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# Hidden Acid Retention with Normal Serum Bicarbonate Level in Chronic Kidney Disease

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Management of metabolic acidosis is crucial for preserving bone, muscle, and renal health, as evidenced by the results of several interventional studies conducted on patients with chronic kidney disease (CKD). Considering the continuity of CKD progression over time, it is reasonable to deduce that a subclinical form of metabolic acidosis may exist prior to the manifestation of overt metabolic acidosis. Covert $H^+$ retention with normal serum bicarbonate level in patients with CKD may result in maladaptive responses that contribute to kidney function deterioration, even in the early stages of the disease. The loss of adaptive compensatory mechanisms of urinary acid excretion may be a key factor in this process. Early modulation of these responses could be an important therapeutic strategy in preventing CKD progression. However, to date, the optimal approach for alkali therapy in subclinical metabolic acidosis in CKD remains uncertain. There is a lack of established guidelines on when to initiate alkali therapy, potential side effects of alkali agents, and the optimal blood bicarbonate levels based on evidence-based practices. Therefore, further research is necessary to address these concerns and establish more robust guidelines for the use of alkali therapy in patients with CKD. Herein, we provide an overview of recent developments on this subject and examine the potential therapeutic approaches that interventional treatments may present for patients with hidden $H^+$ retention, exhibiting normal serum bicarbonate levels - commonly described as subclinical or eubicarbonatemic metabolic acidosis in patients with CKD.

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



## INTRODUCTION

Chronic kidney disease (CKD) is characterized as a set of sustained changes in the structure or function of the kidneys, which have consequences for the overall health of the affected individual[1]. The prevalence of CKD, at all stages, displays regional differences with a range of 7-12%, across various parts of the world. CKD imposes a significant burden of national healthcare costs, especially in treating patients who require renal replacement therapy. Chronic metabolic acidosis is a prevalent condition among individuals diagnosed with CKD, resulting form a primary disruption in the regulation of acid-base equilibrium[2]. As renal function deteriorates, there is a clinical presentation where hyperchloremic acidosis transitions to high anion gap acidosis. The pathogenesis is attributed to inadequate filtration and reabsorption of organic anions. With the progression of renal disease, the amount of functional nephrons eventually becomes inadequate to effectively manage the net production of acids. Therefore, the prevalence and severity of metabolic acidosis in CKD patients progressively rises

as glomerular filtration rate (GFR) falls.

The Kidneys initially make adaptations to excrete acid, which helps prevent a decrease in the concentration of bicarbonate in the blood. In addition, despite significant retention of acid, the serum bicarbonate level does not decrease further, indicating participation of buffers outside the extracellular compartment. In CKD, acid retention occurs, which is buffered by alkali salts derived from bone. Consequently, the reduction of bone calcium carbonate due to chronic acidosis causes an increase in urinary calcium excretion, which is proportional to the accumulated acid secretion. However, as the GFR continues to decrease below 40 ml/min per 1.73 $m^2$, this protective mechanism becomes less effective. Chronic metabolic acidosis is also associated with increased protein catabolism, muscle wasting, impaired cardiac function, CKD progression, and increased mortality[1-4]. The connection between declining serum bicarbonate levels and worsening clinical outcomes has sparked numerous studies where addressing metabolic acidosis has slowed the progression of CKD[5-7]. Consequently, we can infer that managing metabolic acidosis through alkali replacement might be a potential therapeutic approach for improving the previously mentioned health conditions. As one might expect, in the past 20 years, a wealth of research has explored the impact of oral alkali therapy on CKD progression for stage 3-5 patients with reduced serum bicarbonate levels[3]. Although there is evidence of low-to-moderate certainty indicating that oral alkali supplementation or a decrease in dietary acid consumption may decelerate the decline of kidney function in individuals with CKD and metabolic acidosis[8].

The idea that treatment of acidosis could be beneficial in preserving kidney function was first proposed by Richard Bright, followed by Arthur Osman and Lyon et al. who conducted a crossover study showing that supplementation with bicarbonate might help preserve kidney function[5,9,10]. Mathur et al. conducted a randomized trial and showed that correction of metabolic acidosis significantly attenuates the rise in blood urea in patients with mild to moderate CKD. There were no significant differences in baseline characteristics between the bicarbonate and placebo groups[4]. A significant study demonstrating the benefits of alkali administration in patients with CKD and metabolic acidosis was conducted by Brito-Ashurst and his colleagues[6]. They revealed that, over a 2-year period, oral sodium bicarbonate supplementation delayed CKD progression and improved nutritional status, demonstrating its potential benefits for 134 CKD patients with baseline $HCO_3$ level 16 to 20 mEq/L.

Drawing upon this evidence, the KDIGO 2012 Clinical Practice Guideline recommend normalizing serum bicarbonate levels using alkali therapy when levels fall below 22 mEq/L, provided there are no specific contraindications[11]. It is worth noting that the research underpinning these recommendations has focused solely on hypobicarbonatemic CKD patients or animal models. However, several experimental studies and clinical trial results have suggested that $H^+$ retention may be present even when serum bicarbonate levels are within the normal range[12-14]. Considering the continuity of CKD progression over time, it is reasonable to infer that a subclinical form of metabolic acidosis may exist prior to the manifestation of overt metabolic acidosis. However, to date, there has been limited in-depth research regarding the clinical significance and importance of such subclinical forms of metabolic acidosis. In this review, we provide an overview of recent developments on this subject and examine the potential therapeutic approaches that interventional treatments may present for patients with hidden $H^+$ retention, exhibiting normal serum bicarbonate levels - commonly described as subclinical or eubicarbonatemic metabolic acidosis.

## Prevalence and Clinical Course of Subclinical Metabolic Acidosis

Since we do not routinely and accurately assess covert $H^+$ retention in patients with CKD, the actual prevalence of subclinical metabolic acidosis is unknown, but it is likely to be higher than expected. In one study, it has been reported that approximately 85% of non-dialysis patients were found to have normal serum bicarbonate levels[15]. It is unclear what proportion of these individuals exhibit $H^+$ retention, which would consequently classify them as having subclinical metabolic acidosis. In two recent studies, nearly every eubicarbonatemic patient with stage 2 CKD assessed at baseline exhibited an estimated $H^+$ retention greater than 0 mEq[16,17]. Therefore, by embracing the broader definition of the condition, metabolic acidosis can be considered an

early complication of CKD. Nonetheless, the sample size of the tested population is limited, necessitating further research in this area. It can be hypothesized that estimated $H^+$ retention would be greater and virtually ubiquitous in eubicarbonatemic patients with CKD stages 3 and 4. While the exact prevalence is yet to be established, subclinical metabolic acidosis is probably prevalent in the majority of CKD stage 2-4 patients who follow a typical Western diet.

In actual clinical outpatient settings, we can recognize metabolic acidosis using serum total $CO_2$ ($tCO_2$) concentration obtained from venous samples, a surrogate for arterial [$HCO_3^-$]. Venous $tCO_2$ levels are higher than arterial [$HCO_3^-$] levels due to elevated levels of venous $PCO_2$. Under stable clinical conditions, the difference between venous $tCO_2$ and arterial [$HCO_3^-$] levels is usually no greater than 2-4 mEq/L. This difference is mainly attributed to the dissimilarities between venous and arterial blood and the buffering effect of hemoglobin on $CO_2$-mediated $H^+$ buffering, with a negligible contribution from erythrocyte carbamino-$CO_2$[18]. Not all cases with low $tCO_2$ are indicative of metabolic acidosis, as serum $HCO_3^-$ levels can also decrease in respiratory alkalosis[19]. Consequently, it is not easy to determine the presence or absence of metabolic acidosis in CKD patients with respiratory alkalosis based solely on $tCO_2$ measurements. Such considerations make it challenging to diagnose metabolic acidosis based on $tCO_2$ alone, even in cases of simple acid-base disturbances. This difficulty becomes even more pronounced and complex in the context of mixed acid-base disorders. For an accurate diagnosis, recent data published by a Japanese research team recommends incorporating venous sample pH measurements into the interpretation, emphasizing the necessity of such tests[20]. The researchers conducted a retrospective study analyzing 1,058 Japanese patients with an eGFR below 60 ml/min per 1.73 $m^2$. This study evaluated the impact of venous blood pH measurements on the relationship between hypobicarbonatemia and incident ESKD. In their study cohort, approximately three-fourths of the patients had normal serum bicarbonate levels. In contrast, they found that nearly 40% of patients with CKD with hypobicarbonatemia did not have associated acidemia (pH <7.32). While it is possible that not all of these individuals had eubicarbonatemic metabolic acidosis, the findings highlight the importance of considering venous pH samples alongside serum bicarbonate analysis. In addition, even the concentration of $tCO_2$ varies in terms of normal range, as demonstrated by data from the United States, which shows differing reference values across 64 institutions, 2 large commercial clinical laboratories, and the major textbook of clinical chemistry[21]. The reported limits of serum $tCO_2$ values by clinical laboratories are frequently excessively broad and do not consistent with the range of expected in healthy individuals at sea level. Consequently, it is advisable to narrow the normal range for serum $tCO_2$ at sea level to 23-30 mEq/L to accurately identify most cases of covert subclinical metabolic acidosis[22].

It is biologically plausible that a subset of CKD patients with normal $tCO_2$ may experience acid-induced organ damage, which could also contribute to poor kidney outcomes. In the African American Study of Kidney Disease and Hypertension study, as well as in groups of United States veterans and Cleveland Clinic Foundation patients with CKD, individuals with low-normal levels of $tCO_2$ were found to have a higher risk of either mortality or decline in GFR compared to those with high-normal levels of $tCO_2$[2,7,8,23]. It is possible that individuals with low-normal levels of $tCO_2$ are at a higher risk of experiencing adverse outcomes because they require a greater compensatory response in order to maintain normal $tCO_2$ levels, which may result in more acid-mediated injury to their organs compared to those with high-normal levels of $tCO_2$[2].

## Pathophysiologic Aspect of Subclinical Metabolic Acidosis

As previously mentioned, acid accumulation during the early stages of CKD may not be enough to decrease serum bicarbonate below the normal range, yet it can still instigate adverse effects, including bone loss, and muscle protein degradation[9]. Additionally, chronic metabolic acidosis in CKD can induce kidney injury and accelerate CKD progression. In CKD, $H^+$ retention reduces the pH of the interstitial and intracellular compartments within the kidney. This triggers a cascade of reactions, including the stimulation of ammoniagenesis in the remaining nephrons, increased production of proinflammatory cytokines, and elevated levels of angiotensin II, aldosterone and endothelin-1 (ET-1) in the kidneys[24].

Elevated net endogenous acid production from dietary

sources can increase $H^+$ retention in the body. In rats exhibiting normal kidney function or a decrease in nephron mass, the consumption of dietary acid resulted in higher levels of acid in both blood and kidney cortex, along with a rise in net acid excretion in urine, all without causing a discernible drop in plasma pH or bicarbonate concentration[25-27]. In addition, in hypertensive patients with eubicarbonatemia, albuminuria, and stage 2 CKD, who were consuming an acid-promoting Western diet, acid retention was observed along with increased plasma and urine levels of ET-1 and aldosterone, compared to individuals with stage 1 CKD following the same diet[13]. Conversely, reducing net endogenous acid production through dietary modifications or administering alkaline compounds can help alleviate $H^+$ retention. A single oral dose of $NaHCO_3$ led to a smaller reduction in urinary net acid excretion in patients with stage 2 CKD compared to those with stage 1, which aligns with increased acid retention in stage 2 CKD patients. After 30 days of oral $NaHCO_3$ administration, both plasma and urine levels of ET-1 and aldosterone decreased in patients with stage 2 CKD. The compensatory responses observed in response to nonvolatile acids suggest that even in cases of subclinical metabolic acidosis, patients with CKD may be retaining excessive amounts of acid, which could contribute to kidney damage. As CKD progresses continuously, it is important to correct acidosis at an early stage to prevent further deterioration of the kidney's adaptive response.

## Diagnosis of Subclincal Metabolic Acidosis

As eubicarbonatemic metabolic acidosis may be involved in the progression of CKD, additional urinary markers are being investigated to aid in the evaluation of the risk of progression to end stage kidney disease (ESKD) and mortality in CKD patients without apparent acidosis.

### Urine ammonium

Urinary acid excretion measurements may identify patients with CKD with eubicarbonatemic metabolic acidosis. Thus, metabolic acidosis is distinguished by a decreased rate of both the production and excretion of $NH_4^+$. Measuring urinary ammonia was useful in identifying increased dietary $H^+$ and assessing potential renal acid load in the early stages of CKD[28]. In response to metabolic acidosis, the renal proximal tubule undergoes changes in its metabolism and transport properties. The tubule increases the uptake and breakdown of glutamine and citrate, while reducing the recovery of phosphate from the ultrafiltrate. The increased breakdown of glutamine leads to greater ammoniagenesis and gluconeogenesis, with the excretion of ammonium ions helping to eliminate acid. These processes also generate $HCO_3^-$ that are added to the plasma, partially restoring acid-base balance[29]. However, in CKD, the development of metabolic acidosis is often accompanied by a decrease in urine ammonium excretion[30]. In a study with the African American Study of Kidney Disease and Hypertension database, it was found that urine ammonium excretion decreased as measured GFR decreased. The finding that lower urine ammonium excretion is associated with higher mortality or ESKD suggests that early markers of kidney failure affecting acid-base balance may be useful in identifying individuals at risk of these outcomes, even if they have normal serum bicarbonate levels[31]. These studies indicate that acid accumulation can occur in early CKD and may not be reflected by serum acid-base parameters typically used to diagnose metabolic acidosis.

### Urine citrate collection

Patients with CKD tend to have lower levels of acid excretion through ammonium as well as lower levels of base excretion through citrate and other organic anions compared to individuals without CKD. This may be a compensatory mechanism to maintain acid-base balance. As CKD progresses, acid excretion decreases even further while base excretion, such as citrate, increases in response to alkali. Therefore, evaluating urine citrate levels can serve as an early and reliable indicator of impaired acid-base balance in these patients[32].

Recent research provides evidence that measuring urinary citrate excretion, which is the most prevalent organic base in the urine that can be converted to bicarbonate, is a valuable method for detecting acid retention in CKD patients who have normal serum bicarbonate levels. Furthermore, it can also be used to evaluate the effectiveness

of alkali therapy in these patients[16,17]. Patients with CKD stage 2 showed higher baseline acid retention compared to those with CKD stage 1, and had lower urinary excretion of citrate. After consuming base-producing fruits and vegetables for 30 days, acid retention decreased in CKD stage 2 patients but not in CKD stage 1 patients. However, the overall acid retention remained higher and urinary citrate excretion remained lower in CKD stage 2 patients compared to CKD stage 1 patients, supporting the potential utility of low urinary citrate excretion in identifying acid retention in eubicarbonatemic CKD patients.

As a regular process, the body tends to excrete base by means of citraturia in response to fluctuating dietary base loads. The primary mechanism for controlling urinary citrate excretion is the reabsorption that occurs in the proximal tubule[29]. Over the past two decades, extensive studies have investigated the cellular mechanisms of how the proximal tubule handles citrate in response to acid loading. When the body is subjected to systemic acid loading or the proximal tubule cell is intracellularly acidified, a series of coordinated processes are triggered, such as increased luminal citrate uptake, cytoplasmic metabolism, and citrate entry and metabolism by the mitochondria. These processes work together to reduce citrate in the urine as a general response to acid. Therefore, measuring urinary citrate excretion is a more appropriate way to assess acid loading in the body compared to measuring plasma bicarbonate levels. A recent study found that in patients with CKD who are at risk for $H^+$ retention, lower levels of urinary citrate were more effective in detecting eubicarbonatemic acidosis compared to levels of urinary ammonium[17]. However, it is important to note that neither of these tests could accurately diagnose subclinical metabolic acidosis, and there is still no common consensus on such diagnostic methods. This strongly indicates that there is a pressing need for additional research to be conducted in order to develop a more reliable and effective clinical test for this condition.

### Intervention of Subclinical Metabolic Acidosis

Chronic metabolic acidosis is a frequently observed condition in patients with CKD. the KDIGO 2012 Clinical Practice Guideline recommend administering alkali therapy to maintain serum bicarbonate levels above 22 mEq/L in order to prevent the deleterious effects of acid load on bone mineral density and protein catabolism[11]. The results of small-scale intervention studies conducted thus far provide evidence that correcting chronic metabolic acidosis in patients with CKD by correcting acid load can delay the progression of the disease[4,6]. Thus, the initial studies looked into how taking alkali supplements could affect the progression of CKD in participants with overt metabolic acidosis. Subsequent studies focused on the potential benefits of alkali supplements in participants with reduced eGFR but who were at an earlier stage of acid stress with eubicarbonatemia (Table 1). Mahajan et al. investigated the efficacy of sodium-based alkali for reducing acid retention in early-stage CKD patients consuming diets high in acid-producing foods, with reduced but relatively preserved eGFR and eubicarbonatemia. Their findings revealed a significant reduction in the rate of eGFR decline in patients treated with oral $NaHCO_3$ compared to those receiving sodium chloride or placebo[12]. In addition, given that alkali therapy in CKD animal models has demonstrated a reduction in kidney angiotensin II, which mediates GFR decline in partial nephrectomy models of CKD, and that metabolic acidosis may increase kidney angiotensin II in animals, it is hypothesized that alkali treatment for metabolic acidosis in eubicarbonatemic patients with plasma $tCO_2$ levels over 22 mEq/L may preserve GFR[14]. Goraya et al. randomized 108 patients with stage 3 CKD and plasma $tCO_2$ levels of 22-24 mEq/L to either usual care or interventions designed to reduce dietary acid by 50% using sodium bicarbonate or base-producing fruits and vegetables[33]. Plasma $tCO_2$ level decreased in the usual care group but increased in the bicarbonate or fruits and vegetables group. Furthermore, urine excretion of angiotensinogen, an index of kidney angiotensin II, increased in the usual care group but decreased with bicarbonate or fruits and vegetables. Although all groups experienced a decrease in eGFR calculated by creatinine and cystatin C, the loss was less at 3 years with bicarbonate or fruits and vegetables than in the usual care group. Therefore, they concluded that dietary alkali treatment for metabolic acidosis in eubicarbonatemic patients with plasma $tCO_2$ levels over 22 mEq/L reduces kidney angiotensin II activity and preserves eGFR[33].

Table 1. Recent studies with alkali treatment in chronic kidney disease within normal range of serum $HCO_3$

| Study | Year | Study Designs | Study Subjects (n) | Baseline eGFR (ml/min per 1.73 $m^2$) | Baseline serum $HCO_3$ (mEq/L) | Interventions | Follow up duration (months) | Findings in renal outcomes |
|---|---|---|---|---|---|---|---|---|
| Mahajan A, et al.[12] | 2010 | Prospective, randomized, placebo-controlled, blinded | 120 | 75 | 26 ($tCO_2$) | Placebo, NaCl, $NaHCO_3$ | 60 | Renal benefit of $NaHCO_3$ in hypertensive nephropathy (↓eGFR decline, ↓blood pressure) |
| Goraya N, et al.[33] | 2014 | Single center, randomized, open label | 108 | 30-59 | 22-24 ($tCO_2$) | Usual care, F+V, $NaHCO_3$ | 36 | Renal benefit of F+V and $NaHCO_3$ (↓urine angiotensinogen and preserves GFR) |
| Melamed ML, et al.[34] | 2020 | Multicenter, randomized, double-blind, placebo controlled | 149 | 36±11 | 24±2.2 | Placebo, $NaHCO_3$ | 24 | No difference of eGFR between study groups |
| Raphael KL, et al.[36] | 2020 | Multicenter, randomized, double-blind, placebo controlled | 74 | 51±18 | 24±2 ($tCO_2$) | Placebo, $NaHCO_3$ | 6 | No difference of kidney injury markers in diabetic kidney disease |
| Raphael KL, et al.[35] | 2020 | Multicenter, randomized, double-blind, placebo controlled | 192 | 36±9 | 24±2 | Placebo, $NaHCO_3$ | 7 | No significant difference in the eGFR |

eGFR, estimated glomerular filtration rate; $NaHCO_3$, sodium bicarbonate; NaCl, sodium chloride, F+V, fruits and vegetables; $tCO_2$, venous total $CO_2$ level

Nonetheless, recent studies have not reached a consensus on this matter. Melamed and his colleagues randomly divided 149 patients with CKD stages 3-4 into two groups and administered either 0.4 mg/kg body weight of $NaHCO_3$ or placebo, following them up for two years[34]. The baseline eGFR of study population was 36.3±11.2 ml/min per 1.73 $m^2$ with mean serum $HCO_3$, 24.0±2.2 mEq/L. After two years, there were significant differences in serum bicarbonate and potassium levels between the two groups, but there were no differences in renal outcomes or bone mineral densities[34]. The researchers speculated that the differences between their results and previous reports may be attributed to differences in study design, such as randomization. Furthermore, the Base Pilot trial conducted across multiple centers, evaluated the safety, tolerability, adherence, and pharmacodynamics of two doses of $NaHCO_3$ over a period of 28 weeks in adults with eGFR levels between 20-44 or 45-59 ml/min per 1.73 $m^2$ and urinary albumin/creatinine levels above 50 mg/g, and serum bicarbonate levels between 20-28 mEq/L[35]. The researchers concluded that a high dose of 0.8 mEq/kg of lean body weight daily $NaHCO_3$ was also safe and reasonable for future related studies, as no additional side effects were observed. However, the observation period was short, there was no improvement in eGFR in the high-dose $NaHCO_3$ treatment group; on the contrary, there was an increase in albuminuria. The study group assumed that the reasons for the slightly increased albuminuria is related to the effect of urinary pH on urinary protease activity, which warrants further investigation. In addition, Raphael and his colleagues conducted a study that investigated the effects of $NaHCO_3$ on renal fibrosis and injury markers in patients with diabetic nephropathy with eubicarbonatemia[36]. This was a randomized, double-blind, placebo-controlled trial that included 74 participants with type 1 or 2 diabetes, eGFR of 15-89 ml/min per 1.73 $m^2$, and albuminuria, with a $tCO_2$ concentration ranging from 22-28 mEq/L. Participants received either oral $NaHCO_3$ or placebo for six months. The primary outcomes were changes in urinary TGF-β1, renal injury markers including kidney injury molecule-1 (KIM-1), fibronectin, neutrophil gelatinase-associated lipocalin (NGAL), and albuminuria from baseline to 3 and 6 months. Sodium bicarbonate therapy increased the mean blood $tCO_2$ level by 1.2 mEq/L, elevated urine pH, and decreased urinary ammonium excretion. However, it did not significantly reduce TGF-$\beta_1$, KIM-1, fibronectin, NGAL, or amount of albuminuria[36]. These findings are in

contrast to a previous pilot study in patients with hypertensive CKD and normal blood $tCO_2$ levels, where sodium bicarbonate was shown to decrease urinary TGF-β1 levels and preserve renal function in the early stages of the disease[12,33]. The observed disparities in the study outcomes could be due to differences in the design of the studies or variations in the progression of metabolic acidosis, which maybe influenced by the underlying etiology of CKD. As such, further investigation is necessary to shed light on this matter.

It is crucial to take into account the safety concerns related to long-term $NaHCO_3$ supplementation. This matter involves the potential for sodium-mediated fluid retention, which can lead to complications such as elevated blood pressure, pulmonary edema, and heart failure. Nonetheless, the 28-week study revealed no noteworthy disparities in total body weight among the three groups, and the frequency of escalating diuretic therapy was also similar[35]. However, given that a large CKD cohort demonstrated a higher risk of heart failure events and mortality with persistent serum bicarbonate levels exceeding 26 mEq/L, caution must be exercised when considering $NaHCO_3$ supplementation therapy in patients with underlying conditions associated with severe $Na^+$ retention[37,38]. In addition, there may be potential side effects that have not been thoroughly investigated, such as the impact of correcting metabolic acidosis on vascular calcification in CKD. De Solis et al. found that uremic animals treated with intraperitoneal sodium bicarbonate exhibited substantially greater vascular calcification[39]. Notably, the bicarbonate concentration in these animals was similar to that in healthy animals, whereas uremic animals with untreated metabolic acidosis had lower bicarbonate concentrations and similar levels of vascular calcifitcation compared to healthy animals. These results suggested that correcting metabolic acidosis may promote vascular calcification in CKD, and that metabolic acidosis may a protective role against renal calcification and loss of GFR in uremic animals on a high-phosphate diet[40,41]. Therefore, it may be prudent to withhold alkaline therapy in patients with hyperphosphatemia. These findings highlight the need for large-scale clinical trials with long-term follow-up to assess the safety and efficacy of alkaline therapy in humans, given the potential for severe complications[42].

Veverimer, previously known as TRC101, is a new type of non-absorbable polymer that attaches to hydrogen cations and chloride anions in the gastrointestinal tract and is then eliminated through feces. This results in an increase in serum bicarbonate levels without the need for sodium supplementation[43,44]. There are still uncertainties surrounding the mechanism of action, electrolyte profile, potential interaction with colonic bacterial flora, and optimal usage of veverimer[45,46]. We are eagerly anticipating the outcomes of the ongoing research investigating the impact of veverimer on the progression of CKD. In the absence of any significant long-term safety issues, veverimer has the potential to become a valuable addition to our existing treatment arsenal. It is imperative to compare the efficacy of veverimer to that of sodium bicarbonate for treating eubicarbonatemic metabolic acidosis in CKD patients.

Adequate consumption of fruits and vegetables is an important and traditional alkaline supplementation approach. Kelly et al. conducted a meta-analysis of 104 studies with 2,755,719 participants, which revealed that higher intake of potassium and vegetables was associated with reduced odds of CKD, while higher salt intake was linked to increased odds of CKD[47]. The study supports previous findings from Bach et al.'s meta-analysis, which demonstrated that a healthy diet with higher intake of fruits, vegetables, low-fat dairy, whole grains, and fiber, combined with lower intake of sodium is associated with a 30% reduction in kidney damage and improved overall health, including high BP, metabolic acidosis, phosphorus, gut microbiome, and lower glycated hemoglobin[48]. Plant-based diets, which were usually avoided due to concerns of hyperkalemia in CKD patients, have also been shown to provide benefits even for those with ESKD[49]. Additionally, a 24-month study of 47 patients with stage 3 or 4 CKD demonstrated that a dietary potassium-restricted group had only a slightly lower serum $K^+$ concentration compared to the control group, suggesting that plant-based diets may still be an appropriate alkali option for CKD patients[50].

## CONCLUSIONS

CKD patients with hidden $H^+$ retention with normal bicarbonate levels may exhibit maladaptive responses that lead

to deterioration of kidney function due to the loss of adaptive compensatory mechanisms of urinary acid excretion. Modulating these responses early on may be a crucial therapeutic strategy in preventing CKD progression. However, to date, the optimal approach for alkali therapy in subclinical metabolic acidosis in CKD remains uncertain. There is a lack of established guidelines on when to initiate alkali therapy, potential side effects of alkali agents, and the optimal blood bicarbonate levels based on evidence-based practices. Addressing these knowledge gaps is likely to have significant clinical implications. Therefore, further research is necessary to address these concerns and establish more robust guidelines for the use of alkali therapy in CKD patients.

### Declaration of Interest

The authors have no financial conflict of interest to declare.

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