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Epidemiology of acid-base derangements in CKD

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Abstract

Acid-base disorders are common in patients with chronic kidney disease, with chronic metabolic acidosis receiving the most attention clinically in terms of diagnosis and treatment. A number of observational studies have reported on the prevalence of acid-base disorders in this patient population and their relationship with outcomes, mostly focusing on chronic metabolic acidosis. The majority have used serum bicarbonate alone to define acid-base status due to the lack of widely available data on other acid-base disorders. This review discusses the time course of acid-base alterations in CKD patients, their prevalence, and associations with CKD progression and mortality.

Keywords

Renal insufficiency; chronic; acidosis; alkalosis; epidemiology; mortality

INTRODUCTION

Acid-base disorders are common in patients with chronic kidney disease (CKD) and may contribute to its sequelae. Accumulating evidence suggests benefit from treating chronic metabolic acidosis in this patient population. It is thus important to understand the methods used to define acid-base derangements in published observational studies, the prevalence of such disorders in CKD patients, and their relationship with outcomes.

EVALUATION OF ACID-BASE STATUS IN CKD

Before we begin to examine acid-base status in CKD using epidemiologic data, we should discuss the limitations in its measurements used in the majority of studies. First, most studies only had serum bicarbonate concentrations available and defined metabolic acidosis using these bicarbonate levels. This approach presumes the absence of a meaningful respiratory contribution. The specificity of low serum bicarbonate for presence of metabolic

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acidosis is likely greater in people with CKD than in the general population. Second, consideration should be given to the accuracy of serum bicarbonate measurement. There are two methods to measure bicarbonate.¹ The first is the measurement of serum total carbon dioxide (CO₂) concentration on an automated chemistry analyzer using either an electrode-based or enzymatic method. The second is a part of blood gas measurement, calculated using the Henderson-Hasselbalch equation from directly measured values of pH and partial pressure of CO₂.

Most epidemiologic studies have measured serum bicarbonate using an autoanalyzer. The specimens are often shipped to a central laboratory by air freight to minimize assay variability. Kirschbaum found that there was a difference in the bicarbonate concentrations between blood being measured at a local laboratory and shipped to a central laboratory.² Bicarbonate measured at a central laboratory was usually lower than that measured at a local laboratory, which he hypothesized was due to potential gas leak from a different atmospheric pressure during air freight.³ The time that samples were exposed to air in commercial laboratories also contributed to the variability in bicarbonate values.⁴

There are few studies that measured arterialized venous blood gas. Arterialized venous blood gas samples can be obtained from a cannulated hand or wrist vein after the participant's hand or wrist have been placed in a warmer set to 42°C and warmed for a minimum of 15 minutes prior to blood sampling.⁵ Blood gas measurement provides a full assessment of acid-base status and is usually measured at the point of care, thus eliminating the errors that might have occurred during specimen transport. Due to difficulties in obtaining arterial blood gas, arterialized venous blood gas is often used in research.

There is generally acceptable clinical agreement between serum bicarbonate concentration calculated from blood gas and estimated from measurement of total CO₂, but some studies have found them to differ by a clinically unacceptable margin.^{6,7} There are several potential causes for the disagreement. These include the difference in arterial and venous bicarbonate concentration due to the transit of blood through tissues, loss of CO₂ gas from serum during processing and when the vacuum collection tube is underfilled, which will result in a falsely low serum bicarbonate concentration if measured.¹

ONSET AND PREVALENCE OF LOW BICARBONATE

To discuss the onset and prevalence of low bicarbonate in patients with non-dialytic CKD, we examined 3 adult CKD cohorts—NephroTest, Chronic Renal Insufficiency Cohort (CRIC) and African American Study of Kidney Disease and Hypertension (AASK), 3 adult non-CKD cohorts—Health, Aging and Body Composition (Health ABC) study, National Health and Nutrition Examination Survey (NHANES) and a single center study in the Bronx, NY as well as a pediatric CKD cohort—Chronic Kidney Disease in Children (CKiD) Study. The relevant details of the cohorts are listed in Table 1. Overall, the prevalence of acidosis begins to rise when GFR falls below ~40 ml/min per 1.73m² and increases as GFR decreases.

Onset and Prevalence of Low Bicarbonate in Adult CKD Cohorts

The NephroTest study in France included 1,038 adults with CKD stage 2 to 5 and not on dialysis.⁸ In this study, acidosis was defined as bicarbonate <22 mEq/L or on bicarbonate therapy. Glomerular filtration rate (GFR) was measured by ⁵¹Cr-EDTA renal clearance⁹ and estimated using equations derived from the Modification of Diet in Renal Disease study. The mean measured GFR (mGFR) was 37±17 ml/min per 1.73m², and 79% of participants were classified as CKD stage 3 or 4. The overall prevalence of acidosis was 15%, and 22% of participants with acidosis were on bicarbonate therapy. The prevalence of acidosis began to rise when GFR was below ~40 ml/min per 1.73m² and increased as GFR decreased: as eGFR decreased from 60–90 to <20 ml/min per 1.73m², the prevalence of acidosis increased from 2 to 39%. The onset of acidosis occurred after the onset of hyperparathyroidism and anemia (at mGFR 50 and 44 ml/min per 1.73m², respectively), around the same level of GFR as the onset of hyperkalemia (at mGFR 39 ml/min per 1.73m²) and before the onset of hyperphosphatemia (at mGFR 37 ml/min per 1.73m²).

The CRIC study is a multicenter, observational study of 3,939 participants aged 21 to 74 years with eGFR between 20 and 70 ml/min per 1.73m².¹⁰ The median serum bicarbonate level was 24 (interquartile range (IQR) 22–26) mEq/L.¹¹ The prevalence of low bicarbonate (defined as bicarbonate <22mEq/L) was 17.3%. Similar to the NephroTest study, the prevalence of low bicarbonate increased with the severity of kidney disease: 7% for CKD stage 2, 13% for stage 3 and 37% for stage 4.¹² There were only 8 participants with CKD stage 1 and none of them had low bicarbonate. Of the 5 participants with CKD stage 5, 4 had low bicarbonate. Serum bicarbonate >30 mEq/L was quite uncommon, present in 2.4% of participants.

The AASK trial is a multicenter, 3×2 factorial, randomized, controlled trial of intensive vs. standard blood pressure control in self-identified African Americans with hypertensive CKD, which was defined as GFR between 20 and 65 ml/min per 1.73m² by I¹²⁵ iothalamate clearance and diastolic blood pressure >95 mmHg.¹³ The mean serum bicarbonate was 25.1 mEq/L; 4.3% had bicarbonate <20 mEq/L, 35.5% had bicarbonate between 20 to 24.9 mEq/L, and 5.5% had bicarbonate ≥30mEq/L.¹⁴ Lower GFR was associated with lower bicarbonate: the mean GFR was 34±13 ml/min per 1.73m² for those with bicarbonate <20mEq/L and 49±12 ml/min per 1.73m² for those with bicarbonate ≥30mEq/L.¹⁴

Prevalence of Low Bicarbonate in Non-CKD Cohorts

The prevalence of low bicarbonate was also examined in non-CKD cohorts.^{5,15,16} The Health ABC study is a prospective study of well-functioning adults aged 70–79 years old.⁵ There were 2,287 participants who had arterialized venous blood gas measured at point of care, and bicarbonate was calculated using the Henderson-Hasselbalch equation. Measurement of arterialized venous blood gas allowed detailed evaluation of acid-base status. The mean eGFR was 82.1 ml/min per 1.73m² and 12% had CKD (defined as eGFR<60 ml/min per 1.73m²).⁵ Mean pH was 7.41 and mean bicarbonate was 25.1 mEq/L. Eleven percent (11%) had bicarbonate <23 mEq/L and 10% had bicarbonate ≥28 mEq/L. When participants were categorized into acid-base categories, 9.3% had metabolic acidosis (defined as pH <7.41, bicarbonate<25.5 mEq/L and PCO₂ <40 mmHg) and 9.4% had

metabolic and respiratory acidosis (defined as pH 7.41, bicarbonate <25.5 mEq/L and PCO₂ 40 mmHg).

NHANES is a nationally representative survey of the non-institutionalized civilian population in the United States. In NHANES 1999–2004 participants, the mean serum bicarbonate was 24.9 mEq/L.¹⁵ Serum bicarbonate levels were linearly associated with age, with older participants having the highest serum bicarbonate levels. This was in contrast to prior studies that associated older age with lower serum bicarbonate,^{17,18} which was consistent with an age-induced impairment in renal net acid excretion.¹⁹ Among NHANES participants, the age-bicarbonate association was partly explained by lower dietary protein intake among older Americans. The mean estimated net endogenous acid production (NEAP) based on a dietary recall questionnaire was 57.4 mEq/d, and greater dietary acid load was associated with lower serum bicarbonate. Participants within the highest quartile for NEAP had 0.40 mEq/L lower (95% CI, –0.55 to –0.26) serum bicarbonate and a 33% higher (95% CI, 3% to 72%) likelihood of acidosis (defined as bicarbonate <23 mEq/L) compared with those in the lowest quartile.¹⁵

The prevalence of low bicarbonate was also examined in a single center retrospective study of outpatients in the Bronx, NY, which included 5,422 participants with eGFR 15 ml/min per 1.73m² from January 2001 to June 2007.¹⁶ In the study, 69% were women, 25% were African American, 31% were Hispanic and 21% had diabetes. Nine percent of participants had eGFR <60 ml/min per 1.73m². The mean bicarbonate for patients with eGFR 15–29 ml/min per 1.73m² was 23±4.3 mEq/L, compared with 24.8±2.9 mEq/L for those with eGFR ≥60 ml/min per 1.73m². Low bicarbonate (defined as bicarbonate ≤22 mEq/L) was present in 20.7% overall: 20%, 21%, 48% for eGFR ≥60, 30 to 59 and 15 to 29 ml/min per 1.73m², respectively. The prevalence of low bicarbonate in this cohort appears to be higher than that from the CRIC study. This could be due to the difference in the definition of low bicarbonate (≤22 vs. <22 mEq/L in the CRIC study) and in baseline participant demographics (i.e. fewer participants who were African American or diabetic compared to that in the CRIC study).

Prevalence of Low Bicarbonate in a Pediatric Cohort

Lastly, the CKiD study is an observational study with children aged 1 to 16 years and a Schwartz-estimated GFR between 30 and 90 ml/min per 1.73m².^{20,21} According to the CKiD study, children with CKD have lower bicarbonate concentration compared to adults despite higher prevalence of alkali therapy. Furth et al. examined the prevalence of various CKD sequelae across the GFR spectrum²² among 586 children with baseline study visits between January 2005 and August 2009. The median GFR, measured by iothexol plasma disappearance was 44 ml/min per 1.73m². The median bicarbonate level was 22 mEq/L and as GFR declined, bicarbonate levels decreased: median bicarbonate was 24, 22, and 21 mEq/L among those with GFR ≥50, 30 to <50, and <30 ml/min per 1.73m², respectively. The prevalence of alkali therapy was higher in children than adults: 29% vs 2.4%.²³ Its use was highest among children with GFR between 30 and <40 ml/min per 1.73m² (i.e. 37%).²² Children with acidosis are often treated with alkali therapy due to the evidence of

attainment and maintenance of normal stature with alkali therapy in children with renal tubular acidosis.^{24–26}

FACTORS ASSOCIATED WITH LOW AND HIGH BICARBONATE

In the CRIC study, participants who were younger, male, Hispanic and hypertensive were more likely to have serum bicarbonate <22mEq/L.¹¹ Factors associated with higher odds of low bicarbonate, independent of eGFR, included urinary albumin/creatinine (UACR) >10 mg/g, smoking, anemia (hemoglobin <12 g/dL for women or <13 g/dL for men), hyperkalemia (serum potassium concentration >5 mEq/L), non-diuretic use and higher serum albumin.¹² Compared to those with UACR<10 mg/g, those with UACR 10 to <30 mg/g had 55% higher odds of low bicarbonate (Odds Ratio (OR) 1.55, 95% CI 1.04 to 2.29). The ORs for smoking, anemia, and hyperkalemia were 1.43 (95% CI 1.13 to 1.81), 1.40, (95% CI 1.10 to 1.76) and 2.40 (95% CI 1.75 to 3.30), respectively. With every 1 g/dL higher serum albumin, the odds of low bicarbonate increased by 35% (OR 1.35, 95% CI 1.02 to 1.78). Participants who were African- American, older, had diabetes, were taking diuretics, and had higher body mass index were more likely to have serum bicarbonate above 26 mEq/L (Table 2). Caravaca et al.²⁷ examined the difference in severity of metabolic acidosis between CKD patients (creatinine clearance <30 ml/min per 1.73m²) with and without diabetes and found that CKD patients with diabetes had a less severity of metabolic acidosis, which could not be explained by gastrointestinal hydrogen ion losses, drugs or reduced protein catabolic rate. They hypothesized that CKD patients with diabetes may have a more efficient extra-renal generation of bicarbonate than those without diabetes.

ACID-BASE STATUS AND CKD PROGRESSION

Low Bicarbonate and CKD Progression

Lower bicarbonate levels have been associated with faster CKD progression. In the CRIC study, participants with serum bicarbonate ≤ 22 mEq/L were at greater risk of CKD progression (defined as progression to end-stage renal disease or 50% decrease in eGFR) compared to those with bicarbonate >26 mEq/L (10.3 vs. 3.6 renal endpoints per 1000 person-years).²³ The risk of CKD progression was 3% lower per 1 mEq/L higher serum bicarbonate (HR 0.97, 95% CI 0.94 to 0.99, p=0.01). There were significant interactions of serum bicarbonate level with proteinuria and eGFR. The subgroup of participants with proteinuria ≤ 0.2 g/day had 10% risk reduction in CKD progression with each 1mEq/L increase in bicarbonate level (HR 0.90, 95% CI 0.83 to 0.98, p=0.01), while the association was not significant in participants with proteinuria >0.2 g/day. Similar results were seen in the AASK trial. Each 1 mEq/L increase in bicarbonate within the normal range (20 to 30 mEq/L) was associated with reduced dialysis or GFR event, where GFR event was defined as a GFR reduction by 50% or by 25 ml/min per 1.73m² (adjusted HR 0.94, 95% CI 0.89 to 0.996).¹⁴ The lowest risk of GFR event or dialysis was found at serum bicarbonate levels near 28 to 30 mEq/L.

Acid Load and CKD progression

Higher NEAP has been associated with CKD progression. Scialla et al. studied the association between NEAP and progression of kidney disease in the AASK trial.²⁸ In the study, dietary protein intake was estimated from 24 hour urine urea nitrogen and dietary potassium intake was estimated as the total 24 hour urine potassium excretion. NEAP (mEq/day) is determined by the balance of acid and alkali precursors in the diet, where proteins are the major source of acid through metabolism to sulfates and non-volatile acids and alkali is derived from potassium salts from fruits and vegetables²⁹, and was calculated as $54.5 \times (\text{dietary protein (g/d)/dietary potassium (mEq/d)} - 10.2)$.³⁰ The median NEAP was 72.8 mEq/d (IQR 57.2–89.5). Higher NEAP was associated with current smoking, lower income and lower bicarbonate. After adjustment for age, body mass index, baseline GFR, urine protein-to-creatinine ratio and randomized treatment group, higher NEAP was significantly associated with a faster decline in GFR at a rate of 1.01 ml/min per 1.73m² per year faster in the highest compared to the lowest quartile over a median of 3.2 years.

Net Renal Acid Excretion and CKD Progression

Impaired ability of the kidneys to excrete daily net acid load can also be an independent risk factor for CKD progression. After a median follow up of 4.3 years, ~19% participants from NephroTest reached end stage renal disease (ESRD).³¹ Compared with participants in the highest tertile of urinary ammonium excretion, those in the lowest tertile had a significantly higher hazard ratio for ESRD, 1.82 (95% CI 1.06 to 3.13) and a higher odds of having >10% GFR decline per year (OR 1.84, 95% CI 0.98 to 3.48). Similarly, in the AASK trial, compared to participants in the high ammonium tertile, those in the lowest tertile had higher odds of incident acidosis at 1 year (adjusted OR 2.56, 95% CI 1.04 to 6.27) and higher risk of the composite outcome of death or dialysis (hazard ratio (HR) 1.46, 95% CI 1.13 to 1.87), while adjusted for demographics, mGFR, proteinuria, body mass index, NEAP and serum potassium and bicarbonate.³²

Similar results were found when Scialla et al. examined net renal acid excretion as the sum of urine ammonium and titratable acidity in the CRIC study.³³ The mean net acid excretion was 33 ± 18 mEq/d with 46% of acid excreted as ammonium. In univariate analyses, total net acid excretion and the percentage of acid excreted as ammonium were lower with lower eGFR. Higher net acid excretion was associated with male sex, white race, greater body size, greater eGFR, lower serum potassium and higher consumption of animal protein.³³ In multivariable models that adjusted for demographic characteristics, diabetes and eGFR, each 10 mEq/day higher net acid excretion was associated with 0.17 mEq/L lower serum bicarbonate. Over a median follow up of 6 years, ~32% had CKD progression (defined as a 50% reduction in eGFR or new-onset end-stage renal disease). Higher net acid excretion was independently associated with a significantly lower risk of CKD progression (HR 0.88 per 10 mEq/day higher net acid excretion).

ACID-BASE STATUS AND MORTALITY

Several studies have demonstrated a U-shaped association between serum bicarbonate and mortality with the lowest mortality in participants with bicarbonate between 26 and 30

mEq/L.^{5,34,35} In the analysis of the Health ABC study,¹⁴ after a mean follow up of 10.3 years, all-cause mortality was lowest at a bicarbonate concentration of 26 mEq/L. Mortality peaked at ~23 mEq/L and remained flat with lower bicarbonate levels. After adjusting for systemic pH and potential confounders, compared to participants with bicarbonate of 23.0–27.9 mEq/L, the mortality HR was 1.24 (95% CI, 1.02 to 1.49) for participants with bicarbonate <23mEq/L. The data seemed to suggest that the association between low bicarbonate and mortality was present regardless of whether the cause of low bicarbonate was metabolic acidosis or respiratory alkalosis. Compared with the normal acid-base group, mortality HRs were 1.17 (95% CI, 0.94 to 1.47) for metabolic acidosis, 1.21 (95% CI, 1.01 to 1.46) for respiratory alkalosis, and 1.35 (95% CI, 1.08 to 1.69) for metabolic alkalosis categories. Respiratory acidosis did not associate with mortality.

ACID RETENTION IN CKD

Carefully performed balance studies in the 1960s indicated that patients with advanced CKD and stable metabolic acidosis were in positive acid balance,^{36,37} although this conclusion was subsequently challenged.³⁸ More recently, in patients with CKD, unlike those with normal kidney function³⁹, 24 hour net acid excretion was lower than dietary acid load estimated from NEAP.³³ Wesson et al. compared urine net acid excretion of participants with hypertensive CKD stage 2 and UACR >200mg/g with those with CKD stage 1 after sodium bicarbonate therapy.⁴⁰ No metabolic acidosis was present in either group at baseline. Baseline dietary acid and urine net acid excretion were not different between the two groups. They found that with an oral sodium bicarbonate bolus, 8 hour urine net acid excretion decreased in both groups, but it was twofold less in participants with CKD stage 2. This finding is consistent with the presence of acid retention even in patients with mildly impaired kidney function.

ANION GAP AND KIDNEY FUNCTION

According to the NHANES 1999–2004, anion gap was higher among those with lower GFR.⁴¹ Compared with participants with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)-defined eGFR 90–119 ml/min per 1.73m², the anion gap was significantly elevated only among those with eGFR 30–44 ml/min per 1.73m² (12.08 vs. 12.65, respectively). However, after including in the anion gap calculation albumin and other measured ions that are usually considered “unmeasured”, small but statistically significant increases in the anion gap were noted beginning with eGFR <90 ml/min per 1.73m². Higher anion gap levels were associated with an increased risk of all-cause mortality after adjustment for age, gender, race/ethnicity and eGFR, and the relationship with mortality was more robust when the additional solutes were incorporated in the calculation. Similarly, in the single center in the Bronx, NY, the anion gap was higher in patients with eGFR of 15 to 29 and 30 to 44 ml/min per 1.73m² (mean anion gap was 14±3.4 and 13.3±3.4, respectively) compared to those with eGFRs of ≥60 ml/min per 1.73m² (mean anion gap 12.7±2.8).¹⁶

ACID-BASE STATUS IN PATIENTS ON DIALYSIS

Serum bicarbonate values in hemodialysis patients have been increasing in the United States: mean bicarbonate was 19.2mEq/L in 1987–1988,⁴² and increased to 21.4 mEq/L in 1996–2001⁴³ and in 2001–2003.⁴⁴ There are several factors that could explain this trend.⁴⁵ First, the switch from acetate to bicarbonate as the main source of dialysate buffer replacement improved correction of acidosis. Second, nephrologists may have targeted low serum bicarbonate concentration more aggressively. Third, the population initiating dialysis in the United States got older and older Americans tend to have higher bicarbonate levels than younger people. Table 3 summarizes 2 recent studies that examined acid-base status in patients on dialysis— using a Davita database and the Japanese Society of Dialysis Therapy registry.^{46,47}

Vashistha et al. obtained data from 121,351 maintenance dialysis patients (8.6% on peritoneal dialysis (PD), 91.4% on hemodialysis (HD)) treated in DaVita facilities.⁴⁶ Serum bicarbonate was obtained immediately before a hemodialysis session and all samples were shipped to a single central laboratory. Time-average serum bicarbonate was defined as the average value pre-HD in HD patients and the average steady-state measurement in PD patients. Note that predialysis serum bicarbonate in HD patients is a nadir value, representing the state of maximal acid retention, compared with the steady-state measurement in patients receiving PD. PD patients had lower odds of having bicarbonate <22mEq/L compared to HD patients (25% vs. 40%, OR 0.41, 95% CI, 0.39 to 0.43). These patients were then followed for 1 year and mortality data was obtained from the US Renal Data System. Irrespective of dialysis modality, the adjusted risk for all-cause mortality was higher in patients with bicarbonate <22mEq/L compared to those with time-averaged bicarbonate between 24 and <25 mEq/L. Compared to those with bicarbonate between 24 and <25 mEq/L, patients on PD with bicarbonate levels <19 mEq/L had higher all-cause and cardiovascular mortality (HR 1.18, 95% CI 1.01 to 1.37; HR 1.25, 95% CI 1.00 to 1.57, respectively); patients on HD with bicarbonate levels <19mEq/L had higher all-cause and cardiovascular mortality (HR 1.35, 95% CI 1.30 to 1.41; HR 1.46, 95% CI 1.37 to 1.54, respectively).

The renal registry of the Japanese Society of Dialysis Therapy included 15,132 dialysis patients 16 years or older.⁴⁷ Unlike the Davita database, the most common cause of kidney failure in the Japanese registry was glomerulonephritis (41.5%). Acid-base parameters were measured with a blood gas analyzer in local laboratories and bicarbonate level was calculated using the Henderson-Hasselbalch equation. The mean pre-dialysis pH was 7.35 ± 0.05 ; mean bicarbonate was 20.5 ± 2.9 mEq/L. There were 10.2% of patients who had predialysis pH <7.30 and 18.3% had predialysis pH ≥ 7.40 . The mean postdialysis pH was 7.44 ± 0.05 with mean bicarbonate of 25.1 ± 2.8 mEq/L. Patients with higher predialysis pH were more likely to have cardiovascular diseases, less likely to have diabetes, had lower weight gain ratio, lower hemoglobin and normalized protein catabolic rate than patients with lower predialysis pH. Higher predialysis pH was also associated with higher serum bicarbonate and higher dialysate bicarbonate. The presence of diabetes increased the odds of higher predialysis pH but decreased the odds of higher predialysis bicarbonate levels.⁴⁷ During the 1-year follow up period 1,042 patients died. Unlike the Davita database,

predialysis bicarbonate level, postdialysis pH and bicarbonate level were not associated with all-cause and cardiovascular mortality. However, higher predialysis pH was associated with higher all-cause mortality with adjusted HR of 1.18 per 0.1 unit higher pH (95% CI 1.02 to 1.37). Those with predialysis pH ≥ 7.40 had 34% higher odds of all-cause mortality compared to those with predialysis pH between 7.30 and 7.34.

The difference between the results from the Davita database and Japanese registry could be partly explained by the differences in comorbid conditions, diet and methods of bicarbonate measurement. In the Davita study, the samples were shipped overnight to a central laboratory, whereas in the Japanese study, bicarbonate levels were calculated from pH and PCO_2 using the Henderson- Hasselbalch equation. The PCO_2 levels may vary depending on a patient's ventilatory response, modifying the association between the change in serum bicarbonate and the change in pH.⁴⁸

CONCLUSIONS

Chronic metabolic acidosis becomes increasingly common with progression of CKD and is important to recognize in the routine management of CKD patients. A number of studies have associated low serum bicarbonate with more rapid CKD progression, and more recently associations with higher dietary acid load and lower urinary net acid excretion have also been reported. As most epidemiologic studies have used only the serum bicarbonate to define metabolic acidosis, the prevalence of other acid-base disorders has not been as well characterized. In select patients, data from blood gas measurements may be useful to further define acid-base status.

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CLINICAL SUMMARY

Most epidemiologic studies of acid-base disorders in CKD have used only the serum bicarbonate level, as additional data from blood gas measurements is typically not available in large cohorts.

Approximately 15% of CKD patients overall have some degree of metabolic acidosis, and the prevalence increases with lower eGFR.

Several parameters related to acid-base balance have been associated with the risk of CKD progression, including low serum bicarbonate, high dietary acid load, and low urinary ammonium and net acid excretion.

Table 1
Cohort studies of participants with non-dialysis chronic kidney disease and their acid-base status

Cohort	Time period, study design, country of origin	n	Study population	Determination of GFR	Acid-base measurement	Summary of findings on acid-base status
NephroTest ⁸	1/2000–12/2006; prospective hospital-based; France	1,038	CKD stage 2–5 - mean age was 59 years - 31% were women - 6% were black	mGFR: measured by ⁵¹ Cr-EDTA renal clearance; eGFR: estimated using 2 equations from the Modification - mean mGFR was 37 ± 17 ml/min per 1.73m^2	Venous total CO ₂ measured using electrode - acidosis defined as bicarbonate <22mEq/L or on bicarbonate therapy	<ul style="list-style-type: none"> - Overall prevalence of acidosis was 15%. - 22% of participants with acidosis were on bicarbonate therapy. - The mGFR threshold for detecting acidosis with 90% sensitivity was 40 ml/min per 1.73m^2.
Chronic Renal Insufficiency Cohort ^{1,12,23}	6/2003–12/2008 (enrollment); multicenter, observation study; USA	3,939	eGFR 20–70 ml/min per 1.73m^2 - mean age was 58 years - 45.2% were women - 41.8% were African American - 48.5% had diabetes	GFR was assessed by a CRIC internal GFR estimating equation validated against iothalamate ¹²⁵ clearance testing that uses serum Cr, cystatin C, age, sex and race - mean eGFR was 43 ± 14 ml/min per 1.73m^2	Serum bicarbonate measured using an enzymatic procedure with phosphoenolpyruvate carboxylase on the Ortho Vitros platform at the University of Pennsylvania Core Laboratory - low bicarbonate defined as bicarbonate <22mEq/L	<ul style="list-style-type: none"> - Median serum bicarbonate level was 24 (IQR 22–26) mEq/L. - Overall prevalence of low bicarbonate was 17.3%; 7% for CKD stage 2, 13% for stage 3 and 37% for stage 4.
African American Study of Kidney Disease and Hypertension ^{3,14,28}	2/1995–9/2001; multicenter, 3×2 factorial, randomized, controlled trial of intensive vs. standard blood pressure control; USA	1,094	GFR 20–65 ml/min per 1.73m^2 - mean age was 54 years - ~40% were women	GFR was assessed by renal clearance of iodine ¹²⁵ iothalamate clearance - mean GFR was 46 ml/min per 1.73m^2	Serum bicarbonate was measured using either the kinetic ultraviolet method or a CO ₂ electrode	<ul style="list-style-type: none"> - Mean serum bicarbonate was 25.1 mEq/L - 4.3% had bicarbonate <20 mEq/L, 35.5% had bicarbonate between 20–24.9 mEq/L, and 5.5% had bicarbonate 30mEq/L
Health, Aging and Body Composition Study ⁵	From 1997; prospective study of community elders; USA	2,287	Well-functioning adults aged 70–79 years - mean age was 76 years - 51% were women	GFR was estimated using creatinine and cystatin C and CKD-EPI Collaboration creatinine-cystatin C equation ⁴⁹	Arterialized venous blood gas was obtained and measured at the point of care. Bicarbonate was calculated using the Henderson-Hasselbalch equation	<ul style="list-style-type: none"> - mean AVpH was 7.41 - mean bicarbonate was 25.1 mEq/L - 11% had bicarbonate <23 mEq/L and 10% had bicarbonate 28 mEq/L.

Cohort	Time period, study design, country of origin	n	Study population	Determination of GFR	Acid-base measurement	Summary of findings on acid-base status
			<ul style="list-style-type: none"> - 38% were black 	<ul style="list-style-type: none"> - mean GFR was 82.1 ml/min per 1.73m² 		<ul style="list-style-type: none"> - association of bicarbonate and mortality was U-shaped with the lowest mortality at bicarbonate of 26mEq/L
National Health and Nutrition Examination Survey ¹⁵	1999–2004; nationally representative survey, USA	9,781	Noninstitutionalized civilian <ul style="list-style-type: none"> - mean age was 46 years 	GFR was calculated using CKD-EPI Equation	Bicarbonate was measured in 2 labs by the phosphoenolpyruvate carboxylase method from 1999–2001 and with a pH-sensitive electrode from 2002–2004; bicarbonate levels in 1999–2002 was adjusted by adding 1.105 mEq/L <ul style="list-style-type: none"> - acidosis was defined as bicarbonate <23 mEq/L 	<ul style="list-style-type: none"> - mean bicarbonate was 24.9 mEq/L - Mean estimated NEAP was 57.4 mEq/d - Greater dietary acid load is associated with lower bicarbonate.
Bronx, New York ¹⁶	1/2001–12/2003 (baseline); retrospective cohort; USA	5,422	eGFR 15 ml/min per 1.73m ² <ul style="list-style-type: none"> - mean age was 52 years - 69% were women - 25% were African American - 31% were Hispanic - 21% had diabetes 	eGFR was calculated using the 4-variable Modification of Diet in Renal Disease Study equation <ul style="list-style-type: none"> - 9% with eGFR <60 ml/min per 1.73m² 	Serum bicarbonate measured using an enzymatic procedure with phosphoenolpyruvate carboxylase at Montefiore Medical Center <ul style="list-style-type: none"> - low bicarbonate was defined as 22mEq/L 	<ul style="list-style-type: none"> - Prevalence of low bicarbonate was 20.7% for all, 20%, 21%, 48% for eGFR 60, 30–59 and 15–29 ml/min per 1.73m², respectively - mean bicarbonate was 23±4.3, 24.8±2.9 mEq/L for eGFR 15–29, 60 ml/min per 1.73m², respectively
Chronic Kidney Disease in Children ^{21,22}	1/2005–8/2009 [*] ; observational study; USA and Canada	586 [*]	eGFR 30–90 ml/min per 1.73m ² <ul style="list-style-type: none"> - median age was 11 years - 38% were female - 23% were black - 23% had glomerular disease 	GFR was determined by directly measured plasma iohexol disappearance curve ⁵⁰ <ul style="list-style-type: none"> - median GFR was 44 ml/min per 1.73m² 	Bicarbonate was measured locally using enzymatic method	<ul style="list-style-type: none"> - 29% were on alkali therapy - median bicarbonate was 22 mEq/L - median bicarbonate was 24, 22, 21 mEq/L among those with GFR GFR 50, 30 to <50, and <30 ml/min per 1.73m², respectively

Abbreviation: USA, United States of America; GFR, glomerular filtration rate; mGFR, measured GFR; eGFR, estimated GFR; CRIC, Chronic Renal Insufficiency Cohort; Cr, creatinine; IQR, interquartile range; AVpH, arteriovenous pH; NEAP, net endogenous acid production, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

Table 2

Factors associated with lower bicarbonate, higher dietary acid load, higher net acid excretion and higher anion gap^{12,15,28,33,41}

Lower bicarbonate	Higher dietary acid load [#]	Higher urine net acid excretion	Higher anion gap [#]
Younger	Younger	Male	Lower education
Hispanic	Male	White	Lower physical activity levels
Male	Higher GFR	High body mass index and	Hypertensive
Non-diabetic	Current smoking	surface area	Diabetic
Hypertensive	Lower income	Higher GFR	Lower GFR
Low body mass index	Lower bicarbonate	Lower serum potassium	Lower bicarbonate
Non-diuretic use	Higher dietary protein	Lower bicarbonate *	Higher hemoglobin
Lower GFR	Lower dietary potassium	Higher NEAP	Higher serum albumin
Higher urine albumin/creatinine *		Higher consumption of animal protein	High calcium
Smoking *			
Anemia *			
Hyperkalemia *			
Higher serum albumin			

Abbreviation: GFR, glomerular filtration rate; NEAP, net endogenous acid production

* Association was independent of GFR

[#] Dietary acid load was estimated using the NEAP equation, where NEAP (mEq/day) = 54.5×(dietary protein (g/d)/dietary potassium (mEq/d) – 10.2).; Anion gap = as serum sodium (mEq/L) – (serum chloride (mEq/L)+serum bicarbonate (mEq/L))

Table 3

Studies of acid-base status in patients on dialysis

Cohort	Time period, study design, country of origin	n	Study population	Acid-base measurement	Summary of findings on acid-base status
Davita database ⁴⁶	7/2001–6/2006; database; USA	121,351	Maintenance dialysis patients; 8.6% on PD <ul style="list-style-type: none"> - mean age was 56 years - 47% were women - 24% were black - 48% were diabetic - median dialysis vintage was 2.8 years - 91.4% on HD <ul style="list-style-type: none"> - mean age was 61 years - 45% were women - 32% were black - 58% were diabetic - median dialysis vintage was 2.3 years 	Bicarbonate was obtained immediately before hemodialysis session and all samples were shipped to a single central laboratory in Florida. Time-average bicarbonate was defined as the average value of pre-HD in HD patients and steady state measurement in PD patients <ul style="list-style-type: none"> - low bicarbonate defined as <22 mEq/L 	<ul style="list-style-type: none"> - PD patients had lower odds of having low bicarbonate compared to HD patients (OR 0.41, 95% CI 0.36 to 0.43). - Irrespective of dialysis modality, adjusted risk for all-cause mortality was higher in patients with bicarbonate <22mEq/L compared to those with those with bicarbonate between 24 and <25 mEq/L.
Japanese Society of Dialysis Therapy registry ⁴⁷	2008–2009, registry; Japan	15,132	Renal registry of dialysis patients <ul style="list-style-type: none"> - 16 years - median age was 66 years - 38.4% were women - 33.4% were diabetic - 41.5% had glomerulonephritis - median dialysis vintage was 6.5 years 	Acid-base parameters were measured with a blood gas analyzer in local laboratories and bicarbonate level was calculated using Henderson-Hasselbalch equation	<ul style="list-style-type: none"> - Mean pre-dialysis pH was 7.35 ± 0.05; mean bicarbonate was 20.5 ± 2.9 mEq/L. - The mean postdialysis pH was 7.44 ± 0.05; mean bicarbonate was 25.1 ± 2.8 mEq/L. - Higher predialysis pH was associated with higher all-cause mortality with adjusted HR of 1.18 per 0.1 high pH (95% CI 1.02 to 1.37).

Abbreviation: HD, hemodialysis; PD, peritoneal dialysis