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A Randomized Controlled Trial to Assess the Effects of Oral Alkali Therapy in Patients with Diabetic Kidney Disease

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Abstract

Background: To analyze the effects of oral alkali therapy on renal function, nutritional status and bone density in patients of diabetic kidney disease. **Material & Methods:** A randomized controlled trial was conducted on 60 patients of age>18 years with diabetic kidney disease who were not on dialysis and had plasma bicarbonate levels between 16 and 20 mmol/l. Patients were randomly divided into two groups: Test group (n=30) which received oral alkali therapy as sodium bicarbonate and control group (n=30) who did not receive oral alkali therapy. The patients were followed for 12 months to compare the improvement. **Results:** In comparison to controls, test group showed a significant improvement in the Hb (0.7 vs. 0.25, P =0.003), significantly less decrease in eGFR (-2.25 vs. -2.9, P=0.049), non-significant less increase in creatinine (-0.26 ± 0.4 vs. -0.43 ± 0.33, P=0.09), significant improvement in bicarbonate levels (7.5 vs. 1, p<0.0001), significant restoration of albumin (0.32 vs. 0.05, P<.0001), significant fall in iPTH levels (50 vs. 25, p=0.007) and ALP levels (32 vs. 12, p=0.015). Bone density (0.28 ± 0.17 vs. 0.01 ± 0.13, P<.0001) and clinical well-being VAS scores improved significantly among the cases (9.83 ± 5.65 vs. -1.67 ± 7.11, P<.0001). **Conclusion:** In conclusion, oral alkali therapy slows the rate of decline of renal function and the development of end stage renal disease in patients with advanced stages of CKD. This cheap and simple strategy, which is in line with current renal consensus documents, also improves the nutritional status of patients and bone density.

Keywords:- Alkali, bicarbonate, bone density, CKD, diabetes.

INTRODUCTION

Chronic kidney disease (CKD) is a significant health problem worldwide. Global Burden of Disease (GBD, 2017) reports the global prevalence of CKD at 9.1% (697.5 million cases).[1]

Indian data has been restricted to end stage renal disease (ESRD) incidence rates at 151 per million population.[2] CKD is a significant complication in the diabetics,[3] as noted in about 5%–7% of the world population. It is more common in developing countries in comparison to the developed ones. In several developing countries, diabetes leads to 9.1%–29.9% of the cases of end-stage renal disease (ESRD).[3,4] The ongoing degeneration of the kidneys leads to a last resort of Dialysis in such patients.[5] Patients on dialysis experience a plethora of

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complications such as cardiovascular morbidities, Peripheral vascular disease, hypertension, Mineral and bone disorders (secondary to hyperparathyroidism, vitamin D deficiency), Hyperuricemia, Metabolic acidosis, hyperphosphatemia, hypoalbuminemia, anemia, and electrolyte disturbances.[6]

Among them, metabolic acidosis (MA) is a frequent but asymptomatic complication. Usually, MA is not present in majority of the nondialysis-requiring patients with CKD, because of compensatory renal ammonia production as well as bone buffering. However, with the increased worsening of the kidney functions, prevalence of MA increases.[7] In the Chronic Renal Insufficiency Cohort Study (CRIC), it was observed that the prevalence of MA increased proportionately with increasing stage of CKD (7% in stage 2 13% in stage 3, and 37% in stage 4).[8] The study findings led to the conclusion that low serum bicarbonate can independently mark the progression of CKD.[8]

In view of this, correction of the acidosis by base substitution (either by diet or alkali therapy) has shown improvement in GFR, reduction in creatinine and a lower incidence of dialysis initiation (Susantitaphong P et al).[9] Sodium bicarbonate is an inexpensive and well tolerated drug that may be used as oral alkali therapy for correcting metabolic acidosis. Sodium Bicarbonate is a monosodium salt of carbonic acid; it has alkalinizing as well as electrolyte replacement properties. It dissociates into sodium and bicarbonate ions and ion formation raises plasma bicarbonate and buffers excess hydrogen ion concentration, which leads to increased blood pH.[10]

International literature has supported its use in CKD for acidosis correction. de Brito-Ashurst I et al,[11] reported that supplementation of bicarbonate slows the rate of progression of renal failure to ESRD as well as results in improvement of nutritional status in patients having CKD. Melamed ML et al,[12] observed significant stabilization of bicarbonate levels in patients with CKD stage 3 and 4. Currently, studies on outcomes of CKD following base substitution are sparse and thus there are no Indian advisory guidelines on the use of alkali therapy for balancing the serum bicarbonate levels in pre dialysis patients.[9] Diabetics have a high prevalence in India, which is significantly associated with CKD. The management of MA in such patients in the pre-dialysis needs further research which can improve the outcomes and slow the CKD progression. Thus, we did this study to determine the effects of oral alkali therapy on renal function, nutritional status and bone mineral disease in patients of diabetic kidney disease in the pre-dialysis stages.

MATERIAL AND METHODS

A randomized controlled trial was conducted in Institute of Liver and Biliary Sciences, Vasant Kunj New Delhi from July 2018 to June 2020. 60 patients of age>18 years with diabetic kidney disease stage 3- 5 who were not on dialysis with HbA1C levels less than 7% and with plasma bicarbonate levels between 16 and 20 mmol/l were included in the study. Patients with active infection, advanced malignancy, HIV/AIDS, end stage renal disease on maintenance hemodialysis, uncontrolled hypertension (BP >150/90), morbid obesity, congestive heart failure, pregnancy and those who had already undergone renal transplant were excluded.

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The sample size estimation was done based on the study of de Brito-Ashurst I et al,[11] who observed that after four follow ups bicarbonate levels were 18.24±6.47 mmol/l in the alkali group and 14.77 ±5.55 mmol/l in the control group with a decline of 1.88 ±1.13 mmol/l and 5.93±0.86 mmol/l respectively. This was supplanted with an alpha error of 0.05 and power of 90%. The minimal required sample size was 46 patients, i.e., 23 patients in each group. Further assuming an attrition rate of 20% and rounding up, a total of 60 patients were enrolled (30 in each group). The study was approved by institutional ethical committee. A written informed consent was obtained from all the eligible patients. Patients were randomly divided into two groups by random generation of 1 and 2 by RANDBETWEEN. Test group included patients in whom oral alkali therapy in the form of sodium bicarbonate was given (n=30). Control group included patients in whom oral alkali therapy was not given. (n=30). The allocation was not concealed from either the patient or the observer.

Intervention

Oral alkali therapy in the form of sodium bicarbonate at an initial dose of 1 meq/kg and titrated to maintain a serum bicarbonate level above 22 mmol/l at serial follow-ups. The demographic data of all patients were recorded. A complete patient's history was obtained, and clinical examination was done. Patients were subjected to the following investigations baseline and at every 3-monthly follow-up till 12 months: Complete Blood Count (CBC), Blood Urea, Serum Creatinine, Sodium, Potassium, Bicarbonate, Calcium, Phosphate, Intact Parathyroid Hormone Levels, Alkaline Phosphate Levels, Total Protein and Serum Albumin levels, Blood Pressure and weight. Clinical well-being was measured by visual analog scale on a scale of 0-100. DEXA scan was done to assess bone mass. In the event of the study population developing adverse effects such as fluid overload or uncontrolled hypertension not amenable to therapy the study subjects were withdrawn from the study and treated by standard protocol.

Standards and criteria used

American diabetes association (ADA) 2017 for diagnosing diabetes. Chronic Kidney Disease was defined as per KDIGO (Kidney Disease Improving Global Outcomes) guidelines stage 3 or more eGFR(estimated Glomerular Filtration Rate) was calculated using the CKD-EPI equation. Monitoring of the study and control population was done every 3 months for up to a period of 12 months.[13,14,15]

Outcome measures

Data pertaining to kidney function (creatinine, eGFR), nutritional status (Hb, serum albumin and skeletal mass) and bone mineral disease (intact parathyroid hormone levels and alkaline phosphate levels) were compared with the baseline. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Statistical Analysis

Categorical variables [n (%)] and continuous variables (mean ± SD or median with interquartile range) have been represented in the tables. Tests used for association were Independent t test/Mann-Whitney Test (for Quantitative variables) and Chi-Square test (for

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qualitative variables). A p value of <0.05 was considered statistically significant.

RESULTS

A total of 69 patients were screened out of which 60 were enrolled. The patient flow has been shown in [Figure 1] as CONSORT diagram. The baseline demographic and clinical characteristics have been shown in [Table 1]. The mean age of the patients in the study was 55.8 ± 11.8 years which was comparable among the two groups (56.2 ± 11.29 in test group and 55.4 ± 12.47 years in Controls, P=0.795). The gender distribution in this study showed slight male predominance with 41 (68.33%) males and 19(31.67%) females with male female (M:F) ratio of 2.2:1. Both the groups showed comparable gender distribution with Male: female ratio of 2:1 in test group and 2.3:1 in controls, p =0.781). Median duration of CKD in cases was 5(3-7.75) years and in controls was 3.5(2.25-7.75) years with no significant difference between them (p=0.352). In comparison to controls, test group showed a significant improvement in the Hb (0.7 vs. 0.25, P =0.003), significantly less decrease in eGFR (-2.25 vs. -2.9, P=0.049), non-significant less increase in creatinine (-0.26 ± 0.4 vs. -0.43 ± 0.33, P=0.09), significant improvement in bicarbonate levels (7.5 vs. 1, p<0.0001), significant restoration of albumin (0.32 vs. 0.05, P<.0001), significant fall in iPTH levels (50 vs. 25, p=0.007) and significant fall in ALP levels (32 vs. 12, p=0.015) [Table 2]. The improvement in bicarbonate levels was significant from 3 month onwards at each 3 monthly interval among cases (p<0.0001) [Figure 2].

In the period of 12 months, there was a significant improvement in the bone density (0.28 ± 0.17 vs. 0.01 ± 0.13, P<.0001) and significant improvement in the VAS scores indicating clinical well-being among the cases (9.83 ± 5.65 vs. -1.67 ± 7.11, P<.0001) [Figure 3 and 4].

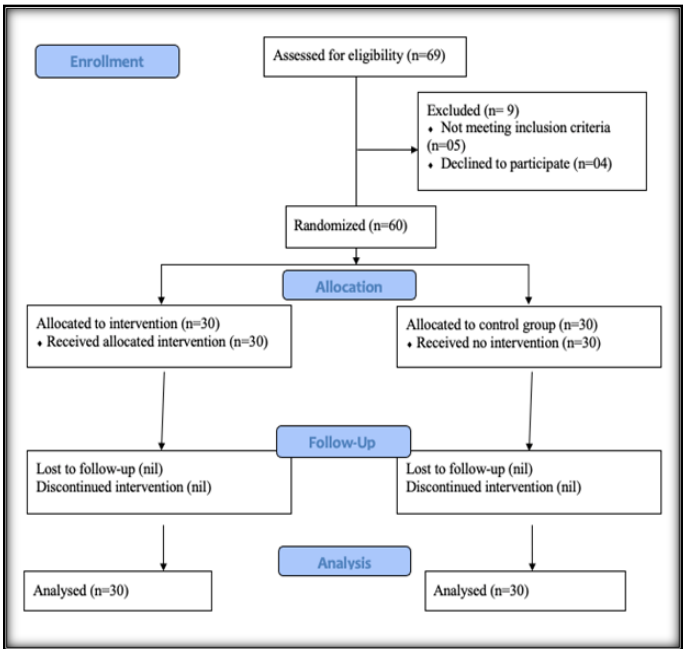

Figure 1: Consort flow diagram

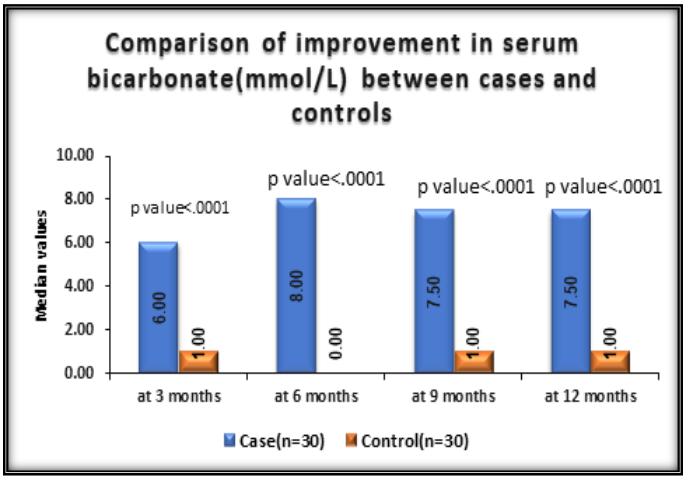

Figure 2: Comparison of improvement in serum bicarbonate(mmol/L) between cases and controls.

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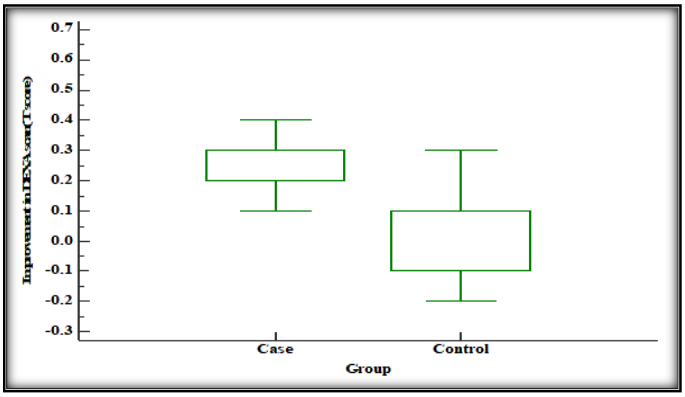

Figure 3: Comparison of improvement in DEXA scan (T score) between cases and controls.

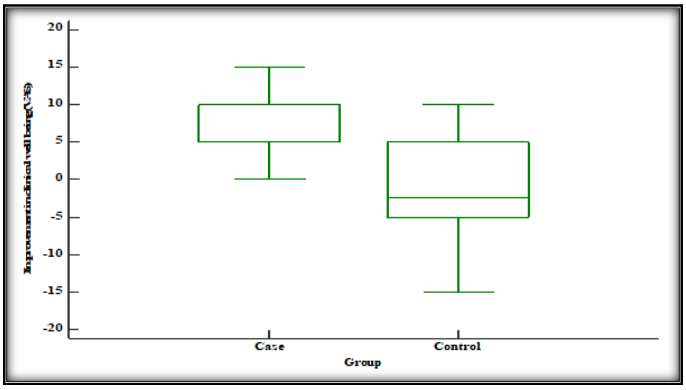

Figure 4: Comparison of improvement in clinical well-being (VAS) between cases and controls.

Table 1: Comparison of baseline demographic and clinical characteristics between cases and controls.

Baseline demographic characteristics	Case	Control	Total	P value
Age(years)	56.2 ± 11.29	55.4 ± 12.47	55.8 ± 11.8	0.795*
Gender				
Female	10 (33.33%)	9 (30%)	19 (31.67%)	0.781‡
Male	20 (66.67%)	21 (70%)	41 (68.33%)	
Duration of CKD in years	5(3-7.75)	3.5(2.25-7.75)	5(3-8)	0.352†

*-Independent t-test, †-Mann Whitney test, ‡-Chi-square test

Table 2: Comparison of investigations between case and control.

Variables		At 0 month	At 12 months	Improvement	P value
Hemoglobin (gm/dl)	Case	9.86 ± 1.43	10.7 ± 1.38	0.7(0.525-0.975)	0.003†
	Control	10.24 ± 1.36	10.37 ± 1.17	0.25(-0.275-0.75)	
Serum creatinine (mg/dL)	Case	2.56 (1.825-3.365)	2.82(1.94-3.752)	-0.26 ± 0.4	0.09*
	Control	2.26(1.805-3.3)	2.56(2.125-3.883)	-0.43 ± 0.33	
eGFR ml/min/1.73 meter square	Case	26.77 ± 10.46	25.09 ± 10.14	-2.25(-3.55--0.7)	0.049†
	Control	29.11 ± 15.7	24.69 ± 12.37	-2.9(-4.9--1.925)	
Serum bicarbonate (mmol/L)	Case	18(16-19)	25(24-26)	7.5(6-8)	<.0001 †
	Control	18(16-18)	18(18-19)	1(0-2)	
iPTH (pg/ml)	Case	248.8 ± 192.55	177.2 ± 132.42	50(26-90.25)	0.007†
	Control	231.83 ± 183.83	202.37 ± 151.62	25(5-48.5)	
ALP (IU/L)	Case	139.83 ± 64.01	107.8 ± 44.79	32(9.25-49.5)	0.015†
	Control	112.07 ± 46.17	96.2 ± 42.08	12(6.5-19.5)	
Serum albumin(gm/dl)	Case	2.83 ± 0.49	3.15 ± 0.43	0.3(0.2-0.4)	<.0001 †
	Control	2.87 ± 0.39	2.89 ± 0.34	0.05(-0.1-0.1)	

*-Independent t-test, †-Mann Whitney test

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DISCUSSION

This was a randomized controlled trial where the study demographics of the population (age, gender, median duration of the disease) were comparable between cases and controls, thereby ensuring that these factors did not affect the outcomes of intervention.[16] The use of oral alkali therapy was found to show a significant improvement in the hemoglobin, creatinine, eGFR, bicarbonate levels, iPTH, ALP, albumin, bone density, and clinical well-being (VAS score) at 12 months of follow ($p<0.05$). This is supported in the previous literature reports by Susantitaphong P et al,[9] de Brito-Ashurst I et al,[11] Mahajan A et al,[17] and Disthabanchong S et al.[18] Diabetic kidney disease is not a specific disease as the kidney derangements affect the hemoglobin levels (due to EPO), the excretory functions (albumin, creatinine, eGFR), the parathyroid hormone levels/ALP levels, associated bone demineralizations and thus the overall clinical well-being.

We found that alkali therapy is an easy to use and administer therapy that may help curb the kidney derangements and help in maintaining the internal milieu of the body. It can be proposed that the kidney-protective benefit of alkali therapy is mediated through reducing kidney ET production and tubulointerstitial injury, similar to animals with reduced nephron mass. Additionally, alkali therapy can also help in delaying the progression of early-stage nephropathy by protecting the kidney architecture. Further, by slowing GFR decline, alkali therapy helps reducing the associated cardiovascular risks.[17] Along with the delaying of kidney derangements, the use of alkali therapy showed significant improvement in the DEXA scan at 12 months with increased density in the bone. With the regenerating bone, there was a decrease in iPTH and ALP levels thus signifying decrease in the bone turnover.[12,19] This may be because of the suppression of the negative effect of metabolic acidosis (MA) on osteoblast-induced collagen synthesis. Normally, MA stimulates osteoclastic function leading to enhanced bone resorption, increases PTH secretion and enhances its biologic action, thereby indirectly stimulating osteoclastic activity. With the oral alkali therapy and bicarbonate restitution, this effect was significantly reduced.[19]

This observation of an increase in serum PTH levels with correction of acidosis is also in agreement with the findings.[20] who found that oral bicarbonate therapy (OBT) in dialysis patients resulted in a decrease in serum ionized calcium levels and a significant increase in the already elevated PTH levels. He proposed that the sustained reduction of serum ionized calcium levels after OBT might promote further increases in PTH secretion and worsening of parathyroid bone disease. Overall, supplementation with alkali reduces bone resorption and enhances bone mineral density and it must be noted that alkali diets may also help reduce bone resorption in such patients.[12] Due to an overall improvement in the Hb, renal functions, and body strength among cases as compared to controls, there was a significant improvement in the clinical well-being (VAS score) of the cases. Among other studies, Mathur RP et al,[19] reported that there were important clinical effects of correction of metabolic acidosis in test group. A sense of well-being was felt in half of the test group, with significant relief in bone and muscle ache in the three patients with ROD. The reason given for

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sense of well-being given was that a lack of a significant increase of blood urea or the correction of metabolic acidosis might have contributed to the sense of well-being observed in 50% patients in test group. In contrast, Melamed et al,[12] failed to find any statistical differences in quality of life after alkali therapy as adjudged by SF-36. This might be because of the inherent limitation of the questionnaires which are subjective and may lead to discrepant results.

The present study holds strength of a long duration to assess clinically meaningful outcomes. The patient compliance was satisfactory as seen by the constant increase of bicarbonate levels and no loss to follow up. Lastly, the randomized study design helped in determining the cause–effect relationships with minimal bias and confounding factors.

Limitations of the Study

The study results must be interpreted under certain limitations. First, protein intake was not assessed which may be a covariate in improvement. Second, study population in present study had fairly normal serum bicarbonate levels at the time of enrolment, which may have limited the effects of the intervention. Third, arterial or venous blood gas analysis was not done which led to somewhat an incomplete picture of participant acid-base status or sodium or calcium balance.

CONCLUSIONS

In conclusion, oral alkali therapy is a novel therapy to slow and delay the rate of decline of renal functions and the development of ESRD in patients with advanced stages of diabetic kidney disease. This therapy is in line with current renal consensus documents. It showed additional improvement in the bone density and overall well-being of the patients. In view of this, we recommend future multicenter trials on the effects of alkali therapy on larger set of patients with different ethnicities and CKD stages so that the therapy can be applied in the clinical practice.

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