DOI: https://doi.org/10.53555/nnmhs.v9i7.1768 Publication URL: https://nnpub.org/index.php/MHS/article/view/1768

EFFECT OF TREATMENT OF METABOLIC ACIDOSIS IN CHRONIC KIDNEY DISEASE (CKD) : A SYSTEMATIC REVIEW

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Abstract

Background: *Plasma anions outweigh cations in metabolic acidosis. Metabolic acidosis may aggravate renal impairment. Sodium bicarbonate may help. Sodium bicarbonate in maintenance dialysis produces metabolic alkalosis. In chronic renal illness, sodium bicarbonate may worsen vascular calcifications.*

Aim: *This article examines the link between effect of treatment of metabolic acidosis in chronic kidney disease (CKD).*

Methods: *By evaluating the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards, this study demonstrated that it met all of the requirements. This enabled the researchers to ensure that the study was as up to date as feasible. Publications published between 2000 and 2023 were included in the search strategy, which included a variety of electronic reference databases (including Pubmed and SagePub). We did not consider review papers, duplicate publications, or half completed articles.*

Result: *In the PubMed database, the results of our search brought up 388 articles, whereas the results of our search on SagePub brought up 201 articles. The results of the search conducted for the last year of 2013 yielded a total of 48 articles for PubMed and 22 articles for SagePub. In the end, we compiled a total of 25 papers, 17 of which came from PubMed and eight of which came from SagePub. We included eight research that met the criteria.*

Conclusion: *The findings of the current investigation demonstrated that supplementation with alkali had a beneficial effect on preserving LBM and GFR in patients with CKD.*

Keyword: *Acid base balance; Bicarbonate sodium; Chronic kidney disease (CKD); Metabolic acidosis*

INTRODUCTION

Kidneys are primarily responsible for maintaining the acid-base balance. Consequently, metabolic acidosis is a common consequence of chronic kidney disease (CKD). Normal evaluation of metabolic acidosis in CKD involves measuring serum bicarbonate levels.[1] However, the pH of the blood must be measured for an acid-base diagnosis. According to the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD), patients with advanced CKD4 had reduced serum total CO2 (carbon dioxide) levels.[2,3]

When metabolic acidosis was defined as serum total CO2 22 mmol/L, 13.2% of CKD patients were found to have metabolic acidosis. The connection between the correction of metabolic acidosis and positive outcomes is also discussed. Several outcomes can be affected by metabolic acidosis in CKD, including progression of the disease, mortality risk, bone demineralization, and muscle catabolism.[1] Adaptive responses such as increased ammoniagenesis, endothelin (ET)-1 production, and renin-angiotensin system expression promote acid excretion in metabolic acidosis in CKD.[4–7]

Metabolic acidosis is prevalent in CKD and is associated with poor prognoses. This article discusses the pathogenesis, clinical effects, and treatment of metabolic acidosis in CKD.[8,9] The prevalence of metabolic acidosis was greater in patients with advanced CKD (27.6% and 46.4%, respectively, in stages 4 and 5 of CKD). Moreover, patients with elevated anionic gap (AG) metabolic acidosis demonstrated a decline in renal function. In CKD stage 1, high AG metabolic acidosis accounted for 33.3% of total metabolic acidosis, while in CKD stage 5, it accounted for 63.0%.[10,11]

This article examines the link between treatment metabolic acidosis in chronic kidney disease.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist served as the foundation for the development of the standards that were used to manage the process of carrying out this systematic review. Articles on the "treatment of metabolic acidosis in CKD" were the focus of this systematic review that was designed to investigate them. These are the subject areas that were investigated in the research that is now being considered.

In order for your work to be taken into consideration, the following prerequisites need to be met: 1) Articles must be written in English; 2) Articles must be available online in their full; and 3) Articles must have been published after 2013, but before this systematic evaluation was carried out. The following kinds of written contributions will under no circumstances be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions that do not have a DOI associated with them, and 3) article reviews and submissions that are comparable.

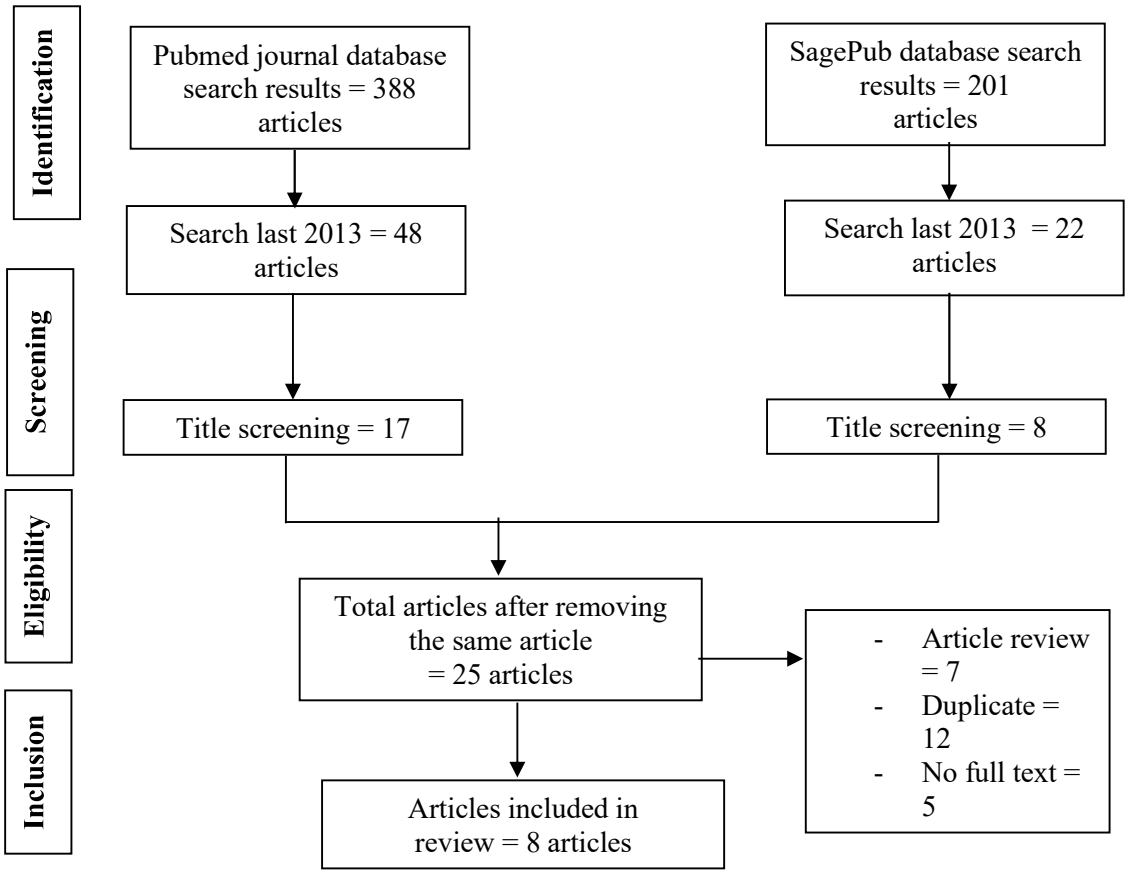

Figure 1. Article search flowchart

The search for papers to be included in the systematic review began on July 17th, 2022 using the PubMed and SagePub databases with the search terms on "treatment"; "metabolic acidosis" and "chronic kidney disease". Where *(("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND ("acidosis"[MeSH Terms] OR "acidosis"[All Fields] OR ("metabolic"[All Fields] AND "acidosis"[All Fields]) OR "metabolic acidosis"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))* is used as search keywords.

The author of the study altered the criteria for what should be included in the study and what should not be included in the study after doing a literature review and looked at the titles and abstracts of previously published studies. Only research studies that fulfilled each and every one of our requirements were taken into consideration at any point during the process of generating the systematic review that we carried out. The following pieces of information of each study are amenable to collection: title, author, publication date, study origin location, research study design, and research variables.

In order to identify which studies ought to be taken into consideration, the authors carried out their own independent evaluations on a selection of the research that was given in the titles and abstracts of the publications. This allowed them to determine which studies ought to be taken into consideration. The next step is to conduct an analysis of the full texts of the studies that meet the criteria for inclusion in the systematic review. The purpose of this analysis is to determine whether pieces of research could be relevant to the objectives of the review. This will be done in order to ensure that the evaluation is as comprehensive as it possibly can be.

RESULT

In the PubMed database, the results of our search brought up 388 articles, whereas the results of our search on SagePub brought up 201 articles. The results of the search conducted for the last year of 2013 yielded a total of 48 articles for PubMed and 22 articles for SagePub. In the end, we compiled a total of 25 papers, 17 of which came from PubMed and eight of which came from SagePub. We included eight research that met the criteria.

Mathur, et al (2023)[12] showed the patients' mean age was 65.1 years old, and female patients made up 42% of the total. The average estimated glomerular filtration rate at baseline was 29.1 mL/min/1.73 m2, and the average serum bicarbonate concentration was 17.5 mmol/L. The median risk of kidney failure over the next five years was 32%, and the urine albumin-to-creatinine ratio at screening was 201 mg/g. Both diabetes and hypertension were prevalent among the subjects, with the former affecting 56% and the latter 98%.

Mathur, et al (2022)[13] showed veverimer-treated women had a greater increase in serum bicarbonate than placebo-treated women (5.4 ± 0.5 versus 2.2 ± 0.6 mmol/L; P <0.001) at week 52. Physical Function as measured by the Kidney Disease and Quality of Life - Physical Function Domain, which includes questions about walking, stair climbing, carrying groceries, and other activities, improved significantly in women randomised to veverimer versus placebo (P <0.001; + 13.2 vs -5.2, respectively). The veverimer group's objectively measured performance time on the repeated chair stand test improved significantly compared to the placebo group (P <0.001).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Mathur, 2023[12]	United State of America (USA)	Randomized clinical trial (RCT)	1480 participants	The purpose of the VALOR-CKD study is to investigate the impact of veverimer on the risk of progressive loss of kidney function by recruiting a large cohort of persons with metabolic acidosis who are at high risk for CKD progression.
Mathur, 2022[13]	United State of America (USA)	Randomized clinical trial (RCT)	196 patients	The use of Veverimer was successful in treating metabolic acidosis in women with CKD, leading to considerable improvements in both the patients' quality of life and their ability to carry out daily tasks.
Kittiskulnam, 2020[14]	Thailand	Randomized clinical trial (RCT)	42 patients	In patients with pre-dialysis CKD, supplementing with bicarbonate to attain a serum level 24 mEq/L results in

				improved muscle mass preservation. The effects of alkaline therapy on renal function may necessitate an extended period of investigation.
Dubey, 2020[15]	India	Randomized clinical trial (RCT)	188 patients	Alkali supplementation to increase venous bicarbonate levels to 24–26 mEq/L is associated with preservation of lean body mass and kidney function in CKD stages 3 and 4 patients.
Di Iorio, 2019[16]	Italy	Randomized clinical trial (RCT)	740 patients	In patients with CKD stages 3-5 who do not have advanced stages of chronic heart failure, treating metabolic acidosis with sodium bicarbonate is not only safe but also increases patient survival and the likelihood of renal function.
Wesson, 2019[17]	United State of America (USA)	Randomized clinical trial (RCT)	124 participants	Effectively and securely, Veverimer corrected metabolic acidosis. Longer-term studies are required to evaluate the effects of veverimer on physical functioning, as well as other adverse effects of metabolic acidosis, such as progression of chronic kidney disease and bone health.
Bellasi, 2016[18]	United State of America (USA)	Randomized clinical trial (RCT)	145 patients	Serum bicarbonate between 24 and 28 mmol/l reduces HOMA-IR most. Bicarbonate alters IR. Treatment affects HOMA index due to serum bicarbonate variations. Validation in diabetic and non-diabetic CKD patients is needed.
Goraya, 2014[19]	United State of America (USA)	Randomized clinical trial (RCT)	108 patients	In CKD patients with metabolic acidosis that is less severe than that for which KDOQI recommends medication, treatment with dietary alkali can reduce renal angiotensin II activity while maintaining eGFR.

Kittiskulnam, et al (2020)[14] conducted a study with serum bicarbonate levels at baseline were 21.0 ± 2.1 mEq/L. After 4 months of treatment, the average serum bicarbonate levels in both groups were 24.0 ± 1.4 and 20.7 ± 2.3 mEq/L ($p < 0.001$). Both BIA-derived total-body muscle mass and appendicular lean balance were increased at 4 months in the higher bicarbonate group (26.0 ± 5.3 to 26.7 ± 5.5 kg, $p = 0.04$ and 19.8 ± 4.1 to 20.7 ± 4.4 kg, $p = 0.06$, respectively) despite comparable body weight and protein intake. Patients in the high bicarbonate group had a significant reduction of plasma myostatin levels, a surrogate of muscle degradation, at the study exit after adjusting for baseline values (-3,137.8; 95% CI -6,235.3 to -40.4 pg/mL, p= 0.04), but unaltered insulin-like growth factor-1 level, as the mediator of muscle cell growth, (141 [106-156] to 110 [87-144] ng/mL, $p = 0.13$) compared to the control group.

Dubey, et al (2020)[15] showed the intervention group had a greater lean body mass (LBM) ([95% confidence interval [CI] = 36.5–37.1) and mid-arm muscle circumference (MAMC) (22.9 cm [95% CI = 22.8–23) than the control group (22.6 cm [95% CI = 22.5–22.7]; P = 0.001). In the intervention group, the estimated glomerular filtration rate (eGFR) was higher (32.74 mL/1.73 m2 [95% CI = 31.5–33.9] versus 28.2 [27–29.4]; P <0.001). 39 (41.5%) patients in the control arm and 19 (20.2%) patients in the intervention arm experienced a precipitous decline in estimated glomerular filtration rate (P <0.001).

Di Iorio, et al (2019)[16] conducted a study with 740 patients. Sodium bicarbonate (SB) and standard care (SC) enrolled 376 and 364 people with mean ± SD age 67.8 ± 14.9 years, creatinine clearance 30 ± 12 ml/min, and serum bicarbonate 21.5 ± 2.4 mmol/l. SC had 29.6 ± 9.8 months of follow-up and SB 30.3 ± 10.7 months. SB daily dosages averaged 1.13 ± 0.10; 1.12 ± 0.11; and 1.09 ± 0.12. 87 participants reached the primary goal (62 ± 17.0% in SC, 25 ± 6.6% in SB, $p < 0.001$). 71 patients started dialysis (45 ± 12.3% in SC and 26 ± 6.9% in SB, $p = 0.016$) and 37 died (25 ± 6.8%) in SC and 12 ± 3.1% in SB, $p = 0.004$). SB did not affect blood pressure, weight, or hospitalisations.

Wesson, et al (2019)[17] conducted a study with 71 (59%) of 120 veverimer patients met the composite primary objective, compared to 20 (22%) of 89 placebo patients (a difference of 37%, 95% CI = 23-49; $p <0.001$). The most prevalent adverse event in the veverimer group was non-treatment-limiting diarrhoea (9% vs 3% in the placebo group). Diarrhoea, flatulence, nausea, and constipation were the most common treatment-related side effects in 13% veverimer patients and 5% placebo individuals. Unstable angina and pneumonia killed two placebo patients.

Bellasi, et al (2016)[18] showed average dose of bicarbonate in the treatment group was 0.7 ± 0.2 mmol/kg. Treated patients showed a better metabolic control as confirmed by lower insulin levels (13.4 ± 5.2 vs 19.9 ± 6.3; for treated and control subjects respectively; $p < 0.001$), Homa-IR (5.9 [5.0-7.0] vs 6.3 [5.3-8.2]; $p = 0.01$) and need for oral antidiabetic drugs. The relationship between serum bicarbonate and HOMA-IR was nonlinear, with the greatest HOMA-IR reduction observed for serum bicarbonate levels between 24 and 28 mmol/l. Adjustment for confounding variables suggests that serum bicarbonate, and not treatment, fuels the HOMA-IR effect.

Goraya, et al (2014)[19] showed all were treated for 3 years with angiotensin converting enzyme inhibition to lower their systolic blood pressure below 130 mm Hg. Plasma TCO2 dropped in Usual Care but increased with bicarbonate or fruits and vegetables. Usual Care increased urine angiotensinogen, an index of renal angiotensin II, but bicarbonate or fruits and vegetables lowered it. At 3 years, bicarbonate and fruits and vegetables lost less eGFR than Usual Care. Thus, dietary alkali treatment of metabolic acidosis in CKD less severe than KDOQI advises lowers renal angiotensin II activity and preserves eGFR.

DISCUSSION

Metabolic acidosis is prevalent in CKD and is associated with poor prognoses. This article discusses the pathogenesis, clinical effects, and treatment of metabolic acidosis in CKD.[8,9] In people with chronic kidney disease (CKD), metabolic acidosis is caused by problems with getting rid of ammonia, reabsorbing bicarbonate in the tubules, and making enough bicarbonate to balance out the acids made in the body and eaten with food. The process of ammoniagenesis is slowed down when more than 80% of nephrons are lost. Chronic metabolic acidosis speeds up the breakdown of proteins, which makes the malnutrition-inflammation-atherosclerosis (MIA) condition more likely to happen.[20]

Metabolic acidosis occurs when plasma anions outnumber cations. Sodium bicarbonate replacement for diarrhoea or renal proximal tubular acidosis is helpful, but there is no evidence that it improves clinical outcomes or mortality in patients with acute metabolic acidosis, such as diabetic ketoacidosis, lactic acidosis, septic shock, intraoperative metabolic acidosis, or cardiac arrest. Hyperchloremia and unmeasured anions cause metabolic acidosis in advanced chronic renal disease patients. Metabolic acidosis may worsen renal dysfunction, but further research is needed to confirm this.[21]

Sodium bicarbonate may mitigate this effect. Maintenance dialysis patients are loaded with sodium bicarbonate, which causes temporary metabolic alkalosis. Sodium bicarbonate therapy causes hypercapnia, hypokalemia, ionised hypocalcemia, and QTc prolongation. Sodium bicarbonate medication may aggravate vascular calcifications in chronic renal disease patients.[21] The metabolic acidosis that a patient is experiencing should be treated with alkaline treatment in order to achieve a serum bicarbonate level of 22 mEq/L or higher, as recommended by the KDIGO guidelines.[22]

Several mechanisms that link metabolic acidosis to CKD progression have been identified. Experimental evidence suggests that metabolic acidosis stimulates endothelin production, the activation of its type A and type B receptors, and the activation of the complement cascade. Other lines of evidence indicate that acidosis stimulates angiotensin II production and upregulates TGF-beta, further associating acidosis with renal function loss.[23] Therefore, impaired renal acid excretion and excessive dietary acid intake contribute to metabolic acidosis and progressive decline in renal function. In animal models, fruit and vegetable consumption and sodium citrate supplementation have been shown to prevent metabolic acidosis, reduce endothelin- and aldosterone-induced fibrosis, and delay the loss of residual renal function.[24,25] In the earlier research, the favourable effect that MA correction had on renal function did not become apparent until after 6 months.[19,25] It's possible that correcting the MA would have helped reduce the interstitial inflammation, which would have led to a temporary increase in GFR. There is also the possibility that the usage of amlodipine, which has been linked to being related with short-term improvements in GFR, played a role in this phenomenon. The improvement in GFR was seen in both the control group as well as the intervention group. There is growing evidence that the progression of chronic kidney disease (CKD) is not linear. In fact, a portion of individuals display alternate GFR trajectories, which can include long-term stabilisation or improvements in GFR across a wide spectrum of aetiologies. This phenomenon is seen in patients with a variety of CKD subtypes.[13,15]

Studies show that bicarbonate therapy is beneficial in preserving muscle mass in patients.[14] Nonetheless, the evidence-based upper therapeutic bicarbonate level in pre-dialysis CKD remains ambiguous, and the potential benefit of correcting metabolic acidosis has been the subject of insufficient interventional controlled trials. In the present study, correction of metabolic acidosis to achieve a serum bicarbonate level of approximately 24 mEq/L was found to be significantly associated with better muscle mass preservation, as measured by BIA-derived total-body muscle mass indexed to height squared, independent of body weight and daily protein intake.[10,26]

Alkaline supplementation to boost venous HCO^{3-} level of 23.5 mEq/L was substantially connected with increased lean body mass determined by Dual X-ray absorptiometry among patients with CKD of unclear aetiology, according to research carried out by Dubey and colleagues.[15,21] This was in comparison to the non-intervention group. In recognition of the fact that metabolic acidosis-induced muscle atrophy is caused by an imbalance between anabolic and catabolic processes in skeletal muscle. Myostatin, a negative regulator of muscle growth, is linked to muscle proteolysis and atrophy in CKD, according to numerous experimental studies.[26,27]

CONCLUSION

The findings of the current investigation demonstrated that supplementation with alkali had a beneficial effect on preserving LBM and GFR in patients with CKD.

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