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Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD?

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Abstract

Metabolic acidosis is a common complication associated with progressive loss of kidney function. The diminishing ability of the kidneys to maintain acid–base homeostasis results in acid accumulation, leading to various complications such as impairment in nutritional status, worsened uremic bone disease and an association with increased mortality. In addition to these adverse effects which are related to acid retention, metabolic acidosis may also cause kidney damage, possibly through the stimulation of adaptive mechanisms aimed at maintaining acid–base homeostasis in the face of decreasing kidney function. Recent clinical trials have suggested that correction or prevention of metabolic acidosis by alkali administration is able to attenuate kidney damage and to slow progression of chronic kidney disease (CKD), and may hence offer an effective, safe and affordable renoprotective strategy. We review the physiology and pathophysiology of acid–base homeostasis in CKD, the mechanisms whereby metabolic acidosis may be deleterious to kidney function, and the results of clinical trials suggesting a benefit of alkali therapy, with special attention to details related to the practical implementation of the results of these trials.

Keywords: bicarbonate; chronic kidney disease; metabolic acidosis; therapy

Introduction

Metabolic acidosis is one of the many complex changes associated with the development of chronic kidney disease (CKD) [1, 2]. Decreasing kidney function causes progressively increased retention of acids, resulting in numerous deleterious consequences, such as protein catabolism and protein-energy wasting [3–18], worsening uremic bone disease [19–22] and an association with decreased functional capacity [23] and with increased mortality in patients with end-stage renal

disease (ESRD) [24–26] and with non-dialysis-dependent CKD [27, 28]. Besides these adverse effects metabolic acidosis has also been linked directly to kidney damage and to increased progression of CKD [28, 29], possibly through mechanisms associated with adaptive responses meant to enhance acid excretion in the face of progressive loss of kidney function [30–36]. Based on observations linking metabolic acidosis to progression of CKD, several recent clinical trials have suggested that alkali supplementation can ameliorate kidney damage and can result in the attenuation of progressive CKD [37–40]. These studies have raised the possibility that the administration of sodium bicarbonate (or alternative sources of it) may emerge as a universally applicable renoprotective strategy in patients with various stages of non-dialysis-dependent CKD, pending confirmation by larger clinical trials.

We will review the physiology and pathophysiology of metabolic acidosis and its consequences in CKD of all stages (including ESRD), with special emphasis on its effects on kidney function and progression of non-dialysis-dependent CKD. We will discuss in detail the results of clinical trials aimed at utilizing alkali therapy as a renoprotective strategy, and highlight the practical implications of these trials as well as areas in need of further research.

Physiologic considerations

In healthy individuals, the daily consumption and production of acids and bases is in balance with their excretion, resulting in a tightly regulated and stable state of acidity (pH) of body fluids [41]. This implies that the daily net fixed acid production and the renal net acid excretion are equal [42]. An average person generates ∼1 mEq of non-volatile acid/kilogram body weight/day [43]. One of the major roles of the kidney is to the maintain acid–base balance by excreting acid in amounts that are equal to the extrarenal acid production. The kidneys achieve this on the one hand by reclaiming filtered bicarbonate, and on the other hand by regenerating base via the excretion of ammonium and titratable acid [43]. A detailed description of the intricate mechanisms regulating renal acidification mechanisms is beyond the scope of this paper. However, relevant to the development and progression of CKD are a number of humoral regulatory mechanisms that play a role in increasing urinary acidification, the persistent activation of which could result in direct kidney damage [44]. Besides its effects on the glomerular filtration rate (GFR) and sodium balance, angiotensin II also increases Na^+–H^+ antiporter and Na^+–HCO_3^- cotransporter activity and hence increases urine acidification [45]. In addition, mineralocorticoids play a role in urine acidification by stimulating both distal nephron proton secretion and proximal tubule ammonia synthesis [46]. Another regulatory pathway that may have relevance to progressive CKD (vide infra) involves the regulation of Na^+–H^+ exchange in the distal nephron by endothelin through the stimulation of ET-B receptors [34, 47].

Metabolic acidosis in CKD

In the face of CKD, metabolic acidosis ensues once renal excretory mechanisms are unable to keep pace with the daily net acid generation, typically once the GFR falls below ∼30 mL/min. The major reason for this is a decrease in total renal ammoniagenesis as a result of decreasing numbers of functioning nephrons, even while single nephron ammoniagenesis increases [48]. In the absence of renal tubular acidosis the ability of the kidneys to maximally acidify urine and to reabsorb bicarbonate is, however, maintained even in advanced stages of CKD [49, 50]. Clinically, CKD is characterized by a mild metabolic acidosis, with serum bicarbonate values typically remaining above ∼15 mEq/L in the absence of concomitant comorbidities [51]. Typically the anion gap remains normal until the late stages of CKD when it begins to widen [52]. In spite of the persistently positive proton balance of patients with CKD, their pH and serum bicarbonate remain stable due to additional buffering that occurs most likely in the bone [53, 54].

The prevalence of metabolic acidosis increases with advancing stages of CKD [55]. In a cohort of over 570 000 US veterans with non-dialysis-dependent CKD stages 1–5, there was a linear increase in the prevalence of serum bicarbonate levels <22 mEq/L in patients with more advanced stages of CKD (Figure 1, based on data obtained from reference [56]). Interestingly, the total number of patients with low serum bicarbonate was much higher among patients with CKD stages 3A and 3B in spite of their lower proportions, simply by virtue of the much larger overall number of patients in these CKD categories (Figure 1).

The clinical consequences of the chronic metabolic acidosis of CKD include osteopenia [53, 54], potential aggravation of secondary hyperparathyroidism [57], reduced respiratory reserve and exhaustion of body buffer systems, which make patients more sensitive to the effects of acute intercurrent illnesses [58], and the reduction of Na^+–K^+-ATPase activity in red blood cells [59] and myocardial cells [60], which could lead to reduced myocardial contractility and congestive heart failure [61]. Other clinical complications linked to metabolic acidosis include abnormalities in the glucose homeostasis, accumulation of beta-2 microglobulin, chronic inflammation and disturbances in growth hormone and thyroid function [1, 2, 4]. Observational studies have also linked metabolic acidosis to increased mortality in patients with ESRD [24–26] and in those with non-dialysis dependent CKD [27, 28]. These associations could be explained by some or all of the deleterious effects of metabolic acidosis listed above, but the observational nature of these studies and the lack of clinical trials of alkali supplementation targeting survival as an end point precludes the invoking of metabolic acidosis as a direct cause of higher mortality in these patient populations.

The role of metabolic acidosis in the progression of CKD

Besides systemic effects discussed above, an important outcome associated with metabolic acidosis is kidney

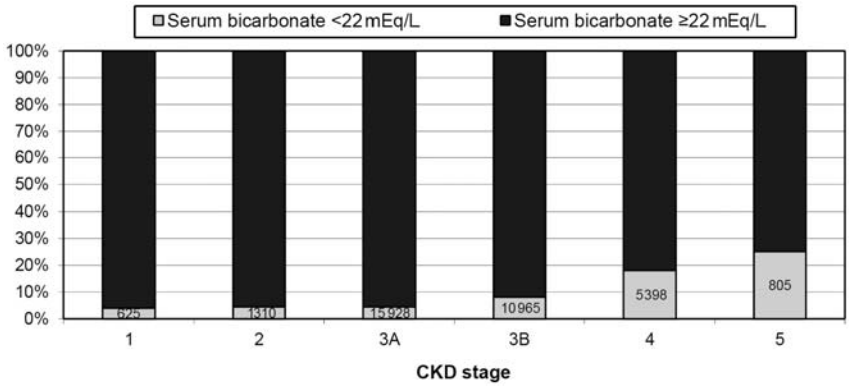

Fig. 1. Prevalence of metabolic acidosis (defined as proportion of patients with serum bicarbonate of <22 mEq/L) in a population-based cohort of 570 170 US veterans with non-dialysis-dependent CKD stages 1–5, by CKD stage. Numbers within the columns represent the actual number of patients with serum bicarbonate <22 mEq/L within the respective groups. Based on data from reference [56].

damage and progression of CKD. In a study of 80 patients with stage 4 CKD followed for 2 years in a single medical center, those with baseline serum bicarbonate levels of 15–20 mEq/L experienced significant steeper slopes of the estimated GFR (eGFR) compared with patients with serum bicarbonate >20 mEq/L [62]. In a larger observational study of 5422 patients visiting a single outpatient medical clinic (most of whom had normal kidney function), those with baseline serum bicarbonate levels <22 mEq/L experienced a significantly higher risk of a composite renal outcome (defined as either a decrease in the estimated GFR by 50% or reaching an eGFR <15 mL/min/1.73 m^2) [29]. A third study examined 1240 male US veterans with moderate and advanced non-dialysis-dependent CKD, and found a significant association between a higher serum bicarbonate level and lower incidence of ESRD [27, 63]. Interestingly, the benefit associated with higher serum bicarbonate did not appear to have an upper threshold in this study [63]. Similar findings were reported by a study that examined patients enrolled in the African American Study of Kidney Disease and Hypertension (AASK) trial, which described an association between higher serum bicarbonate levels in the normal range and lower incidences of various renal outcomes, with the most optimal renal outcome detected at a serum bicarbonate level of 28–30 mEq/L, even after adjustment for measured GFR levels [28]. Contradicting the results of the previously detailed studies was a *post hoc* analysis of patients enrolled in the Modification of Diet in Renal Disease (MDRD) study, which was primarily designed to examine the effects of dietary protein restriction and of blood pressure control on the progression of CKD. In this study lower baseline serum bicarbonate was associated with a higher crude incidence of ESRD, but this association became non-significant after adjustment for measured GFR [64]. Potential limitations of this study include limited external validity (since it examined patients enrolled in a clinical trial that used strict inclusion–exclusion criteria) and lack of assessment of longitudinal serum bicarbonate levels, especially since the dietary intervention (protein restriction) probably affected serum bicarbonate values differently in the different intervention arms.

The potential role of metabolic acidosis in progressive CKD is bolstered by numerous experimental studies that implied a direct role for metabolic acidosis in inducing kidney damage via complex mechanisms of action (Figure 2). More than two decades ago Nath *et al.* [31] suggested that increased renal production of ammonia in response to metabolic acidosis leads to complement activation and increased tubulointerstitial damage (Figure 2), which could be alleviated by the administration of sodium bicarbonate. Later, Wesson *et al.* invoked the role of endothelin which plays a role in renal acidification through the activation of ET-B receptors, but which can also simultaneously activate ET-A receptors with resultant tubulo interstitial injury (Figure 2). This effect was also alleviated by the simultaneous administration of sodium bicarbonate [35]. Interestingly, the administration of dietary alkali appears to be a more effective renoprotective strategy than the administration of endothelin antagonists [65], suggesting a complex mechanism of action for the nephrotoxic effects of metabolic acidosis. Another potential mechanism of action could involve the activation of the rennin–angiotensin system, which also plays a role in urinary acidification (vide supra), and the persistent activation of which can also result in proteinuria [32], renal damage and progressive CKD [32, 65]. In summary, metabolic acidosis activates a series of regulatory mechanisms that are meant to correct the disordered acid–base balance brought about by the development of CKD, and the persistent activation of which can subsequently induce additional renal damage and contribute to progressive CKD (Figure 2).

Correction of metabolic acidosis: an effective, safe and affordable renoprotective strategy?

Given the suggestive pathophysiologic pathways and the experimental data from animal studies, it is plausible to postulate that the administration of alkali to patients with CKD could attenuate the maladaptive mechanisms induced by metabolic acidosis and could hence be

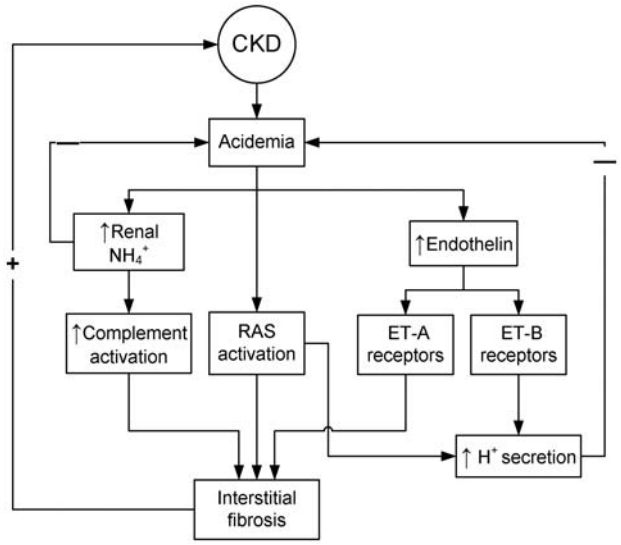

Fig. 2. Putative mechanisms of action responsible for the deleterious effects of metabolic acidosis on kidney function. ET-A, endothelin type A receptor; ET-B, endothelin type B receptor; RAS, renin–angiotensin system.

renoprotective. An early study confirmed the plausibility of this by showing significant improvement in urinary markers of proximal tubular damage over 26 h in response to oral sodium bicarbonate in 11 patients with mild/moderate kidney impairment and proteinuria [40]. In this study neither proteinuria, nor renal hemodynamics or systemic blood pressure were altered by the administration of sodium bicarbonate.

Subsequently, the hypothesis that alkali administration is renoprotective has been tested in a number of clinical trials using hard clinical end points (Table 1). De Brito-Ashurst *et al.* [37] examined 134 patients with baseline creatinine clearance of 15–30 mL/min and baseline serum bicarbonate of 16–20 mEq/L from a single center. Patients were randomized to receive oral sodium bicarbonate tablets 600 mg 3×/day, titrated to achieve target serum bicarbonate levels of ≥23 mEq/L, versus standard care in an open label design, and were followed for 2 years. Examined endpoints were the slopes of creatinine clearance and the incidences of rapid loss of kidney function (defined as slopes of creatinine clearance of >3 mL/min/year) and of ESRD (defined as creatinine clearance <10 mL/min). The intervention group experienced significantly attenuated slopes of creatinine clearance and fewer renal endpoints [37]. A second study by Phisitkul *et al.* [39] examined 59 patients with an eGFR 20–60 mL/min/1.73 m^2 and baseline serum bicarbonate of <22 mEq/L. All patients were offered Na citrate 1 mEq of HCO_3 equivalent/kilogram body weight/day in three divided doses, and the 30 patients who accepted the treatment formed the intervention arm, which was compared with the 29 patients who refused this treatment. Patients were treated for 24 months, with the primary study endpoint being the change in urine endothelin-1 levels; secondary endpoints were changes in urine markers of tubular damage and eGFR. After 2 years of therapy, patients who received Na citrate displayed a slower decline in eGFR and a decrease in urinary endothelin-1, tubular injury markers and albuminuria. Finally, Mahajan *et al.* [38] examined 120 patients with hypertensive nephropathy with baseline eGFR of 75 ± 6 mL/min/1.73 m^2 and macroalbuminuria, and a serum bicarbonate level of at least 24.5 mEq/L. Patients were randomized to oral Na bicarbonate (0.5 mEq/kg lean body weight/day, $n = 40$) versus oral NaCl (0.5 mEq/kg lean body weight/day, $n = 40$) versus placebo ($n = 40$) after matching for age, eGFR, albuminuria and ethnicity, and were followed for 5 years. The primary study endpoint was the reduction in the rate of eGFR decline in the sodium bicarbonate group compared with the placebo and NaCl groups; secondary endpoints were changes in urine endothelin, albuminuria and markers of tubular injury. Patients who received sodium bicarbonate experienced significantly more favorable slopes of the eGFR compared with both the placebo and the NaCl group, decreases in urinary markers of tubular injury and urine endothelin, and stabilization of albuminuria (versus worsening in the placebo and NaCl arms). This study enrolled patients with early stage CKD and without manifest metabolic acidosis, suggesting that renoprotective interventions with oral alkali therapy could be applied preemptively at stages when renal adaptive mechanisms are fully capable of maintaining the body's acid–base balance. It also suggests that measures other than serum bicarbonate should be considered to better identify those patients in whom the kidneys may already be exposed to the effects of persistently activated adaptive mechanisms but in whom frank metabolic acidosis has not yet developed.

Practical implementation of alkali therapy

The available evidence suggests that administration of alkali therapy over an extended period of time (2–5 years) is renoprotective in patients with CKD stages 2–4. Unfortunately, the single-center nature of the trials, the relatively small size of these clinical trials and the different therapeutic approaches used by each of these studies do not yet allow us to generalize their findings. Larger clinical trials will be needed to better define the population that has the highest chance to respond to alkali therapy, and the treatment target(s) and therapeutic regimen(s) that offer the best balance between efficacy and safety. The question regarding what an ideal treatment target should be is particularly important in light of observational studies showing a U-shaped association between serum bicarbonate levels and mortality [27], suggesting that overdosing alkali therapy may be hazardous. Furthermore, it remains to be determined if the administration of sodium that accompanies bicarbonate therapy could cause volume overload and increase in blood pressure. There are indications from physiologic experiments that NaCl and Na bicarbonate may have different effects on blood pressure and electrolyte homeostasis in spite of identical sodium loads [66], and Na bicarbonate appeared to be beneficial when compared head-to-head with NaCl [38], but the

Table 1. Clinical trials of alkali supplementation in patients with non-dialysis dependent CKD

Study	Population	Baseline serum bicarbonate	Intervention	Duration of intervention	Outcome measure (s)	Results
De Brito-Ashurst *et al.* [37]	$n = 134$; CrCl 15–30 mL/min	16–20 mEq/L	Oral Na bicarbonate (600 mg 3×/day titrated to achieve and maintain a serum bicarbonate level ≥23 mEq/L) versus standard care (open label)	2 years	Rate of CrCl decline	CrCl slope 5.93 versus 1.88 mL/min; $P < 0.0001$
					Proportion of patients with rapid decline of CrCl (>3 mL/min/year)	HR of rapid progression 0.15 (0.05–0.40), $P < 0.001$
					ESRD (CrCl < 10 mL/min)	HR of ESRD 0.13 (0.04–0.40), $P < 0.001$
Phisitkul *et al.* [39]	$n = 59$; eGFR 20–60 mL/min/1.73 m^2	<22 mEq/L	Na citrate 1 mEq of HCO_3 equivalent/kg BW/day in three divided doses was offered to all patients Patients who accepted the treatment ($n = 30$) formed the intervention arm	2 years	Urine endothelin-1 levels	In the intervention arm after 2 years:
					Urine markers of tubular damage	Rate of eGFR decline was lower
					Changes in eGFR over time	Urine excretion of endothelin was lower Markers of tubular damage, urine albumin were lower
Mahajan *et al.* [38]	$n = 120$; eGFR 75 ± 6 mL/min/1.73 m^2 and macroalbuminuria	≥24.5 mEq/L	Na bicarbonate 0.5 mEq/kg lean body weight/day versus NaCl 0.5 mEq/kg lean body weight/day versus Placebo	5 years	Rate of eGFR decline	In the Na bicarbonate arm after 5 years:
					Changes in urine endothelin, albuminuria, and markers of tubular injury	Favorable slopes of the eGFR Decreases in urinary markers of tubular injury and urine endothelin Stabilization of albuminuria

CrCl, creatinine clearance; ESRD, end-stage renal disease; HR, hazard ratio.

definitive safety of this approach will have to be ascertained in larger clinical trials. In this author's opinion at this point in time it is prudent to apply alkali therapy in patients with manifest metabolic acidosis (serum bicarbonate level <22 mEq/L), which is currently also recommended by the Kidney Disease Outcome Quality Initiative primarily because of the deleterious effects of metabolic acidosis on the nutritional status [67]. With proper monitoring to prevent overdosing of alkali and metabolic alkalosis and with careful management of volume status and blood pressure control, such an approach may have multiple benefits including improved nutritional status and renoprotection, it is probably safe and it is affordable to most patients. Short of definitive trials comparing the different agents available for alkali replacement (e.g. Na bicarbonate, Na citrate, K citrate, Ca citrate, Ca acetate, Ca carbonate) the applied regimen should be individualized based on patient tolerance, affordability and individual comorbidities and biochemical characteristics.

Conclusions

Metabolic acidosis is a risk factor for progressive CKD, possibly through various mechanisms that involve renal adaptation to chronic acidemia and that could cause renal injury when persistently activated. The administration of alkali to patients with early-to-advanced stages of CKD in small single-center clinical trials has been proved to be renoprotective. Larger clinical trials are awaited to better define treatment targets and therapeutic regimens that are applicable to a broad range of patients with CKD. For the time being it is advised to administer alkali therapy to patients with serum bicarbonate <22 mEq/L primarily due to its beneficial effects on the nutritional status [67], which may also be beneficial toward retarding the progression of CKD. Monitoring of serum bicarbonate is prudent in order to avoid metabolic alkalosis or other complications.

Conflict of interest statement. None declared.

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