 (−1.25, 2.1)	0.863
Systolic blood pressure (mmHg)	1.75 (−5.35, 8.85)	0.22 (−6.13, 6.57)	0.744
Diastolic blood pressure (mmHg)	0.22 (−4.41, 4.84)	0.19 (−4.48, 4.85)	0.992

Table 4. Effect of oral sodium bicarbonate. Data presents as mean (95%CI).

Adverse events

No participants discontinued the intervention due to adverse events. Serum electrolyte levels, including sodium, potassium, and bicarbonate, remained stable in both groups. Changes in systolic and diastolic blood pressure were minimal and did not differ significantly between the two groups ($p = 0.744$). These results confirm the safety profile of high-dose $NaHCO_3$ over 12 weeks (Table 4).

Discussion

Our study assessed the effect of high-dose alkali therapy in patients with moderate to severe non-diabetic CKD and normal serum bicarbonate levels. High-dose oral $NaHCO_3$ supplementation (0.8 mEq/kg/day) was investigated for its effects on urinary profibrotic biomarkers levels over 12 weeks. We found that there are no statitically significant reduction in urinary TGF-β. However, our findings provide valuable data on the safety, tolerability, and potential mechanistic pathways of high-dose alkali therapy in CKD management.

The lack of significant change in urinary TGF-β aligns with prior studies such as Raphael et al. (2020)[9], which reported minimal effects of lower-dose $NaHCO_3$ (0.5 mEq/kg/day) on profibrotic biomarkers in diabetic CKD patients. The BASE Pilot Trial[10] has demonstrated that a high oral dose of sodium bicarbonate ($NaHCO_3$) at 0.8 mEq/kg/day can reduce urinary ammonium excretion more effectively than a low dose of 0.5 mEq/kg/day. However, our study extends these findings by demonstrating the safety of higher-dose $NaHCO_3$ and its effect on urinary pH without significant adverse events.

The effect of alkali therapy in chronic kidney disease patients with overt metabolic acidosis, who have serum bicarbonate levels below 22 mEq/L, has been extensively investigated. Studies have found that treatment targeting a serum bicarbonate concentration of 24 to 26 mEq/L may help prevent bone demineralization, skeletal muscle catabolism, and CKD progression[3]. A prior study assessed the supplementation of alkali in patients with

early-stage CKD, using either fruits and vegetables or sodium bicarbonate. The intervention lowered urinary acid excretion and urinary TGF-β levels in patients with or without overt metabolic acidosis[7]. In a 2010 study by Mahajan A et al., the effect of sodium bicarbonate on hypertensive nephropathy in CKD stages 1 and 2 was investigated. The findings showed that after five years, the rate of GFR decline was slower, and eGFR was higher in the intervention group. Additionally, alkali therapy was found to ameliorate kidney endothelin-1 production.

The absence of a significant reduction in urinary TGF-β suggests that high-dose $NaHCO_3$ may not directly modulate this biomarker within a 12-week timeframe. However, the increase in urinary pH observed in the $NaHCO_3$ group supports the hypothesis that alkali therapy can effectively counteract subclinical metabolic acidosis. This finding is clinically relevant, as urinary alkalinization may play a role in mitigating acid-mediated tubulointerstitial damage over longer durations.

This finding may be explained by the salt load effect of sodium bicarbonate, which elevates intraglomerular pressure and increases albuminuria, thereby activating profibrotic biomarkers[14]. For future studies, we recommend using alternative alkali preparations, such as potassium citrate, to mitigate the effects of salt load.

The diagnosis of subclinical metabolic acidosis still lacks a standard. Therefore, some patients selected for this study may not have subclinical metabolic acidosis, and administering oral sodium bicarbonate may not be beneficial. For future studies, we recommend using the measurement of urinary ammonium excretion to identify patients with subclinical metabolic acidosis.

The significant increase in urinary pH suggests that high-dose $NaHCO_3$ effectively addresses subclinical metabolic acidosis without increasing adverse events, which may be clinically relevant in preventing CKD progression over a longer timeframe. This finding aligns with the KDIGO 2024 guidelines[13], which recommend alkali therapy to help maintain acid-base balance in CKD patients.

This study adds to the growing body of literature on alkali therapy in CKD by exploring a higher dose of $NaHCO_3$ supplementation (0.8 mEq/kg/day) than previously studied. The results support the safety of this dose, providing a foundation for future dose-response studies to refine the therapeutic window for bicarbonate supplementation in CKD.

Clinical implications, strengths, and limitations

Our findings have several clinical implications. The safety profile of high-dose sodium bicarbonate ($NaHCO_3$) demonstrated in this study supports its potential use in CKD patients without acidemia, particularly as a strategy for managing subclinical metabolic acidosis. The significant increase in urinary pH suggests that urine alkalinization may serve as an accessible biomarker for monitoring alkali therapy response. While the study did not show a significant reduction in urinary TGF-β, the absence of adverse effects with high-dose $NaHCO_3$ reinforces its potential role in CKD management. Furthermore, these findings align with KDIGO (2024) guidelines, which support alkali therapy for maintaining acid-base balance in CKD patients.

This study has several notable strengths, including its randomized controlled design and the novel exploration of a high-dose sodium bicarbonate ($NaHCO_3$) regimen (0.8 mEq/kg/day) in CKD patients with normal serum bicarbonate levels. The comprehensive monitoring of safety parameters provides valuable evidence to the existing literature on alkali therapy. However, several limitations must be acknowledged. The 12-week follow-up period may have been insufficient to detect meaningful long-term changes in urinary TGF-β. Additionally, the single-center design and relatively small sample size ($N = 64$) may limit the generalizability of our findings. Baseline imbalances in age and UACR between groups also highlight the need for refined randomization strategies in future studies.

Future directions

Future research should focus on longer follow-up durations to determine whether extended exposure to alkali therapy leads to significant reductions in profibrotic biomarkers and impacts CKD progression. Alternative alkali therapies, such as potassium-based agents or dietary alkali sources, should be explored to mitigate potential sodium load effects. Biomarker-driven patient selection may enhance therapeutic targeting by identifying individuals with high urinary ammonium excretion who are more likely to benefit from alkali therapy. Additionally, investigating the combination of $NaHCO_3$ with existing CKD treatments, such as SGLT2 inhibitors or RAAS blockade, may provide synergistic benefits. Finally, future studies should incorporate subgroup-specific analyses to determine whether baseline eGFR, UACR, or metabolic acidosis markers influence treatment response, allowing for a more personalized approach to CKD management.

Conclusion

This study contributes to the growing body of evidence on alkali therapy in CKD. While high-dose sodium bicarbonate ($NaHCO_3$) did not significantly reduce urinary TGF-β over 12 weeks, it demonstrated excellent safety and tolerability, along with a significant impact on urinary pH. These findings provide a foundation for future research into dose optimization, alternative alkali formulations, and extended intervention periods. Our results highlight the importance of precision medicine in tailoring CKD therapies to individual patient profiles.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author, Narongrit Siriwattanasit, upon reasonable request (Email: nsiriwattanasit@gmail.com).

Received: 20 February 2025; Accepted: 22 May 2025
Published online: 01 July 2025

References

1. Ingsathit, A. et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. *Nephrol. Dial Transpl.* **25** (5), 1567–1575 (2010).
2. Wesson, D. E. & Simoni, J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. *Kidney Int.* **78** (11), 1128–1135 (2010).
3. Raphael, K. L. Metabolic acidosis in CKD: core curriculum 2019. *Am. J. Kidney Dis.* **74** (2), 263–275 (2019).
4. Nath, K. A., Hostetter, M. K. & Hostetter, T. H. Increased ammoniagenesis as a determinant of progressive renal injury. *Am. J. Kidney Dis.* **17** (6), 654–657 (1991).
5. Rende, U., Guller, A., Goldys, E. M., Pollock, C. & Saad, S. Diagnostic and prognostic biomarkers for tubulointerstitial fibrosis. *J. Physiol.* **601** (14), 2801–2826 (2023).
6. Raphael, K. L., Zhang, Y., Ying, J. & Greene, T. Prevalence of and risk factors for reduced serum bicarbonate in chronic kidney disease. *Nephrol. (Carlton).* **19** (10), 648–654 (2014).
7. Goraya, N., Simoni, J., Jo, C. H. & Wesson, D. E. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int.* **86** (5), 1031–1038 (2014).
8. Mahajan, A. et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int.* **78** (3), 303–309 (2010).
9. Raphael, K. L. et al. Sodium bicarbonate supplementation and urinary TGF-beta1 in nonacidotic diabetic kidney disease: A randomized, controlled trial. *Clin. J. Am. Soc. Nephrol.* **15** (2), 200–208 (2020).
10. Raphael, K. L. et al. A randomized trial comparing the safety, adherence, and pharmacodynamics profiles of two doses of sodium bicarbonate in CKD: the BASE pilot trial. *J. Am. Soc. Nephrol.* **31** (1), 161–174 (2020).
11. Hultin, S. et al. A systematic review and Meta-Analysis on effects of bicarbonate therapy on kidney outcomes. *Kidney Int. Rep.* **6** (3), 695–705 (2021).
12. Beynon-Cobb, B., Louca, P., Hoorn, E. J., Menni, C. & Padmanabhan, S. Effect of sodium bicarbonate on systolic blood pressure in CKD: A systematic review and Meta-Analysis. *Clin. J. Am. Soc. Nephrol.* **18** (4), 435–445 (2023).
13. Kidney Disease. Improving global outcomes CKDWG. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* **105** (4S), S117–S314 (2024).
14. Kalantar-Zadeh, K. & Fouque, D. Nutritional management of chronic kidney disease. *N Engl. J. Med.* **377** (18), 1765–1776 (2017).

Acknowledgements

All nephrology staffs from division of nephrology, Department of Medicine, Phramongkutklao Hospital and College of medicine.

Author contributions

Narongrit Siriwattanasit and Nipon Ngupis conceived and designed the study. Narongrit Siriwattanasit and Nipon Ngupis contributed to patient recruitment and data collection. Bancha Satirapoj and Ouppatham Supasyndh performed statistical analysis. Narongrit Siriwattanasit, Nipon Ngupis and Bancha Satirapoj interpreted the results and drafted the manuscript. Narongrit Siriwattanasit, Bancha Satirapoj, Theerasak Tangwonglert and Paramat Thimachai critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding

A part of the present study was supported by department of medicine, Phramongkutklao Hospital and College of medicine.

Declarations

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the Ethics Committee of the Institute Review Board at the Royal Thai Army Medical Department and was conducted according to the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all participants.

Additional information

Correspondence and requests for materials should be addressed to N.S.