Epidemiology of Acid-Base Derangements in CKD

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Acid-base disorders are 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.

Key Words: Renal insufficiency, Acidosis, Alkalosis, Epidemiology, Mortality

INTRODUCTION

Acid-base disorders are common in patients with 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 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 2 methods to measure bicarbonate.[1] The first is the measurement of serum total carbon dioxide (CO_2) 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 CO_2.

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[2] found that there was a difference in the bicarbonate concentrations between blood being measured at a local laboratory and shipped to a central laboratory. 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 CO_2, 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 CO_2 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 nondialytic 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 glomerular filtration rate (GFR) falls below ~40 mL/min per 1.73 m^2 and increases as GFR decreases.

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Onset and Prevalence of Low Bicarbonate in Adult CKD Cohorts

The NephroTest study in France included 1038 adults with CKD stages 2–5 and not on dialysis.[8] In this study, acidosis was defined as bicarbonate <22 mEq/L or on bicarbonate therapy. GFR was measured by ^{51}Cr-EDTA renal clearance[21] 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 1.73 m^2, 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 1.73 m^2 and increased as GFR decreased: as eGFR decreased from 60-90 to <20 mL/min per 1.73 m^2, 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 1.73 m^2, respectively), around the same level of GFR as the onset of hyperkalemia (at mGFR 39 mL/min per 1.73 m^2) and before the onset of hyperphosphatemia (at mGFR 37 mL/min per 1.73 m^2).

The CRIC study is a multicenter, observational study of 3939 participants aged 21-74 years with eGFR between 20 and 70 mL/min per 1.73 m^2.[22] The median serum bicarbonate level was 24 (interquartile range, 22-26) mEq/L.[9] The prevalence of low bicarbonate (defined as bicarbonate <22 mEq/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.[10] 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 1.73 m^2 by ^{125}I iothalamate clearance and diastolic blood pressure >95 mm Hg.[12] The mean serum bicarbonate was 25.1 mEq/L; 4.3% had bicarbonate <20 mEq/L, 35.5% had bicarbonate between 20 and 24.9 mEq/L, and 5.5% had bicarbonate ≥30 mEq/L.[13] Lower GFR was associated with lower bicarbonate: the mean GFR was 34 ± 13 mL/min per 1.73 m^2 for those with bicarbonate <20 mEq/L and 49 ± 12 mL/min per 1.73 m^2 for those with bicarbonate ≥30 mEq/L.[13]

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 estimated glomerular filtration rate.
- 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.

Prevalence of Low Bicarbonate in Non-CKD Cohorts

The prevalence of low bicarbonate was also examined in non-CKD cohorts.[5,16,17] The Health ABC study is a prospective study of well-functioning adults aged 70-79 years old.[5] There were 2287 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 1.73 m^2, and 12% had CKD (defined as eGFR <60 mL/min per 1.73 m^2).[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 PCO_2 <40 mm Hg) and 9.4% had metabolic and respiratory acidosis (defined as pH ≤ 7.41, bicarbonate<25.5 mEq/L, and PCO_2 ≥40 mm Hg).

NHANES is a nationally representative survey of the noninstitutionalized civilian population in the United States. In NHANES 1999-2004 participants, the mean serum bicarbonate was 24.9 mEq/L.[16] 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,[23,24] which was consistent with an age-induced impairment in renal net acid excretion.[25] 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% confidence interval [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.[16]

The prevalence of low bicarbonate was also examined in a single-center retrospective study of outpatients in the Bronx, NY, which included 5422 participants with eGFR ≥15 mL/min per 1.73 m^2 from January 2001 to June 2007.[17] 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 1.73 m^2. The mean bicarbonate for patients with eGFR 15-29 mL/min per 1.73 m^2 was 23 ± 4.3 mEq/L, compared with 24.8 ± 2.9 mEq/L for those