

Metabolic Acidosis in Chronic Kidney Disease: Pathogenesis, Clinical Consequences, and Treatment

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The kidneys play an important role in regulating the acid-base balance. Metabolic acidosis is common in chronic kidney disease (CKD) patients and can lead to poor outcomes, such as bone demineralization, muscle mass loss, and worsening of renal function. Metabolic acidosis is usually approached with evaluating the serum bicarbonate levels but should be assessed by counting blood pH. Current guidelines recommend oral bicarbonate supplementation to maintain the serum bicarbonate levels within the normal range. However, a slow decline in the glomerular filtration rate might occur, even though the serum bicarbonate levels were in the normal range. Because the serum bicarbonate levels decrease when metabolic acidosis advances, other biomarkers are necessary to indicate acid retention for early diagnosis of metabolic acidosis. For this, urine citrate and ammonium excretion may be used to follow the course of CKD patients. Metabolic acidosis can be treated with an increased fruit and vegetable intake and oral alkali supplementation. Previous studies have suggested that administration of oral sodium bicarbonate may preserve kidney function without significant increases in blood pressure and body weight. Veverimer, a non-absorbed, counterion-free, polymeric drug, is emerging to treat metabolic acidosis, but further researches are awaited. Further studies are also needed to clarify the target therapeutic range of serum bicarbonate and the drugs used for metabolic acidosis.

Key Words: Chronic kidney disease, Metabolic acidosis, Serum bicarbonate, Total carbon dioxide

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INTRODUCTION

The kidneys play a principal role in the maintenance of the acid-base balance¹. Therefore, metabolic acidosis is a common complication of chronic kidney disease (CKD)². Metabolic acidosis in CKD is usually assessed by measuring serum bicarbonate levels. However, blood pH should be evaluated for the acid-base diagnosis³. According to the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD), serum total CO₂ (carbon dioxide) levels were lower in patients with advanced CKD⁴.

When serum total CO₂ <22 mmol/L was defined as metabolic acidosis, 13.2% of the patients with CKD were found to have metabolic acidosis. The prevalence of metabolic acidosis was higher in patients with advanced CKD (27.6% and 46.4% in stage 4 and stage 5 of CKD, respectively). In addition, patients with high anionic gap (AG) metabolic acidosis showed an increase in renal function decline. High AG metabolic acidosis accounted for 33.3% of total metabolic acidosis in CKD stage 1 and 63.0% in CKD stage 5.

Metabolic acidosis is common in CKD and can lead to poor outcomes. This paper reviews pathogenesis, clinical consequences, and treatment of metabolic acidosis in CKD.

Whether the correction of metabolic acidosis can be connected to the beneficial outcomes is also discussed.

Pathogenesis of Metabolic Acidosis in CKD

Mechanism of maintaining acid-base balance in the kidney

The kidneys regulate the acid-base balance following two major mechanisms: the reabsorption of bicarbonate and the generation of new bicarbonate. Healthy kidneys can filter 4,500 mEq of bicarbonate per day, and approximately 80% of the bicarbonate filtered through the glomerulus is reabsorbed in the proximal tubule^{5,6}. In addition, the kidney causes the formation of new bicarbonate via ammonia production and distal nephron acid secretion. Urinary NH_4^+ is produced primarily in the proximal tubule cells from systemically derived glutamine⁷. In the proximal tubule, the conversion of glutamine to glutamate, and then oxaloacetate, produces 2 ammonium (NH_4^+) and 2 bicarbonate (HCO_3^-) ions. H^+ ions secreted into the urine are mainly bound by H^+ acceptors; even maximally acidified urine is unable to excrete the daily acid load in the absence of buffering⁶. Urinary phosphate (HPO_4^{2-}), as well as other buffers, perform this role and are usually described as titratable acids. The production of ammonia by the kidney is the major mechanism of new bicarbonate formation in metabolic acidosis and is increased several times more than titratable acid excretion⁷. Most of the filtered bicarbonate is reabsorbed in a steady state. Therefore, increasing the reabsorption of filtered bicarbonate is not a principal adaptation of the kidneys to an acid load, although an acid load enhances ammoniogenesis in the proximal tubule and thus intracellular bicarbonate production.

Development of metabolic acidosis in CKD

Metabolic acidosis develops as CKD progresses, due to a decreased acid-excretory capacity and high daily endogenous and exogenous acid loads⁶. In CKD, metabolic acidosis develops when the kidneys are incapable of excreting the acid load, resulting in a positive H^+ balance and low total CO_2 concentration. As the nephron mass decreases in CKD patients, the remaining viable nephrons filter more blood per nephron, thereby increasing the single nephron glomer-

ular filtration rate (GFR)⁸. Single nephron acid excretion, especially ammoniogenesis, improves in progressive CKD cases even though the net renal acid excretion decreases. Although the renal excretion of a single nephron is enhanced, the remaining nephrons do not sufficiently excrete the acid load. A decrease in the ability of the kidney to produce ammonia is directly related to the inability to uptake glutamine from the proximal tubule in CKD. The inability of the kidneys to generate enough ammonia to neutralize the daily acid load leads to non-anion gap metabolic acidosis that develops in patients with moderate CKD. The titratable acid excretion is relatively preserved, in contrast to the reduced renal ammonia production in CKD. Although renal function declines, the kidney preserves the ability to excrete titratable acid until the GFR decreases below 15 ml/min/1.73 m². In CKD stage 5, the titratable acid excretion decreases, leading to a positive AG secondary to the accumulation of phosphate and other anions. In addition, as kidney function declines, the decreased bicarbonate reabsorption in the proximal tubule is associated with the increased bicarbonate load per nephron, exceeding the reabsorptive capacity⁷. Since metabolic acidosis in CKD is associated with an increased daily endogenous and exogenous acid load, as well as a decreased kidney excretion ability, a diet low in acid-producing foods is needed.

Serum bicarbonate concentration is the most commonly used acid-base parameter in CKD, but there are other factors such as net endogenous acid production (NEAP), protein intake, net renal acid excretion, and so on⁶. Blood pH should be evaluated for an accurate acid-base diagnosis^{3,9}. Bicarbonate ion (HCO_3^-) concentration can be evaluated through blood gas analysis. However, blood gas analysis is not easy to measure in the usual clinical practice, especially in the outpatient setting⁹. Therefore, the serum total CO_2 is usually used as a surrogate for HCO_3^- . In contrast, in Japan, blood-gas analyzers are available in most hospitals and venous gas test including pH, HCO_3^- is routinely performed for diagnosis acid-base disorders in the clinical outpatient setting^{9,10}. There are several technical problems associated with measuring total CO_2 levels. Total CO_2 values may have different results when testing is delayed after blood collection or if the sample is exposed to air¹¹. In addition, the assay methods can influence the

measured values. Total CO₂ levels were lower when measured by the enzymatic assay method, as compared to when they were measured directly by an electrode¹¹. Therefore, to reduce error, the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline has recommended that the exposure of the collected sample to air must be reduced, the sample processing must not be delayed, and the same laboratory and methods of analysis should be used for serial measurements¹². Recently, metabolic acidosis in CKD was further subdivided according to the type of metabolic acidosis associated with progressive renal function¹³. When the renal function deteriorates and acid accumulation occurs, but the serum bicarbonate level or blood pH remains normal, it is called eubicarbonatemic metabolic acidosis or subclinical metabolic acidosis. As acid accumulation progresses further and the serum bicarbonate level decreases, the case progresses from non-acidemic hypobicarbonatemia to acidemic hypobicarbonatemia, depending on the degree of respiratory compensation. Even if the serum bicarbonate level is normal, acid accumulation can occur. Therefore, other biomarkers that can detect metabolic acidosis at an early stage are needed.

Consequences of Metabolic Acidosis in CKD

Metabolic acidosis in CKD can affect several outcomes, including CKD progression, the risk of death, bone demineralization, and muscle catabolism¹⁴. Prolonged metabolic acidosis in CKD can lead to renal interstitial fibrosis. In metabolic acidosis in CKD, adaptive responses such as increased ammoniogenesis, endothelin (ET)-1 production, and renin-angiotensin system expression promote acid excretion^{7,15}. However, sustained expression of this adaptive response can lead to the activation of the complementary cascade due to increased NH₄⁺ removal per nephron along with the production of proinflammatory and profibrotic mediators. ET-1 is a potent intrarenal and systemic vasoconstrictor that induces oxidative stress, inflammation, and extracellular matrix accumulation in the kidneys. Angiotensin II is also a potent vasoconstrictor that promotes tubulointerstitial fibrosis. Thus, compensatory mechanisms to control metabolic acidosis become maladaptive and cause tubulointerstitial fibrosis, leading to the loss of nephron

function and exacerbation of CKD. Clinical studies have also shown that metabolic acidosis in CKD is associated with CKD progression. In the Chronic Renal Insufficiency Cohort (CRIC), a CKD cohort in the United States, the halving of eGFR or end-stage kidney disease (ESKD) occurred less frequently as the serum total CO₂ levels increased¹⁶. When the serum total CO₂ level was <22 mmol/L, the occurrence of renal events increased 1.97 times compared to that in patients with 22-26 mmol/L. In the KNOW-CKD cohort study, the development of renal events (doubling of serum creatinine, 50% reduction of eGFR, or development of ESKD) was significantly higher when the serum total CO₂ level was <22 mmol/L than when the serum total CO₂ levels in 22-26 mmol/L¹⁷. The eGFR slope was lower in the low serum total CO₂ group.

Previous studies have demonstrated a relationship between metabolic acidosis and patient death. In the United States, veterans with CKD and those with metabolic acidosis (serum total CO₂ level <22 mmol/L) had 43% higher all-cause mortality than those with normal serum total CO₂ concentrations (26-29 mmol/L)¹⁸. In the CRIC study, metabolic acidosis (serum total CO₂ level <22 mmol/L) was associated with a 26% higher risk of death, although this result was not statistically significant¹⁶. The risk of death and heart failure was significantly higher in patients who sustained serum total CO₂ levels >26 mmol/L for the entire duration of follow-up¹⁶. In the KNOW-CKD cohort study, there was no significant association between the serum total CO₂ levels and the composite outcome of cardiovascular events and death¹⁷. The results may have differed due to the different characteristics of the study population, renal function, and mortality rate.

Metabolic acidosis is associated with bone mineral density (BMD) loss and muscle wasting⁷. Bone is an important buffer system that responds to excess acid. Bone buffering causes hypercalciuria, a negative calcium balance, and loss of BMD. In vivo studies have shown that extracellular acidification inhibits osteoblast activity and increases osteoclast activity¹⁹. These effects lead to a reduced BMD. Serum bicarbonate was positively correlated with BMD and inversely correlated with bone loss in the Health, Aging and Body Composition (Health ABC) study participants comprising of elderly people living in a community²⁰. The National Health

and Nutrition Examination Survey (NHANES) data also showed that lower serum total CO₂ levels were associated with lower BMD²¹. In CKD patients, the serum total CO₂ concentration is directly related to BMD, but further research is needed on the relationship between the serum total CO₂ concentration and fractures⁷. Metabolic acidosis can also cause muscle weakness and protein-energy malnutrition. In the Health ABC study, the incidence of incident functional limitation was higher in the group with serum bicarbonate levels <23 mmol/L for six months compared to serum bicarbonate levels in ≥26 mmol/L²². In the NHANES data, serum total CO₂ levels <23 mmol/L were more likely to be associated with low gait speed and lower quadriceps muscle strength⁷. Thus, excess acid has detrimental effects on the musculoskeletal health.

In the KNOW-CKD cohort study, metabolic acidosis was associated with arterial stiffness, which was evaluated using the brachial-ankle pulse wave velocity (baPWV). baPWV was significantly higher in patients with metabolic acidosis (P<0.001) and showed a significant inverse correlation with serum total CO₂ levels in an unadjusted model, which was retained after adjustment (β -5.4 cm/sec; 95% confidence interval -9.9, -1.0; P=0.017)⁴. These associations may be related to several factors, including the effects of metabolic acidosis on bone buffers, arterial inflammation, and endothelial dysfunction. Bone acts as a buffer in response to acidosis, and metabolic acidosis induces phosphate and calcium efflux from the bone into the blood²³. However, it is difficult to simply explain that phosphate and calcium efflux lead to vascular calcification since the link between metabolic acidosis and vascular calcification is complicated. Metabolic acidosis also increases phosphate and calcium solubilities, downregulates phosphate uptake transporters, decreases parathyroid hormone secretion, and prevents vascular calcification^{24,25}.

When and How to Correct Metabolic Acidosis in CKD

Current treatment guidelines

The current guideline recommendations for the management of metabolic acidosis in CKD are as follows: In 2003, the KDOQI guidelines recommended that the serum levels of total CO₂ should be maintained at ≥22 mEq/L, and if

necessary, supplemental alkali salts should be administered to achieve this goal¹². In 2007, the Care of Australians with Renal Impairment (CARI) guidelines recommended correction of metabolic acidosis to achieve serum bicarbonate levels >22 mmol/L²⁶. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines also recommended that if the serum bicarbonate level was <22 mmol/L, oral bicarbonate be supplemented to maintain serum bicarbonate levels within the normal range unless contraindicated²⁷. These recommendations are based only on serum bicarbonate levels.

Expanded concept of metabolic acidosis and subclinical metabolic acidosis

In the classic concept of metabolic acidosis in CKD, hypobicarbonatemia results from H⁺ retention and is required for the diagnosis of metabolic acidosis. However, the recently expanded concept of metabolic acidosis suggests that H⁺ retention occurs even in eubicarbonatemic conditions, and may induce renal progression²⁸. Daily oral sodium bicarbonate preserves the GFR slope by slowing its decline in early hypertensive nephropathy without metabolic acidosis²⁹. The baseline creatinine-based eGFR was approximately 75±6 ml/min, and the venous total CO₂ was 26 mmol/L, which could be categorized as eubicarbonatemia. Since serum total CO₂ is normal in such cases, it is not easy to detect subclinical metabolic acidosis, and other biomarkers are required.

Hypocitratemia has long been recognized as an indicator of H⁺ retention³⁰. Wesson et al.³¹ evaluated the 10-year eGFR decline in early hypertensive patients (eubicarbonatemic patients) who were randomly prescribed oral sodium bicarbonate, sodium chloride, or a placebo on a daily-basis. In the bicarbonate-treated group, the eGFR decrease was the least and H⁺ retention was also lower than that in the sodium chloride or placebo group. In addition, urine citrate excretion was higher in the sodium bicarbonate group. Intracellular acidification induces physiological adaptations that lead to increased proximal reabsorption of citrate and hypocitratemia²⁸. Therefore, higher urinary citrate excretion in the oral bicarbonate group reflects less H⁺ retention and less acidosis. In another study, H⁺ retention decreased, and urinary citrate excretion increased when patients with CKD

stages 1 and 2 were on a base-producing diet including vegetables and fruits³¹. Urine citrate excretion could be a marker of acid retention and can be used for the guiding and monitoring of base therapy in patients with CKD without overt metabolic acidosis. However, it is difficult to measure easily in the current clinical setting, and further researches are necessary because appropriate standards are not available.

Previous studies have shown that decreased urine ammonia excretion is associated with the progression of CKD. In the NephroTest cohort (1,065 patients with CKD stage 1-4), there was 92% eubicarbonatemia at baseline, but the lowest tertile of baseline urine ammonium excretion was associated with increased ESKD risk and increased rapid GFR decline³². It is suggested that the inability of daily acid load excretion causes deleterious renal outcomes. In the African American Study of Kidney Disease and Hypertension cohort (1,044 hypertensive patients with a GFR of 20-65 ml/min/1.73 m², 88% with eubicarbonatemia) study, compared to the highest tertile of urine ammonium, the lowest urine ammonium tertile showed a higher risk of ESKD or death even after adjustment for various confounding factors³³. However, similar to urine citrate, it is not easy to measure urine ammonium in daily practice.

How to correct metabolic acidosis in CKD

In CKD, metabolic acidosis can lead to tubulointerstitial fibrosis and CKD progression⁶, which needs to be controlled. The dietary acid load is also significant; thus, reducing acid intake, and it is necessary to consume fruits and vegetables containing alkali or undergo alkali treatment. Treatment with sodium bicarbonate is currently the most commonly used alkali treatment, and it is also available in Korea. It has the advantage of being cheap, but it may cause discomfort such as bloating or flatus after taking it³⁴. Although oral sodium citrate is also recommended in the KDOQI guidelines³⁵, there is currently no single sodium citrate formulation in Korea. In previous studies, oral sodium bicarbonate (NaHCO₃) was prescribed at 0.4 meq/kg of body weight per day³⁶, 0.5 meq/kg of lean body weight per day³⁷, or up to 3,000 mg/day³⁸. A recent Bicarbonate Administration to Stabilize eGFR (BASE) pilot trial showed the efficacy and safety of and adherence to a higher dose of sodium bicarbonate pre-

scription in CKD³⁹. In this randomized trial, the groups were treated with either a higher dose of sodium bicarbonate (0.8 meq/kg of body weight per day), a lower dose of sodium bicarbonate (0.5 meq/kg of body weight per day), or a placebo for 28 weeks and compared. The serum total CO₂ level was higher and urinary ammonium excretion was lower in the higher-dose sodium bicarbonate group than in the lower-dose sodium bicarbonate group at week 28. However, a higher dose of sodium bicarbonate was associated with a greater increase in albuminuria. Therefore, further research is needed on the safety of prescribing higher doses of sodium bicarbonate. Current guidelines recommend oral bicarbonate supplementation at a serum total CO₂ level of <22 mmol/L, and existing interventional and observational studies suggest that 24-26 mmol/L of serum total CO₂ is ideal⁷. Further studies are needed to clarify the target therapeutic range of the supplements and drugs used for metabolic acidosis.

Nutritional approaches are also helpful in treating metabolic acidosis. Eating fruits and vegetables containing alkali or targeted dietetic-nutritional treatments can be used¹⁴. In a previous study, apples, oranges, apricots, peaches, strawberries, carrots, eggplant, lettuce, tomatoes, and spinach were provided as alkali-containing fruits or vegetables to treat metabolic acidosis⁴⁰. However, since patients with CKD are at a risk of developing hyperkalemia, caution is required when consuming fruits and vegetables. The following methods can be used as dietary approaches to counteract metabolic acidosis in CKD patients¹⁴. In early CKD, up to stage 3a, a Mediterranean diet⁴¹ or an alkaline diet can be used. An alkaline diet for CKD patients can be planned according to the potential renal acid load (PRAL) and potassium quantity of different foods⁴². Meat has a positive PRAL, and vegetables or fruits have a negative PRAL and can neutralize the acid. In more advanced CKD, with stage 3b or higher, there is a way to limit protein intake. A low-protein diet can reduce acid production and reduce proteinuria, thereby slowing renal progression. In addition, a vegan low-protein diet can be administered. In this case, it is important to eat cereals or legumes for the intake of essential amino acids.

Veverimer has been developed as a novel drug for metabolic acidosis; it is a non-absorbed, counterion-free, poly-

meric drug that removes hydrochloric acid from the gastrointestinal lumen. A multicenter study examined changes in CKD patients with metabolic acidosis (eGFR 20-40 ml/min/1.73 m²) using vevermier and a placebo⁴³. During the 12-week follow-up period, serum bicarbonate levels increased more in the vevermier group than in the placebo group, no adverse reactions occurred, and the serum bicarbonate elevation or normal range maintenance rate was higher in the vevermier group. Currently, a large-scale randomized controlled trial (RCT) to evaluate the renal and mortality outcomes according to the use of vevermier is in progress (NCT03710291). Further research is needed to determine whether vevermier is better than oral sodium bicarbonate or whether there are other adverse reactions such as GI infection risk while neutralizing gastric acid.

Clinical outcomes of alkali treatment in CKD

Goraya et al.⁴⁰ compared changes in the GFR for three years after the administration of the usual care, oral bicarbonate, or fruits and vegetables in patients with CKD stage 3 and plasma total CO₂ in the range of 22-24 mmol/L. There was no decrease in plasma total CO₂, and the GFR was

better preserved in the oral bicarbonate or fruit and vegetable treatment group compared to the usual care group. A meta-analysis with several RCTs revealed that the eGFR was better preserved with oral bicarbonate (pooled mean difference, 3.10; 95% CI, 1.29-4.92)^{29,40,44-48}. There was no difference in the systolic blood pressure or body weight between the oral bicarbonate group and the control group. When sodium bicarbonate was administered in the Use of Bicarbonate in Chronic Renal Insufficiency study (UBI study), the serum bicarbonate level was higher compared to the standard of care during the follow-up period⁴⁹. The incidence of serum creatinine doubling and dialysis initiation was significantly lower in the sodium bicarbonate group, even after multivariable adjustment. The all-cause mortality was also significantly lower in the sodium bicarbonate group. The effects of alkali treatment on renal progression in previous studies are summarized in Table 1.

In many studies to date, oral bicarbonate administration had a significant beneficial effect on CKD progression. However, there were also recent RCTs showing no differences in CKD progression. According to data from the BiCARB study group, the eGFR decline, doubling of serum creatinine, a 40% reduction in the eGFR, or initiation of renal replacement therapy

Table 1. Clinical trials evaluating sodium bicarbonate treatment in chronic kidney disease

Reference	Year	Study design	CKD stage	Intervention (participant number)	Renal outcomes of sodium bicarbonate treatment
De Brito-Ashurt et al. ⁴⁵	2009	Single-center, randomized, open label	4 & 5	NaHCO ₃ (67) vs. usual care (67)	Benefit
Mahajan et al. ²⁹	2010	Prospective, randomized, placebo-controlled, blinded	2 & 3	NaHCO ₃ (40) vs. NaCl (40) vs. placebo (74)	Benefit
Goraya et al. ⁴⁰	2014	Single-center, randomized, open label	3	NaHCO ₃ (36) vs. F + V (36) vs. usual care (36)	Benefit
Jeong et al. ⁴⁶	2014	Single-center, randomized, paralleled;	4 & 5	NaHCO ₃ (40) vs. usual care (40)	Benefit
Bellasi et al. ⁴⁷	2016	Multicenter, randomized, open-label	3b & 4	NaHCO ₃ (71) vs. usual care (74)	No benefit
Dubey et al. ⁴⁸	2018	Single-center, randomized, open label	3 & 4	NaHCO ₃ (94) vs. usual care (94)	Benefit
Di Iorio et al. ⁴⁵	2019	Multicenter, randomized, open-label	3-5	NaHCO ₃ (376) vs. usual care (364)	Benefit
BiCARB study group ³⁸	2020	Multicenter, randomized, double-blind, placebo controlled	4 & 5	NaHCO ₃ (116) vs. placebo (104)	No benefit
Melamed et al. ³⁶	2020	Multicenter, randomized, double-blind, placebo controlled	3 & 4	NaHCO ₃ (74) vs. placebo (74)	No benefit

NaHCO₃, sodium bicarbonate; NaCl, sodium chloride; F + V, fruits and vegetables; CKD, chronic kidney disease.

was not significantly different between treatment with sodium bicarbonate and the placebo³⁸⁾. Additionally, Melamed et al.³⁶⁾ failed to show any significant differences in eGFR decline between patients on sodium bicarbonate supplementation and those on the placebo. In both studies, post-treatment serum bicarbonate values were similar between the treatment and placebo groups, and in the BiCARB study, the number of patients initially planned for was not enrolled; thus, the statistical power may have been limited. In the previous two studies, there were no significant differences in BMD, physical function, and quality of life between the sodium bicarbonate treatment group and the placebo group^{36,38)}. Further research is needed to determine whether oral alkali treatment improves BMD or physical function.

CONCLUSION

Metabolic acidosis is common in patients with CKD and can lead to poor outcomes. Therefore, proper management of metabolic acidosis is important for patients with CKD. Previous studies have suggested that administration of oral sodium bicarbonate may preserve kidney function without significant increases in blood pressure and body weight. Further studies are needed to clarify the target therapeutic range of serum bicarbonate and the benefits of treatment in subclinical metabolic acidosis.

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Conflict of Interest

The author has no conflicts of interest to declare.

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