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

Hyo Jin Kim[1,2]

[1]Department of Internal Medicine, Pusan National University School of Medicine, Busan;
[2]Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

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

INTRODUCTION

The kidneys play a principal role in the maintenance of the acid-base balance[1]. 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 diagnosis[3]. According to the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD), serum total CO_2 (carbon dioxide) levels were lower in patients with advanced CKD[4].

When serum total CO_2 <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 glutamine[7]. 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 buffering[6]. 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 excretion[7]. 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 ammoniagenesis 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 loads[6]. 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 ammoniagenesis, 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 m^2. 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 capacity[7]. 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 on[6]. 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 setting[9]. 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 air[11]. In addition, the assay methods can influence the

measured values. Total CO_2 levels were lower when measured by the enzymatic assay method, as compared to when they were measured directly by an electrode[11]. 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 measurements[12]. Recently, metabolic acidosis in CKD was further subdivided according to the type of metabolic acidosis associated with progressive renal function[13]. 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 catabolism[14]. Prolonged metabolic acidosis in CKD can lead to renal interstitial fibrosis. In metabolic acidosis in CKD, adaptive responses such as increased ammoniagenesis, 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 NH^{4+} 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 CO_2 levels increased[16]. When the serum total CO_2 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 CO_2 level was <22 mmol/L than when the serum total CO_2 levels in 22-26 mmol/L[17]. The eGFR slope was lower in the low serum total CO_2 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 CO_2 level <22 mmol/L) had 43% higher all-cause mortality than those with normal serum total CO_2 concentrations (26-29 mmol/L)[18]. In the CRIC study, metabolic acidosis (serum total CO_2 level <22 mmol/L) was associated with a 26% higher risk of death, although this result was not statistically significant[16]. The risk of death and heart failure was significantly higher in patients who sustained serum total CO_2 levels >26 mmol/L for the entire duration of follow-up[16]. In the KNOW-CKD cohort study, there was no significant association between the serum total CO_2 levels and the composite outcome of cardiovascular events and death[17]. 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 wasting[7]. 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 activity[19]. 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 community[20]. The National Health

and Nutrition Examination Survey (NHANES) data also showed that lower serum total CO_2 levels were associated with lower BMD[21]. In CKD patients, the serum total CO_2 concentration is directly related to BMD, but further research is needed on the relationship between the serum total CO_2 concentration and fractures[7]. Metabolic acidosis can also cause muscle weasekness 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/L[22]. In the NHANES data, serum total CO_2 levels <23 mmol/L were more likely to be associated with low gait speed and lower quadriceps muscle strength[7]. 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 CO_2 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 blood[23]. 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 CO_2 should be maintained at ≥22 mEq/L, and if

necessary, supplemental alkali salts should be administered to achieve this goal[12]. In 2007, the Care of Australians with Renal Impairment (CARI) guidelines recommended correction of metabolic acidosis to achieve serum bicarbonate levels >22 mmol/L[26]. 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 contraindicated[27]. 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 progression[28]. Daily oral sodium bicarbonate preserves the GFR slope by slowing its decline in early hypertensive nephropathy without metabolic acidosis[29]. The baseline creatinine-based eGFR was approximately 75±6 ml/min, and the venous total CO_2 was 26 mmol/L, which could be categorized as eubicarbonatemia. Since serum total CO_2 is normal in such cases, it is not easy to detect subclinical metabolic acidosis, and other biomarkers are required.

Hypocitraturia has long been recognized as an indicator of H^+ retention[30]. 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 hypocitraturia[28]. 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 fruits[31]. 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 decline[32]. 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 m^2, 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 factors[33]. 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 progression[6], 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 it[34]. Although oral sodium citrate is also recommended in the KDOQI guidelines[35], there is currently no single sodium citrate formulation in Korea. In previous studies, oral sodium bicarbonate ($NaHCO_3$) was prescribed at 0.4 meq/kg of body weight per day[36], 0.5 meq/kg of lean body weight per day[37], or up to 3,000 mg/day[38]. 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 CKD[39]. 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 CO_2 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 CO_2 level of <22 mmol/L, and existing interventional and observational studies suggest that 24-26 mmol/L of serum total CO_2 is ideal[7]. 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 used[14]. 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 acidosis[40]. 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 patients[14]. In early CKD, up to stage 3a, a Mediterranean diet[41] 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 foods[42]. 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 gastro-intestinal lumen. A multicenter study examined changes in CKD patients with metabolic acidosis (eGFR 20-40 ml/min/1.73 m^2) using vevermier and a placebo[43]. 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 veverimer 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 CO_2 in the range of 22-24 mmol/L. There was no decrease in plasma total CO_2, 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 period[49]. 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

$NaHCO_3$, 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 placebo[38]. 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.

Conflict of Interest

The author has no conflicts of interest to declare.

ORCID: 0000-0001-9289-9073

REFERENCES

1. Karim Z, Attmane-Elakeb A, and Bichara M: Renal handling of NH4+ in relation to the control of acid-base balance by the kidney. J Nephrol 2002;15 Suppl 5:S128-134.

2. Kraut JA and Madias NE: Metabolic Acidosis of CKD: An Update. Am J Kidney Dis 2016;67:307-317.

3. Batlle D, Chin-Theodorou J, and Tucker BM: Metabolic Acidosis or Respiratory Alkalosis? Evaluation of a Low Plasma Bicarbonate Using the Urine Anion Gap. Am J Kidney Dis 2017;70:440-444.

4. Kim HJ, Kang E, Ryu H, et al.: Metabolic acidosis is associated with pulse wave velocity in chronic kidney disease: Results from the KNOW-CKD Study. Sci Rep 2019;9:16139.

5. Kraut JA and Kurtz I: Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis 2005;45:978-993.

6. Chen W, Levy DS, and Abramowitz MK: Acid Base Balance and Progression of Kidney Disease. Semin Nephrol 2019;39:406-417.

7. Raphael KL: Metabolic Acidosis in CKD: Core Curriculum 2019. Am J Kidney Dis 2019;74:263-275.

8. Nagami GT and Hamm LL: Regulation of Acid-Base Balance in Chronic Kidney Disease. Adv Chronic Kidney Dis 2017;24:274-279.

9. Kraut JA and Raphael KL: Assessment of Acid-Base Status: Beyond Serum Bicarbonate. Clin J Am Soc Nephrol 2021;16:1429-1431.

10. Hirai K, Ookawara S, Morino J, et al.: Relationship between serum total carbon dioxide concentration and bicarbonate concentration in patients undergoing hemodialysis. Kidney Res Clin Pract 2020;39:441-450.

11. Bray SH, Tung RL, and Jones ER: The magnitude of metabolic acidosis is dependent on differences in bicarbonate assays. Am J Kidney Dis 1996;28:700-703.

12. National Kidney F: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1-201.

13. Melamed ML and Raphael KL: Metabolic Acidosis in CKD: A Review of Recent Findings. Kidney Med 2021;3:267-277.

14. Noce A, Marrone G, Wilson Jones G, et al.: Nutritional Approaches for the Management of Metabolic Acidosis in Chronic Kidney Disease. Nutrients 2021;13.

15. Wesson DE, Buysse JM, and Bushinsky DA: Mechanisms of Metabolic Acidosis-Induced Kidney Injury in Chronic Kidney Disease. J Am Soc Nephrol 2020;31:469-482.

16. Dobre M, Yang W, Pan Q, et al.: Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): A report from the Chronic Renal Insufficiency Cohort (CRIC) study. J Am Heart Assoc 2015;4.

17. Kim HJ, Ryu H, Kang E, et al.: Metabolic Acidosis Is an Independent Risk Factor of Renal Progression in Korean Chronic Kidney Disease Patients: The KNOW-CKD Study Results.

Front Med (Lausanne) 2021;8:707588.

18. Kovesdy CP, Anderson JE, and Kalantar-Zadeh K: Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant 2009; 24:1232-1237.

19. Mehrotra R, Kopple JD, and Wolfson M: Metabolic acidosis in maintenance dialysis patients: clinical considerations. Kidney Int Suppl 2003;S13-25.

20. Tabatabai LS, Cummings SR, Tylavsky FA, et al.: Arterialized venous bicarbonate is associated with lower bone mineral density and an increased rate of bone loss in older men and women. J Clin Endocrinol Metab 2015;100:1343-1349.

21. Chen W, Melamed ML, and Abramowitz MK: Serum bicarbonate and bone mineral density in US adults. Am J Kidney Dis 2015;65:240-248.

22. Yenchek R, Ix JH, Rifkin DE, et al.: Association of serum bicarbonate with incident functional limitation in older adults. Clin J Am Soc Nephrol 2014;9:2111-2116.

23. Krieger NS, Frick KK, and Bushinsky DA: Mechanism of acid-induced bone resorption. Curr Opin Nephrol Hypertens 2004;13:423-436.

24. Mendoza FJ, Lopez I, Montes de Oca A, Perez J, Rodriguez M, and Aguilera-Tejero E: Metabolic acidosis inhibits soft tissue calcification in uremic rats. Kidney Int 2008;73:407-414.

25. Yonova D: Vascular calcification and metabolic acidosis in end stage renal disease. Hippokratia 2009;13:139-140.

26. Voss D, Hodson E, and Crompton C: Nutrition and growth in kidney disease: CARI guidelines. Aust Fam Physician 2007; 36:253-254.

27. Andrassy KM: Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. Kidney Int 2013;84:622-623.

28. Madias NE: Metabolic Acidosis and CKD Progression. Clin J Am Soc Nephrol 2021;16:310-312.

29. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, and Wesson DE: Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010;78:303-309.

30. Alpern RJ and Sakhaee K: The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis 1997;29:291-302.

31. Goraya N, Simoni J, Sager LN, Madias NE, and Wesson DE: Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. Kidney Int 2019;95:1190-1196.

32. Vallet M, Metzger M, Haymann JP, et al.: Urinary ammonia and long-term outcomes in chronic kidney disease. Kidney Int 2015;88:137-145.

33. Raphael KL, Gilligan S, and Ix JH: Urine Anion Gap to Predict Urine Ammonium and Related Outcomes in Kidney Disease. Clin J Am Soc Nephrol 2018;13:205-212.

34. Goraya N, Simoni J, Jo CH, and Wesson DE: A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. Clin J Am Soc Nephrol 2013;8:371-381.

35. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis 2000;35:S17-S104.

36. Melamed ML, Horwitz EJ, Dobre MA, et al.: Effects of Sodium Bicarbonate in CKD Stages 3 and 4: A Randomized, Placebo-Controlled, Multicenter Clinical Trial. Am J Kidney Dis 2020;75:225-234.

37. Raphael KL, Greene T, Wei G, et al.: Sodium Bicarbonate Supplementation and Urinary TGF-beta1 in Nonacidotic Diabetic Kidney Disease: A Randomized, Controlled Trial. Clin J Am Soc Nephrol 2020;15:200-208.

38. Bi Csg: Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC Med 2020;18:91.

39. Raphael KL, Isakova T, Ix JH, et al.: A Randomized Trial Comparing the Safety, Adherence, and Pharmacodynamics Profiles of Two Doses of Sodium Bicarbonate in CKD: the BASE Pilot Trial. J Am Soc Nephrol 2020;31:161-174.

40. Goraya N, Simoni J, Jo CH, and Wesson DE: Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int 2014;86:1031-1038.

41. Chauveau P, Aparicio M, Bellizzi V, et al.: Mediterranean diet as the diet of choice for patients with chronic kidney disease. Nephrol Dial Transplant 2018;33:725-735.

42. Passey C: Reducing the Dietary Acid Load: How a More Alkaline Diet Benefits Patients With Chronic Kidney Disease. J Ren Nutr 2017;27:151-160.

43. Wesson DE, Mathur V, Tangri N, et al.: Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. Lancet 2019; 394:396-406.

44. Hu MK, Witham MD, and Soiza RL: Oral Bicarbonate Therapy in Non-Haemodialysis Dependent Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. J Clin Med 2019;8.

45. de Brito-Ashurst I, Varagunam M, Raftery MJ, and Yaqoob MM: Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009; 20:2075-2084.

46. Jeong J, Kwon SK, and Kim HY: Effect of bicarbonate supplementation on renal function and nutritional indices in predialysis advanced chronic kidney disease. Electrolyte Blood Press 2014;12:80-87.

47. Bellasi A, Di Micco L, Santoro D, et al.: Correction of metabolic acidosis improves insulin resistance in chronic kidney disease. BMC Nephrol 2016;17:158.

48. Dubey AK, Sahoo J, Vairappan B, Haridasan S, Parameswaran S, and Priyamvada PS: Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial. Nephrol Dial Transplant 2020;35:121-129.

49. Di Iorio BR, Bellasi A, Raphael KL, et al.: Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study. J Nephrol 2019; 32:989-1001.