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Comparison of Increased Dose of Oral Sodium Bicarbonate vs Standard Dose in Reduction of Progression of Chronic Kidney Disease

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Author`s Contribution

[1]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, [2]Drafting the work or revising it critically for important intellectual content, [3]Analysis, Literature review, proof read, [4]Active participation in active methodology

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ABSTRACT

Objective: To compare the effect of an increased dose of oral sodium bicarbonate versus the standard dose on the reduction of CKD progression.

Methodology: A randomized controlled trial was conducted at the Department of Nephrology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, between January 2023 and December 2023. The study enrolled 180 patients aged 18-75 years with chronic kidney disease (CKD), defined as either kidney damage or a glomerular filtration rate (GFR) <60 mL/min/1.73 m² persisting for ≥3 months, regardless of etiology. Participants had CKD stages III-V (eGFR 15-59 mL/min/1.73 m²) and were randomized into two treatment groups: Group A received sodium bicarbonate 300 mg three times daily (TDS), while Group B received 300 mg twice daily (BD), with doses titrated to maintain serum bicarbonate levels at 21±1 mmol/L. Both groups continued standard CKD management and were monitored biweekly for the first 3 months.

Results: Group A had 63.3% males and 36.7% females; Group B had 62.2% males and 37.8% females (P=0.877). Demographic features and baseline comorbidities were similar (P>0.05). Mean serum creatinine was 3.4 mg/dL in Group A and 3.3 mg/dL in Group B (P=0.983). Mean eGFR was 30.6 ml/min in Group A and 30.3 ml/min in Group B (P=0.876). Baseline HCO3 levels were 18.7 mmol/L in Group A and 18.5 mmol/L in Group B (P=0.956). Starting doses were 2700 mg/day in Group A and 1800 mg/day in Group B. eGFR was not significantly different at 3, 6, and 9 months. At 12 months, eGFR was significantly lower in Group B (25.3 ml/min) compared to Group A (26.8 ml/min) (P<0.05). Mean percentage decline in eGFR was significantly different at 9 and 12 months, favouring Group A (P=0.001). The rate of CKD progression was significantly lower in Group A at 12 months (P=0.028).

Conclusions: Higher initial doses of sodium bicarbonate in CKD patients resulted in a significantly lower rate of CKD progression at 12 months compared to the standard dose.

Keywords: Chronic kidney disease, Metabolic acidosis, Sodium bicarbonate

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Introduction

Chronic Kidney Disease (CKD) is characterized by progressive loss of renal function.[1] As the 16th leading cause of death worldwide, CKD is projected to become the 5th leading cause by 2040.[2,3] The condition places a significant burden on Pakistan's healthcare system,[2] compounded by inadequate screening and delayed risk assessment that often postpones timely management.[4]

One of the important kidney functions is to maintain acid base balance and to eradicate nonvolatile acids from the body. Hence the kidney acts as a buffer to maintain the acid base environment of the body. Ammonium is the primary acid produced by the kidney. Its elimination and

regeneration and reabsorption of bicarbonate is a key function of the kidney.[5]

When kidney function deteriorates, acid starts to retain in the body and metabolic acidosis occurs.[6] Metabolic acidosis causes complex changes that increase progression of chronic kidney disease as it stimulates the production of vasoconstrictors like endothelin, aldosterone, and angiotensin II. These substances cause inflammation of the kidney and in long term fibrosis in the kidney.[7,8] In CKD the body is unable to produce an amount of bicarbonate (HCO3) which neutralises the net acid production.[9] Decline in kidney function causes other harmful consequences like mineral and bone disorder, muscle wasting and protein catabolism.[10]

Many interventions have been practiced in CKD patients including low potassium diet, low protein diet versus normal diet, low protein diet versus very low protein diet, good glycemic control in diabetic patients and iron therapy and erythropoietin therapy for anemia.[11] Bicarbonate replacement (HCO3) is an essential intervention to produce an alkaline environment and to neutralise the acid produced in the body from acidic diet and protein catabolism.[12] Addition of exogenous bicarbonate supplementation to compensate for the deficiency of endogenous bicarbonate production can reduce progression of chronic kidney disease and improve the function of the kidney.[13] Sodium bicarbonate is a cost effective and easily available drug.[14] There remains a concern over side effects of sodium bicarbonate, most notably bloating and fluid retention, especially with higher doses.[15] Therefore titration of the dose of oral sodium bicarbonate based on the change in serum bicarbonate level.[16]

Exogenous bicarbonate supplementation can compensate for deficient endogenous bicarbonate production, potentially slowing chronic kidney disease (CKD) progression and preserving kidney function.[3] Sodium bicarbonate represents a cost-effective and widely accessible therapeutic option with a generally favorable safety profile. However, some concerns remain regarding potential adverse effects, particularly gastrointestinal symptoms (e.g., bloating) and fluid retention, which may occur with higher doses. Therefore, careful dose titration based on serial serum bicarbonate measurements is recommended to optimize therapeutic efficacy while minimizing side effects.[6]

Only a few studies have been conducted focused on the effect of oral sodium bicarbonate on CKD progression which showed positive results.[1,2,3] The aim of this study is to evaluate and establish the effect of increased oral sodium bicarbonate supplementation on progression of chronic kidney disease with an objective to compare the effect of increased dose of oral sodium bicarbonate versus standard dose on reduction of progression of CKD in the Pakistani patient population.

Methodology

This randomized controlled trial was conducted over one year at the Department of Nephrology, PIMS, Islamabad. Ethical approval was obtained from the hospital's ethical and scientific board. A total of 180 patients, aged 18-75 years with CKD grades III-V, were enrolled using non-probability consecutive sampling. Sample size was calculated using the WHO sample size calculator with a 5% level of significance and 90% power, based on an anticipated primary outcome rate of 17% in the standard care group and 6.6% in the treatment group.[17]

Inclusion criteria were CKD grades III-V and age 18-75 years. Whereas patients suffering from Acute kidney injury, patients with comorbid like morbid obesity (BMI > 40kg/m2), uncontrolled hypertension (despite using antihypertensives) and congestive heart failure (NYHA class III & IV) were excluded. Similarly, patients having hypocalcemia, hypokalemia, respiratory alkalosis, Active autoimmune disease, Active malignant and hemodialysis were not included in this study.

Participants were randomized 1:1 to either the treatment or control group. Group A received sodium bicarbonate orally (300mg x 3 TDS), titrated to maintain serum sodium bicarbonate level at 24±1 mmol/L. Group B received sodium bicarbonate (300mg x 2 TDS), titrated to maintain 21±1 mmol/L. Both groups received standard CKD treatments, including phosphate binders, iron supplements, and erythropoietin. Blood pressure and diabetes were controlled, and dietary advice was provided similarly to both groups.

The study was designed to compare the effect of increased dose of oral sodium bicarbonate compared to standard dose on reduction of rate of progression of CKD.

Patients were followed biweekly for the first three months and monthly thereafter. At each follow-up, vital signs were checked, and blood samples were taken for renal function tests and venous blood gas analysis. eGFR was calculated using the CKD-EPI 2009 equation. Further follow-ups occurred at weeks 16, 20, 24, 28, 32,

36, 40, 44, 48, and 52. Patients who developed acute CKD due to factors like dehydration, infection, or drugs were excluded.

Outcomes were assessed according to the KDIGO 2012 guidelines by eGFR calculated by the CKD-EPI 2009 equation.[18] Data were analyzed using SPSS version 21. Quantitative variables (age, bicarbonate level, serum creatinine level, BMI, and eGFR) were presented as mean ± S.D. Qualitative variables (gender) were presented as frequency and percentage. Comparisons between groups were made using the chi-square test for qualitative variables and the t-test for quantitative variables. A P-value ≤0.05 was considered significant.

Results

A total of 180 patients with CKD stages III-V were randomly allocated to two treatment arms. The high-dose sodium bicarbonate group (Group A) received 300 mg orally three times daily, adjusted to maintain serum bicarbonate levels at 24±1 mmol/L, while the standard-dose group (Group B) received 300 mg twice daily, targeting levels of 21±1 mmol/L. All participants continued their standard CKD treatment regimens throughout the study period. The protocol included biweekly monitoring during the initial three months followed by monthly assessments for a total duration of twelve months.

Baseline demographic characteristics showed no significant differences between groups. Group A consisted of 63.3% male and 36.7% female participants, compared to Group B's 62.2% male and 37.8% female distribution (P=0.877). The mean age was 48.5±13.1 years in Group A versus 49.1±9.5 years in Group B (P=0.750). Additional parameters including height, weight, and body mass index demonstrated comparable distributions across both cohorts (P>0.05 for all comparisons). Table I

The groups exhibited similar comorbidity profiles at baseline. Mean serum creatinine values were 3.4±1.3 mg/dL in Group A and 3.3±1.1 mg/dL in Group B (P=0.983). Baseline estimated glomerular filtration rates and bicarbonate levels are presented in Table II.

Initial sodium bicarbonate dosing was established at 2700 mg/day for Group A and 1800 mg/day for Group B, with subsequent titration to achieve protocol-specified bicarbonate targets. At the three-month evaluation, the mean daily dose in Group A was 2396.7±319.6 mg compared to 1673.3±190.7 mg in Group B (P=0.001). This dosing pattern persisted at six months, with Group A maintaining 2380.1±329.9 mg/day versus Group B's 1676.7±190.2 mg/day (P=0.001).

Renal function outcomes demonstrated no significant intergroup differences. At three months, mean eGFR was 30.1±13.6 mL/min in Group A and 29.8±12.2 mL/min in Group B (P=0.879). Six-month measurements showed comparable values of 29.7±13.6 mL/min and 29.4±12.2 mL/min for Groups A and B respectively (P=0.878). Detailed eGFR trajectories and percentage decline are provided in Table III.

Table I: Demographic Characteristics of the study population.

Variable	Group A (High Dose)	Group B (Standard Dose)	P-Value
Males (%)	63.3	62.2	0.877
Females (%)	36.7	37.8	
Age (years)	48.5 ± 13.1	49.1 ± 9.5	0.75
Height (m)	1.66 ± 0.05	1.67 ± 0.06	0.172
Weight (kg)	73.7 ± 10.3	73.6 ± 9.8	0.971
BMI (kg/m²)	27.1 ± 4.3	26.5 ± 4.2	0.448

Table II: Mean Creatinine, eGFR, HCO3 at Baseline

Variables	Group A (High Dose)	Group B (Standard Dose)	P-Value
Serum Creatinine (mg/dL)	3.4 ± 1.3	3.3 ± 1.1	0.983
eGFR (ml/min)	30.6 ± 13.6	30.3 ± 12.2	0.876
HCO3 (mmol/L)	18.7 ± 1.04	18.5 ± 0.86	0.956

Table III. Mean Creatinine, eGFR, HCO3 at Baseline.

Variables	Group A (High Dose)	Group B (Standard Dose)	P-Value
Serum Creatinine (mg/dL)	3.4 ± 1.3	3.3 ± 1.1	0.983
eGFR (ml/min)	30.6 ± 13.6	30.3 ± 12.2	0.876
HCO3 (mmol/L)	18.7 ± 1.04	18.5 ± 0.86	0.956

At nine months, the mean eGFR was 27.8 ml/min ± 13.6 SD in Group A and 26.5 ml/min ± 12.2 SD in Group B (P=0.501). At 12 months, the mean eGFR was 26.8 ml/min ± 13.6 SD in Group A and 25.3 ml/min ± 12.2 SD in Group B (P=0.045). Table IV

The rate of CKD progression (decline of ≥25% of eGFR within one year) was not significantly different between groups at three, six, and nine months (P>0.05). However,

Table IV: eGFR and Percentage Decline in eGFR.

Time Point	Variable	Group A (High Dose)	Group B (Standard Dose)	P-Value
3 Months	eGFR (ml/min)	30.1 ± 13.6	29.8 ± 12.2	0.879
	Decline in eGFR (%)	1.97 ± 0.94	1.92 ± 0.85	0.733
6 Months	eGFR (ml/min)	29.7 ± 13.6	29.4 ± 12.2	0.878
	Decline in eGFR (%)	3.63 ± 1.73	3.54 ± 1.58	0.712
9 Months	eGFR (ml/min)	27.8 ± 13.6	26.5 ± 12.2	0.501
	Decline in eGFR (%)	11.6 ± 5.6	15.3 ± 6.8	0.001
12 Months	eGFR (ml/min)	26.8 ± 13.6	25.3 ± 12.2	0.045
	Decline in eGFR (%)	15.6 ± 7.4	19.8 ± 8.8	0.001

Table IV: Comparison of Progression of CKD in both groups.

Time Point	CKD Progression	Group A (High Dose)	Group B (Standard Dose)	P-Value
9 Months	Present (%)	2.2	5.6	0.247
	Absent (%)	97.8	94.4	
12 Months	Present (%)	14.4	27.8	0.028
	Absent (%)	85.6	72.2	

at 12 months, the rate of CKD progression was significantly lower in Group A (14.4%) compared to Group B (27.8%) (P=0.028). Table V

Discussion

Our results showed that mean eGFR was insignificant in both groups at 3, 6 and 9-month intervals (P>0.05), eGFR was however significantly lower at 12 months (25.3 ml/min ± 12.2 SD versus 26.8 ml/min ± 13.6 SD) in patients who treated with standard dose when compared to those treated with higher oral dose of sodium bicarbonate (P<0.05). Mean percentage decline in eGFR at 3 months and 6 months was not significant in both groups (P>0.05). However, it was significantly lower at 9 months (11.6% vs 15.3%, P=0.001) and at 12 months (15.6% vs 19.8%, P=0.001) in Group A patients. Similarly, the rate of CKD progression (decline of ≥25% of eGFR within one year) was not significant in both groups at 3, 6 and 9 months (P>0.05), but at 12 months it was significantly lower (14.4% versus 27.8%) in Group A compared to Group B (P=0.028).

The results of our study are concurrent with previously published studies cited in the literature demonstrating bicarbonate supplementation results in slowing the progression of CKD.[19,20] In a recent meta-analysis of 14 clinical trials (n=1394 patients),it as shown that oral alkali supplementation for treatment of metabolic acidosis raised serum bicarbonate concentrations (14 studies, 1378 patients, mean difference 3.33 mEq/L, 95% CI, 2.37 to 4.29) and led to a reduced decline in eGFR (13 studies, 1329 patients, mean difference 23.28 mL/min per 1.73 m², 95% CI, 24.42 to 22.14), and decreased the risk of progression to ESKD (relative risk, 0.32; 95% CI, 0.18 to 0.56).[21]

In a two-year, single-center, open-label trial involving 134 patients with stage four chronic kidney disease (CKD) (creatinine clearance 15–30 mL/min/1.73 m²) and metabolic acidosis (baseline serum bicarbonate 16–20 mEq/L), participants were randomly assigned to receive either oral sodium bicarbonate or no treatment. The sodium bicarbonate regimen began at 600 mg three times daily, with dose adjustments as needed to achieve a serum bicarbonate level of ≥23 mEq/L. Compared to the untreated group, patients receiving sodium bicarbonate exhibited a significantly lower risk of progressing to end-stage kidney disease (ESKD) (6.5% vs. 33%), a slower mean annual decline in creatinine clearance (1.88 vs. 5.93 mL/min/1.73 m² per year), and a reduced likelihood of experiencing an annual decline in creatinine clearance of at least 3 mL/min/1.73 m² (9% vs. 45%).[22]

An additional study involving 740 participants with stage 3–5 CKD (mean creatinine clearance 30 mL/min) and a mean baseline serum bicarbonate level of 21.5 mmol/L yielded consistent findings.[23] Patients were randomized to receive either oral sodium bicarbonate or no treatment. After three years, those in the bicarbonate group exhibited a significantly lower risk of serum creatinine doubling (6.6% vs. 17%) compared to the control group. Additionally, the bicarbonate group demonstrated reduced all-cause mortality (3.1% vs. 6.8%) and a lower incidence of kidney replacement therapy requirement (6.9% vs. 12.3%). In the present study, we did not take into account mortality and need of kidney replacement therapy as our outcome variables.

Two additional trials have reported benefits of alkali therapy in patients with mild chronic kidney disease (CKD) who did not exhibit metabolic acidosis (serum bicarbonate levels 22–24 mEq/L). In the first trial, 120 patients with a mean estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m² and an albumin-to-

creatinine ratio >300 mg/g were randomized to receive sodium bicarbonate, sodium chloride, or a matching placebo.[24] After five years, the sodium bicarbonate group demonstrated a modest but statistically significant reduction in the annual rate of eGFR decline (–1.5 mL/min/1.73 m²) compared to both the control and placebo groups (–2.0 and –2.1 mL/min/1.73 m², respectively).

The second trial enrolled 108 patients with stage 3 CKD (eGFR 30–59 mL/min/1.73 m²), randomizing them to either usual care or alkali therapy. The alkali intervention consisted of sodium bicarbonate supplementation along with a diet rich in base-producing fruits and vegetables.

After 3 years, eGFR in the high alkali group showed lesser decline.[25] In a meta-analysis of fifteen trials, including 2445 patients with CKD, alkali therapy in fact resulted in slowing the decline of eGFR (mean difference of -2.6 mL/min/1.73m2, 95% CI -4.6 to -0.7) as well as statistically a lesser risk of end-stage kidney disease (ESKD) (relative risk 0.53, 95% CI 0.32-0.89).[26]

The results of the present study and some previously published literature[24,25,26] showed that addition of exogenous bicarbonate supplementation to compensate for the deficiency of endogenous bicarbonate production can reduce progression of chronic kidney disease. Some studies showed that oral alkali supplementation was associated with worsening hypertension or the requirement for increased antihypertensive therapy, however the evidence was of very-low certainty.

Conclusion

In patients with chronic kidney disease (CKD stages III-V), treatment initiated with higher doses of sodium bicarbonate demonstrated significantly slower disease progression compared to standard-dose therapy at 12-month follow-up. This study's randomized controlled design, incorporating rigorous inclusion and exclusion criteria, represents its primary methodological strength. Furthermore, the comparative assessment of two distinct dosing regimens provides robust evidence supporting the superior efficacy of initial higher-dose bicarbonate therapy.

Several limitations should be acknowledged in the interpretation of these findings. The sample size, while adequate for primary outcome assessment, remains modest relative to larger multicenter trials reported in the literature. The one-year follow-up period constitutes a relatively shorter observation window compared to longer-term studies of CKD progression. Additionally, this study did not evaluate several clinically relevant endpoints including mortality rates, hospitalization frequency, or requirements for renal replacement therapy, which represent important considerations in comprehensive CKD management.

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