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Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial

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ABSTRACT

Background. Metabolic acidosis (MA) is associated with a loss of muscle mass and faster deterioration of kidney function in patients with chronic kidney disease (CKD). A few single-centre randomized trials have reported favourable outcomes following correction of MA. Additional good quality evidence on the safety and efficacy of alkali supplementation is required in epidemiologically different patient subsets with CKD.

Methods. A single-centre, open-label, randomized, prospective parallel-group study was conducted to assess the effect of correction of MA on body composition and kidney function. A total of 188 patients with CKD stages 3 and 4, with venous bicarbonate levels <22 mEq/L were randomized. The intervention arm received standard care as per Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines along with oral sodium bicarbonate supplementation to maintain

venous bicarbonate levels at 24–26 mEq/L, whereas the control group received standard care alone. The mid-arm muscle circumference (MAMC), lean body mass (LBM) and estimated glomerular filtration rate (eGFR) were compared between the groups at the end of 6 months.

Results. The intervention arm showed a higher LBM {36.8 kg [95% confidence interval (CI) 36.5–37.1] versus 36 [35.7–36.4]; $P=0.002$ } and MAMC [22.9 cm (95% CI 22.8–23) versus 22.6 (22.5–22.7); $P=0.001$] when compared with the control group. The GFR in the intervention arm was higher [32.74 mL/1.73 m² (95% CI 31.5–33.9) versus 28.2 (27–29.4); $P\leq 0.001$]. A rapid decline in GFR was documented in 39 (41.5%) patients in the control arm and 19 (20.2%) patients in the intervention arm ($P=0.001$).

Conclusions. Alkali supplementation to increase venous bicarbonate levels to 24–26 mEq/L is associated with preservation of LBM and kidney function in patients with CKD stages 3 and 4.

Keywords: acidosis, CKD of unidentified etiology, DXA, malnutrition, sodium bicarbonate

INTRODUCTION

Metabolic acidosis (MA) is a well-recognized complication of chronic kidney disease (CKD). As the kidney function deteriorates, tubular ammoniogenesis and reclamation of bicarbonate are reduced. This leads to a reduction in the renal excretion of hydrogen (H⁺) ions. The glomerular filtration rate (GFR) threshold for the development of MA is not clearly defined. It is estimated that 30–50% of the patients with CKD develop MA as the estimated GFR (eGFR) falls to 30–40 mL/min/1.73 m² [1]. Certain diseases such as obstructive uropathies, tubulointerstitial diseases, diabetes mellitus and younger age predispose to MA early in the course of the disease.

MA is associated with faster deterioration of kidney function and increased mortality in CKD [2–5]. MA is also associated with enhanced muscle catabolism, reduced protein synthesis, insulin resistance, low leptin levels and malnutrition–inflammation complex syndrome (MICS) [6–8]. Even though MA is a recognized risk factor for morbidity, mortality and disease progression, there are only limited data on the safety and effectiveness of correction of MA in predialysis CKD. A few small randomized controlled trials demonstrated that correction of MA leads to preservation of GFR in predialysis CKD [9–11]. However, more studies are warranted to assess the potential risks and benefits of prolonged administration of bicarbonate in different population subsets with CKD. Even though acidosis is strongly correlated with protein-energy wasting (PEW) and inflammation, there is a lack of good quality evidence on the impact of correction of MA on muscle mass and other nutritional indices in predialysis CKD. There is some evidence that correction of MA leads to increases in mid-arm muscle circumference (MAMC) and exercise capacity [10, 12]. In addition to enhanced morbidity and mortality, a lower muscle mass can also affect the functional status of the individual, with repercussions on quality of life as well.

An accurate assessment of muscle mass using conventional anthropometric parameters have limitations in CKD. Most of the anthropometric measurements, including body weight and body mass index (BMI), can be significantly altered by changes in body water content. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommended dual-energy X-ray absorptiometry (DXA) as the reference method for assessing body composition in CKD [13]. There are no published data on the effect of alkali supplementation on muscle mass in predialysis CKD using a sensitive method such as DXA. In the current study we assessed the effect of correction of MA with oral sodium bicarbonate on the body composition and eGFR in CKD stages 3 and 4.

MATERIALS AND METHODS

Study design and population selection

A randomized, open-label, single-centre, parallel-group study was conducted from May 2015 to November 2016. All patients between 18 and 65 years of age with CKD stages 3 and 4 attending nephrology outpatient clinics and who completed a minimum follow-up period of 3 months were screened. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 formula was used to estimate the GFR. Patients with venous bicarbonate levels <22 mEq/dL with a stable eGFR (defined as <5% fluctuations during a 4-week observation period) were randomized. Patients with structural and functional anomalies of the gastrointestinal tract, decompensated chronic liver disease, decompensated heart failure, morbid obesity (BMI ≥ 40 kg/m²), malignancy, chronic infections, prior bicarbonate therapy for a duration of >2 weeks or receiving immunosuppression were excluded. The study period was 6 months. The primary outcome was changes in MAMC and lean body mass (LBM). The whole-body LBM was assessed with a three-compartment model DXA. The secondary outcome was the change in eGFR from baseline. The protocol was approved by the Institute Ethical Committee for Human Research (JIP/IEC/2014/10/475). The trial data set was uploaded to Clinical Trial Registry of India (CTRI) in March 2015 and final confirmation of registration was received in September 2015 (CTRI/2015/09/006161).

The sample size was estimated to be 84 patients in each arm, with an expected difference in mid-arm circumference of 0.45 cm between groups, with a standard deviation (SD) of 1.1, at 5% α error and 80% power. Considering an attrition rate of 10% during follow-up, 94 patients were enrolled in each arm. The sample size estimates were derived from unpublished observational data in patients with CKD stages 4 and 5ND from the same centre. A block randomization using computer-generated random numbers with equal allocation in two groups in blocks of four were used. The allocation was concealed using sequentially numbered, opaque, sealed envelopes. The random allocation sequence generation was done by a statistics expert, who was not part of the study.

A predefined diagnostic criterion was used to identify patients with CKD of unidentified aetiology (CKDu). The

criterion was adopted from Jayatilake *et al.* [14], with partial modifications. CKDu was diagnosed in patients with absent or traces of proteinuria, if they satisfied the following criteria:

1. No past history of glomerulonephritis, pyelonephritis, renal calculi, snake bite, reflux nephropathy, acute interstitial nephritis, previous acute kidney injury or an alternate aetiology for CKD.
2. Normal fasting and 2-h post-prandial blood sugar values with no history of treatment for diabetes mellitus.
3. Absence of severe hypertension, defined as blood pressure <140/90 mmHg if on treatment for hypertension and <160/100 mmHg if not on treatment for hypertension.

Protocol and data collection

The intervention arm received standard care as per the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, with oral sodium bicarbonate supplementation to keep venous bicarbonate levels between 24 and 26 mEq/L. Bicarbonate estimation was done from venous blood with an ABL FLEX blood gas analyser (Radiometer Medical, Copenhagen, Denmark). The starting dose of sodium bicarbonate was 0.5 mEq/kg body weight. The dosage was titrated with weekly monitoring of venous bicarbonate levels. Generic sodium bicarbonate tablets (500 mg/6 mEq) were used. Once the target level was attained, bicarbonate levels were measured at 3 and 6 months in the intervention arm. Patients were instructed to take the tablets 1 h after food to reduce the gastrointestinal side effects. The compliance to medication was checked by pill counts on monthly follow-up visits. Intake of >80% of the prescribed drug was considered acceptable. Calcium-based phosphate binders were avoided in the intervention arm because of potential concerns of vascular calcification. The control group did not receive sodium bicarbonate supplementation but received other standard care for CKD according to the KDIGO 2012 guidelines. Bicarbonate levels were measured at enrolment and exit in the control arm.

Demographic, clinical, biochemical and anthropometric parameters were collected at enrolment and the end of the study. The anthropometric measurements included body weight, height, mid-arm circumference and triceps skinfold thickness (SFT). Body weight was measured to the nearest 0.1 kg on a balance beam scale with a margin of error of 0.01 kg. Height was measured to the nearest 0.5 cm, with patients standing erect with the head in the Frankfort plane. The triceps SFT was measured in the non-dominant arm using Slim Guide Skinfold Caliper (Creative Health Products, Ann Arbor, MI, USA) according to standard techniques. The mid-arm circumference was measured using a flexible plastic tape with a graduated scale, at the point halfway between the acromion of the scapula and the olecranon of the ulna, in a sitting position with the arm relaxed and flexed at 90°, the tape adjusted to surround the arm and avoiding skin compression. The mean value of three consecutive measurements was taken. MAMC was calculated using Bishop's formula [$\text{MAMC} = \text{mid-arm circumference} - [0.314 \times \text{triceps SFT (mm)}]$]. All measurements were done by a single trained observer.

All patients were given comprehensive nutritional counselling at the time of enrolment. This included calculating the patients' protein intake from a 3-day diet recall diary and assessment of anthropometric parameters [15]. Dietary regulations were re-emphasized and a model diet was prescribed based on the patient's dietary preferences and socio-economic status. A DXA scan (Discovery Wi System, Hologic, Bedford, MA, USA) was used to assess the body composition. DXA performs rectilinear scans with an X-ray beam. The subject lies in a supine position and the scan begins from the top of the head, moving towards the feet. The programme allows scanning up to 205 lines. A three-compartment model was used for estimating whole body fat, LBM and mineral density using the software provided by the manufacturer (QDR software version 13.4.1; Hologic). The manufacturer-provided phantom was scanned once a week for quality control. The coefficient of variation was <2% for both LBM and fat mass, expressed in grams. Patients were clinically euvoletic at the time of DXA scans. For patients who presented with oedema, diuretics were prescribed to attain clinical euvoemia. All the scans were performed by a single trained individual. All the laboratory parameters were subjected to internal and external standardizations. The outcome measures were assessed by individuals who were blind to treatment allocation.

Statistical analysis

All categorical variables were expressed as percentages and compared using chi-squared tests. Numeric variables were expressed as the mean with 95% confidence intervals (CIs) or median with interquartile range, wherever appropriate. Continuous variables between the two arms were compared using independent Student's *t*-test or Mann-Whitney U test, according to the distribution. The changes in LBM, eGFR and MAMC from baseline to exit in each arm were compared using a paired *t*-test. Anthropometry, body composition and creatinine and eGFR between the two groups on study completion were compared using analysis of covariance, with the baseline parameter included as a covariate. The outcomes were compared with an intention-to-treat analysis. Logistic regression analyses were performed to identify the independent predictors of outcomes. Statistical analysis was undertaken before unmasking of treatment group allocation. P-values <0.05 were considered statistically significant. The data were analysed using the statistical software SPSS, version 19.0 (IBM, Armonk, NY, USA).

RESULTS

Among 252 patients with prevalent CKD stages 3 and 4 who met the exclusion criteria, 214 (85%) showed bicarbonate levels <22 mEq/L. A total of 188 patients were randomized. Five patients in the control arm and six patients in the intervention arm did not participate in the final follow-up. All patients were included for the final analysis (Figure 1). The baseline characteristics of the study population are given in Table 1.

CKDu was the most common cause of CKD (52.1%; $n = 98$); 72.3% ($n = 136$) of the study population were from poor socio-economic backgrounds and engaged in farming-related activities. A total of 92 patients in the intervention arm

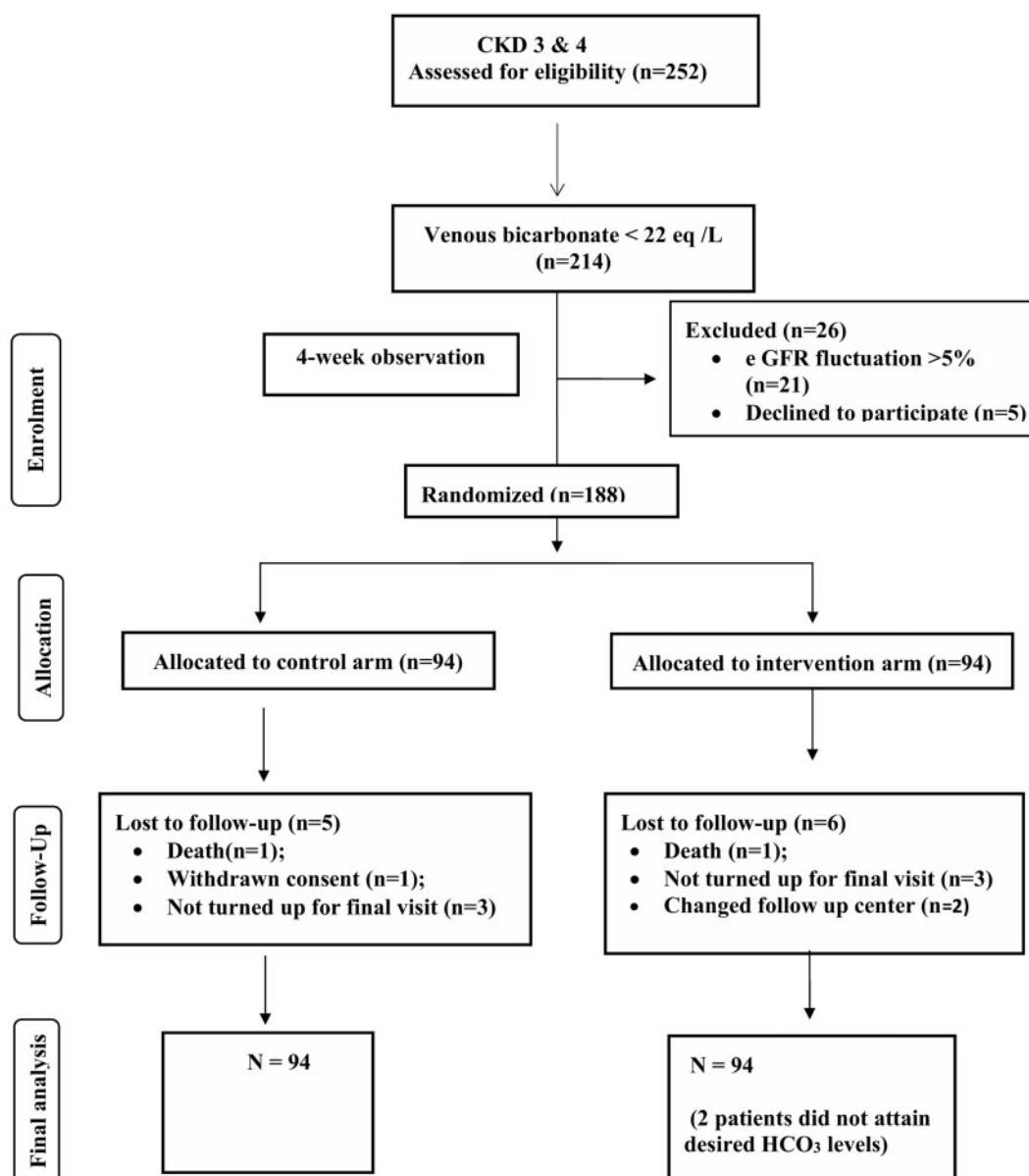


FIGURE 1: CONSORT diagram.

attained target bicarbonate levels. The mean dose of sodium bicarbonate required for attaining the target level was 2.3 g/day (0.5 mEq/kg of body weight/day). Overall, 85% ($n=80$) patients in the intervention arm were compliant with bicarbonate administration. The increased sodium intake in the intervention arm was compensated by an increase in urinary sodium excretion. The serum calcium levels showed a non-significant decline in the intervention arm. Lanthanum carbonate and sevelamer were prescribed as phosphorus binder in the intervention arm. The choice of phosphorus binder in the control group was left to the discretion of treating physicians. Calcitriol was the vitamin D analogue prescribed. The clinical and biochemical parameters at exit are given in Table 2.

Body composition, anthropometric parameters and renal function on completion of study

The parameters are given in Tables 3 and 4. From baseline, the LBM decreased by 378 g (95% CI −686 to −70) in the

control group whereas it increased by 383 g (95% CI 21–744) in the intervention arm. The MAMC decreased by 2 mm in the controls (95% CI −3 to −1) whereas it remained unchanged in the intervention arm (95% CI 0.6–1). The eGFR in the control arm decreased by −2.3 mL/min/1.73 m² (95% CI −3.4 to −1.1). The intervention arm showed an increase in GFR by 2.4 mL/min/1.73 m² (95% CI 1.2–3.6). The adjusted means for primary and secondary outcomes at exit are given in Tables 3 and 4. The changes from baseline to exit are shown in Figure 2.

Three separate logistic regression models were created to identify the independent predictive value of age, gender, CKD stage and bicarbonate supplementation on improvements in LBM, MAMC and eGFR values. Bicarbonate supplementation and age were independent predictors of improvement in eGFR. Only bicarbonate supplementation turned out to be an independent predictor for improvements in LBM and MAMC (Table 5).

Table 1. Baseline characteristics of the control and intervention groups

Parameter	Control arm	Intervention arm	P-value
Age (years), mean $\pm$ SD	50.30 $\pm$ 11.4	50.12 $\pm$ 11.6	0.91
Male, <i>n</i> (%)	66 (70.2)	68 (72.3)	0.43
Comorbidities, <i>n</i> (%)			
Diabetes mellitus	19 (20.2)	23 (24.5)	0.48
Systemic hypertension	70 (74.5)	75 (79.8)	0.38
Coronary disease	12 (13.0)	13 (13.8)	0.82
CKD stage, <i>n</i> (%)			
Stage 3	50 (58.1)	36 (41.9)	0.04
Stage 4	44 (43.1)	58 (56.9)	
Aetiology of CKD, <i>n</i> (%)			
CKD of unidentified aetiology	52 (55.3)	46 (48.9)	0.38
Diabetes mellitus	15 (16)	14 (14.9)	0.83
Glomerulonephritis	9 (9.5)	12 (12.8)	0.48
Others (cystic kidney diseases, obstructive uropathies, etc)	18 (19.2)	22 (23.4)	0.47
Diuretics, <i>n</i> (%)	43 (45.7)	36 (38.3)	0.30
Antihypertensives, <i>n</i> (%)			
Calcium channel blockers	57 (60.6)	53 (56.4)	0.35
RAAS blockers	23 (24.4)	29 (30.8)	0.32
β -blockers	29 (30.8)	20 (21.2)	0.13
Others	11 (11.7)	05 (05.3)	0.11
Proteinuria $\geq 1+$, <i>n</i> (%)	29 (30.9)	31 (33)	0.75
Phosphorus binders, <i>n</i> (%)	13 (13.8)	13 (13.8)	1
Vitamin D analogues, <i>n</i> (%)	09 (09.5)	11 (11.7)	0.22
Non-vegetarians, <i>n</i> (%)	82 (87.2)	83 (88.2)	0.82
Clinical and biochemical parameters, mean (95% CI)			
Haemoglobin (g/dL)	11.9 (11.6–12.2)	11.8 (11.4–12.1)	0.70
Urea (mg/dL)	53 (50–57)	56 (53–59)	0.29
Creatinine (mg/dL)	2.4 (2.2–2.5)	2.6 (2.4–2.7)	0.12
eGFR (mL/min/1.73 m ²)	31.5 (29.3–33.8)	29.2 (27–31.3)	0.13
Cholesterol (mg/dL)	178 (167–184)	174 (165–183)	0.64
Albumin (g/dL)	3.9 (3.9–4.0)	3.9 (3.9–4.0)	0.67
Calcium (mg/dL)	9.0 (8.9–9.1)	9.2 (9.1–9.3)	0.17
Phosphorus (mg/dL)	3.5 (3.3–3.7)	3.4 (3.3–3.6)	0.59
Bicarbonate mEq/L	18.1 (17.6–18.6)	18.1 (17.7–18.6)	0.99
pH	7.33 (7.31–7.34)	7.33 (7.32–7.34)	0.98
Urinary sodium (spot; mEq/L)	77.4 (68.7–86.17)	63.3 (57.5–69.2)	0.008
Systolic blood pressure (mmHg)	131 (127–135)	130 (127–134)	0.85
Diastolic blood pressure (mmHg)	83 (81–86)	82 (80–85)	0.68
No. of antihypertensives, median (IQR)	2 (0.05–3)	2 (1–2)	0.22
Protein intake (g/day), median (IQR)	34 (27–42)	35 (29.5–40.50)	0.40
Anthropometry and body composition, mean (95% CI)			
Weight (kg)	53.8 (52.0–55.6)	54.0 (52.4–55.7)	0.84
BMI (kg/m ²)	21.3 (20.6–22.0)	21.2 (20.6–21.8)	0.83
MAMC (cm)	22.9 (22.4–23.3)	22.8 (22.3–23.3)	0.72
Fat mass (kg)	15.6 (14.5–16.7)	15.6 (14.5–16.7)	0.82
LBM (kg)	36.2 (34.9–37.5)	36.5 (35.4–37.8)	0.85

IQR, interquartile range.

The adverse effects are given in Table 6. A significant proportion of patients in the intervention arm required an increase in diuretic prescriptions. None of the patients in either arm progressed to ESRD.

DISCUSSION

MA is a common complication of CKD. Bicarbonate levels tend to have a U-shaped association with mortality in CKD. The mortality rates start increasing at levels <17 and >27 mEq/L [16]. Evidence-based optimum therapeutic targets of venous bicarbonate levels in pre-dialysis CKD are not known. The existing guidelines are based on low-quality evidence. The KDIGO

2012 guidelines suggest alkali therapy when bicarbonate levels are <22 mEq/L but do not mention any evidence-based upper target levels [13]. Similarly, the Renal Association of Great Britain and Caring for Australians with Renal Impairment suggest maintaining serum bicarbonate levels >22 mEq/L [17, 18].

In the current study, 85% of the CKD population showed MA, which is considerably higher when compared with the reported prevalence of MA (21–39%) in CKD stages 3 and 4 [1, 4]. Apart from GFR, multiple factors such as the dietary acid load, smoking, obesity, use of renin–angiotensin–aldosterone system (RAAS) blockade and native kidney disease can affect the magnitude of MA [18]. The high prevalence of CKDu seems to be the potential reason for the higher incidence of MA in the

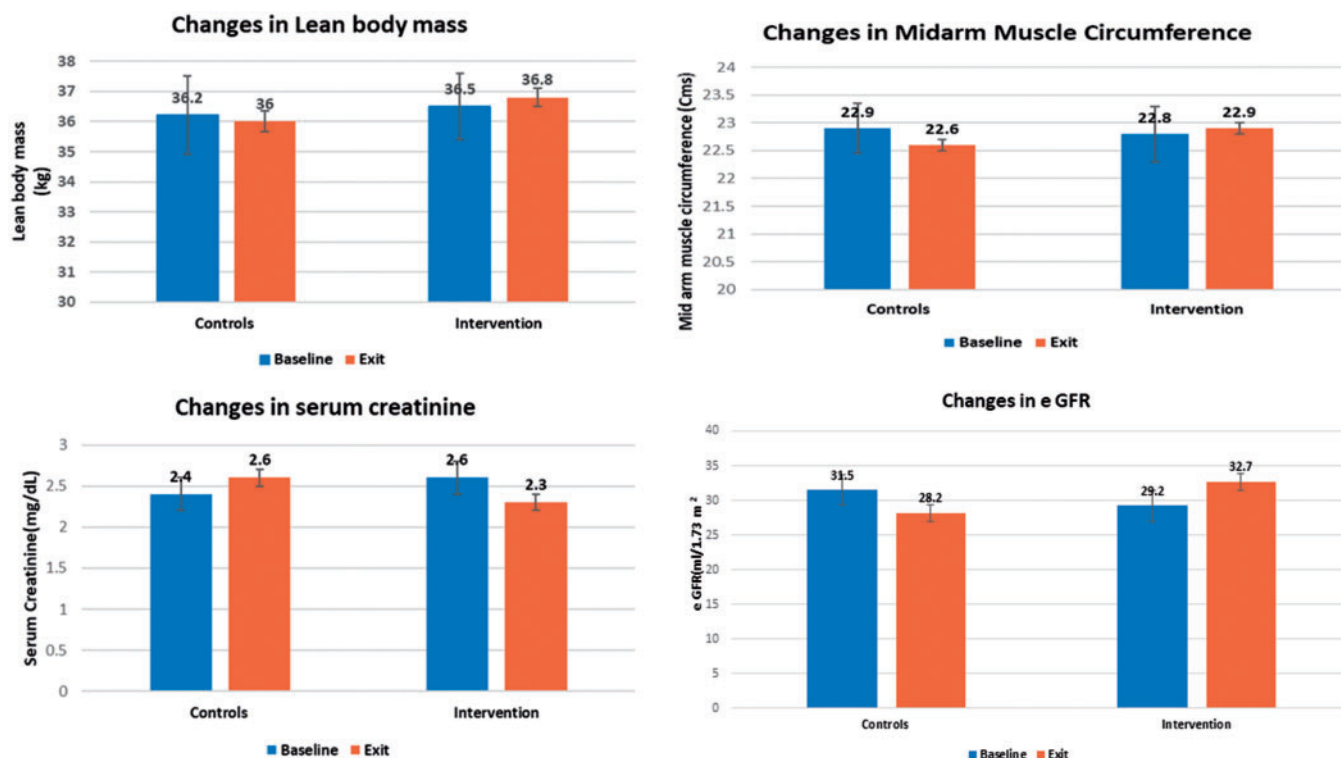


FIGURE 2: Changes in LBM, MAMC, serum creatinine and eGFR during the study period.

Table 2. Characteristics of the control and intervention arms at exit

Parameter	Control arm	Intervention arm	P-value
Clinical and biochemical parameters, mean (95% CI)			
Haemoglobin (g/dL)	11.7 (11.4–12.1)	11.6 (11.3–12.0)	0.67
Urea (mg/dL)	55 (51–59)	56 (53–61)	0.49
Total cholesterol (mg/dL)	180. (172–188)	175 (167–183)	0.36
Serum albumin (g/dL)	4.0 (3.9–4.1)	3.9 (3.9–4.0)	0.54
Serum calcium (mg/dL)	9.1 (8.9–9.25)	8.9 (8.8–9.1)	0.14
Serum phosphorus (mg/dL)	3.5 (3.24–3.55)	3.45 (3.2–3.5)	0.58
pH	7.2 (7.29–7.31)	7.40 (7.38–7.41)	<0.001
Bicarbonate mEq/L	17.8 (17.4–18.4)	23.45 (22.9–24)	<0.001
Urinary sodium, spot (mEq/L)	84 (75.1–94.6)	99.83 (92–107.7)	0.011
Systolic blood pressure (mmHg)	128 (122–132)	124 (120–128)	0.19
Diastolic blood pressure (mmHg)	82 (80–85)	80 (79–83)	0.27
Protein intake (g/day), median (IQR)	35 (26–40.8)	36 (29–40)	0.48

IQR, interquartile range.

Table 3. Anthropometry and body composition at exit

Parameter, mean (CI)	Control arm	Intervention arm	P-value
Weight (kg)	53.3 (52.7–54)	54.1 (53.4–54.7)	0.10
BMI (kg/m ²)	21.2 (20.9–21.4)	21.5 (21.2–21.7)	0.11
MAMC (cm)	22.6 (22.5–22.7)	22.9 (22.8–23)	0.001
Fat mass (kg)	15.8 (15.3–16.2)	15.9 (15.5–16.4)	0.51
LBM (kg)	36.0 (35.7–36.4)	36.8 (36.5–37.1)	0.002

Data presented as mean (95% CI).

current study. Multiple CKDu hot spots were described recently in predominantly agrarian communities across various parts of Central America, Sri Lanka and the eastern coast of India [19, 20]. CKDu, by virtue of the tubulointerstitial involvement,

might lead to earlier and severe MA [4]. The bicarbonate requirements in the current study are in concordance with dosage recommendations from a previous meta-analysis [21].

The majority of the patients attending our CKD clinic are employed in the unorganized sector and are dependent on agriculture-related activities for sustenance. Enhanced proteolysis of muscles secondary to activation of adenosine triphosphate-dependent ubiquitin–proteasome systems is documented in CKD [6, 8]. Low muscle mass translates to lower endurance and affects employment prospects, especially for occupations demanding hard labour. We observed that MA correction leads to the preservation of LBM and MAMC in the intervention arm. The increments in muscle mass were not associated with an appreciable change in total body weight, fat mass or protein

Table 4. Renal function at exit

Parameter	Control arm	Intervention arm	P-value
Creatinine (mg/dL) mean (CI)	2.6 (2.5–2.7)	2.3 (2.2–2.5)	<0.001
eGFR (mL/min/1.73 m ²) mean (CI)	28.2 (27.0–29.4)	32.7 (31.5–33.9)	<0.001
Decline in GFR >3 (mL/1.73 m ²), n (%)	39 (41.5)	19 (20.2)	0.001
Improvement in GFR, n (%)	19 (20.2)	53 (56.4)	<0.001

Table 5. Logistic regression analyses: independent predictors of improvements in MAMC, LBM and eGFR

Dependent variable	Independent variables	P-value	Exp(B)	95% CI for Exp(B)
MAMC	Intervention	<0.001	7.36	2.66–20.37
	Age	0.73	0.86	0.38–1.97
	Gender	0.44	1.46	0.58–3.84
	CKD stage	0.73	0.86	0.39–1.97
LBM	Intervention	0.002	2.64	1.43–4.81
	Age	0.22	1.02	0.99–1.04
	Gender	0.33	1.46	0.36–1.41
	CKD stage	0.48	1.25	0.68–2.30
eGFR	Intervention	<0.001	5.09	2.60–9.99
	Age	0.02	1.04	1.01–1.07
	Gender	0.30	1.48	0.70–3.14
	CKD stage	0.66	1.88	0.96–3.67

intake. Alkali supplementation has been shown to improve MAMC and lower limb muscle strength in patients with CKD [10, 12]. Alkali supplementation is also reported to improve the Onodera's prognostic nutritional index in patients with CKD Stage 5ND [9]. These studies used surrogate nutritional, anthropometric or clinical markers to assess the improvements in skeletal muscle mass. This study used DXA, a reliable and sensitive tool for assessing muscle mass in CKD. There were no differences in serum albumin or body weight between the control and intervention arms. Total body weight and serum albumin are reported to have a weak correlation with nutritional indices and muscle mass in predialysis patients, thus limiting their utility as routine nutritional markers [10, 22]. Creatinine production is inherently linked to muscle mass. Greater muscle mass is expected to translate to higher creatinine generation and lower eGFR. Even though the intervention arm had a greater muscle mass at the end of 6 months, the serum creatinine was lower when compared with the control group. This might have resulted from lower muscle catabolism associated with the correction of MA.

We observed that correction of MA was associated with a protective effect on kidney function. Observational data from the African American Study of Kidney Disease and Hypertension showed that serum bicarbonate levels of 20–30 mEq/L were associated with a decreased risk of dialysis or worsening of kidney function [4]. De Brito-Ashurst *et al.* [10] reported that correction of MA slows down the rate of decline in creatinine clearance from 5.93 to 1.88 mL/min/1.73 m²/year in patients with CKD stages 4 and 5. The same authors observed that 45% of patients with uncorrected MA showed a faster decline in kidney function compared with 9% in the intervention arm. In the current study, ~40% of patients in the control arm showed a rapid decline in eGFR compared with 20% in

Table 6. Adverse effect profile during study period

Characteristics	Control group	Bicarbonate group	P-value
Overall adverse effects ^a , n (%)	39 (41.4)	73 (77.7)	0.01
Gastrointestinal, n (%)	0	11 (11.7)	–
Worsening hypertension, n (%)	21 (22.3)	33 (35.1)	0.13
Worsening oedema, n (%)	15 (16)	27 (28.7)	0.09
Increased requirement of diuretics, n (%)	17 (18.1)	33 (35.1)	0.008
AKI, n (%)	3 (3.2)	2 (2.1)	0.65
Hospitalizations, n (%)	3 (3.2)	2 (2.1)	0.65
Progression to ESRD, n	0	0	–
Death, n	1	1	1

^aExcluding an increase in diuretic prescriptions and hospitalizations (all hospitalizations were because of AKI).

the intervention arm. Mahajan *et al.* [11] reported that correction of MA leads to the preservation of GFR in patients with CKD stage 2 resulting from hypertensive nephropathy. Jeong *et al.* [9] also reported a slower decline in GFR in CKD stage 4 following correction of MA. Phisitkul *et al.* [23], in a non-randomized trial, reported the renoprotective effects of sodium citrate in patients with hypertensive nephropathy. Mathur *et al.* [24] reported that sodium bicarbonate supplementation resulted in an improvement of blood urea levels but did not mention creatinine levels or clearance. Raising serum bicarbonate levels through dietary supplementation of fruits and vegetables has been shown to retard the decline in GFR and reduce urinary excretion of angiotensin in patients with CKD stages 3 and 4 [25, 26].

The beneficial effect of MA correction on kidney function was not apparent at 6 months in previous studies [10, 25]. In the current study, the intervention arm showed an overall improvement in GFR when compared with baseline, whereas a decrease was noticed in the control arm. MA is associated with enhanced complement activation and higher levels of aldosterone and endothelin-1 [27, 28]. Correction of MA might have ameliorated interstitial inflammation, with resultant short-term increments in GFR. Another contributory reason might be the use of amlodipine, which is reported to be associated with short-term improvements in GFR. The improvement in GFR was not confined to the intervention arm alone. There is accumulating evidence that CKD progression is non-linear and, in fact, a proportion of patients exhibit alternate GFR trajectories, including long-term stabilization or improvements in GFR across a wide spectrum of aetiologies [29]. Improving GFR trajectories are documented in 14–48% patients with CKD [30–32]. We believe that a high proportion of patients with CKDu might be responsible for the larger than anticipated

renoprotective effects observed in the current study. There are significant lacunae in the existing knowledge of the natural history of CKDu. A seasonal decline in GFR up to 8 mL has been reported in cohorts with early CKD resulting from Mesoamerican nephropathy [33]. The current study is not sufficiently powered to detect the changes in eGFR across different aetiologies of CKD.

It is less likely that undiagnosed episodes of acute kidney injury (AKI) at the time of recruitment might have contributed to the GFR improvement in the intervention arm. Potential contributory factors such as analgesic use, diarrhoeal illness, infections and indigenous medicine intake were excluded at the time of recruitment. Moreover, the enrolment was limited to prevalent CKD patients who completed 3 months of follow-up. Patients with episodes of AKI during this period were not considered for recruitment. The overall use of RAAS blockers was low, as the majority did not have proteinuria. During the study period, <10% of patients had changes in prescriptions for RAAS blockers. Hence it is unlikely that RAAS blockade might be responsible for the observed changes in GFR. During the study period only five patients developed AKI, satisfying the KDIGO criteria. As the geographic area experiences very hot and humid summers, with maximum temperatures exceeding 40°C, the possibility of recurrent subclinical episodes of AKI due to volume depletion cannot be excluded.

The target bicarbonate levels achieved in the current study were higher when compared with previous studies [9, 10, 25, 26]. The overall adverse effect profile was not favourable for sodium bicarbonate. However, none of them was major or required discontinuation of therapy. Sodium bicarbonate supplementation was associated with increasing oedema requiring loop diuretics. The loop diuretic used was frusemide, which was added within 2 months of starting the intervention. The diuretic use would also partially account for the increases in urinary sodium excretion in the intervention arm. Even though blood pressures were comparable, this was at the expense of enhanced antihypertensive and diuretic prescriptions. Fluid retention and worsening hypertension are major concerns with long-term supplementation of sodium bicarbonate. The open label nature of the trial also probably might have contributed to higher reporting rates in the intervention arm. We did not encounter any patients with new-onset cardiac failure. Even though the intervention arm had marginally lower calcium levels, there were no episodes of symptomatic hypocalcaemia. The adherence to bicarbonate was 85%, but in a real-world scenario the adherence could be considerably lower owing to the non-favourable adverse effect profile. Of the five patients who developed AKI (three in the control group and two in the intervention group), three of them presented with acute gastroenteritis, the other two of them presented with pneumonia and septic arthritis.

To the best of our knowledge there are no published data on the benefits of MA correction in populations with a high prevalence of CKDu. The compliance was ensured by pill counts at each follow-up visit. All the measurements for body composition and DXA were done by a single trained person to minimize interobserver variability. All the laboratory measurements were subjected to rigorous internal and external standardizations.

The study has some limitations. Even though statistically significant, the magnitude of the changes in muscle mass was small. There were two co-primary endpoints, but the sample size calculations were based on changes in MAMC only, due to lack of data on changes in LBM. The alpha was not split between the co-primary endpoints. The GFR change, which was the secondary endpoint emerged as much more important than the primary endpoints. This is an open label study and thus prone to observer bias. The spectrum of kidney disease in the current study is different. The use of renoprotective agents such as angiotensin-converting enzyme inhibitors were limited to only a minor proportion of participants. This might affect the generalizability of the results, especially in CKD populations with proteinuria. The staple diet of the area is polished rice, which is low in protein and phosphorus. Even though the majority of the population identified themselves as non-vegetarians, the intake of proteins with high biological value was limited. The protein intake was lower than the recommended standards for CKD stages 3 and 4. Data on net nitrogen balance would have given better insight into the impact of a protein-restricted diet on acidosis and malnutrition.

We took the utmost care to avoid recruitment of patients with AKI, but because of the short pre-recruitment observation period, and considering the climatic conditions of the geographic area, there is the possibility we recruited patients with subclinical AKI resulting from dehydration. Even though the Chronic Kidney Disease Epidemiology Collaboration equation is validated in Asian Indians, measured GFR values would have provided better information on trends in renal function [34].

The DXA technique is affected by fluid overload. DXA cannot distinguish between LBM and fluid. To minimize the error we performed all the measurements in clinically euvoletic patients. It is possible that worsening oedema in the intervention arm could be linked to increases in LBM. Longer follow-up would be required to ascertain whether the renoprotective effect of bicarbonate is sustained. We did not look into factors such as seasonal variations in GFR in patients with CKDu, which could probably be responsible for a non-linear course of disease progression. Even though patients with diseases other than CKDu in the intervention arm also showed an improving trend in eGFR, the study is underpowered to assess the magnitude of changes in GFR, stratified by aetiology of CKD. Sufficiently powered multicentric studies are required to confirm the renoprotective effects of alkali supplementation in CKD with particular reference to CKDu. The recruitment was limited to individuals <65 years of age because of the potential confounding effects of advanced age on LBM. The findings cannot be generalized to paediatric, elderly and morbidly obese CKD populations and patients with decompensated heart failure and liver disease.

CONCLUSION

The results of the current study showed favourable effects of alkali supplementation in preserving LBM and GFR in CKD stages 3 and 4. More studies are required focusing on the reno-protective effects of MA correction in patients with CKDu.

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CONFLICT OF INTEREST STATEMENT

None declared.

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