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Original Investigation

Serum Bicarbonate Concentrations and Kidney Disease Progression in Community-Living Elders: The Health, Aging, and Body Composition (Health ABC) Study

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Background: In populations with prevalent chronic kidney disease (CKD), lower serum bicarbonate levels are associated with more rapid CKD progression, but whether lower bicarbonate levels also are associated with risk of incident estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and CKD progression among community-living persons with predominantly preserved kidney function is unknown.

Study Design: Longitudinal observational cohort study.

Setting & Participants: Well-functioning community-living elders aged 70-79 years at inception.

Predictor: Serum bicarbonate level measured at the time of collection by arterialized venous blood sample using an arterial blood gas analyzer.

Outcomes: Change in eGFR over 7 years, and new eGFR < 60 mL/min/1.73 m^2 with a rate of loss of at least 1 mL/min/1.73 m^2 per year.

Measurements: Linear and logistic regressions were used to evaluate associations of baseline serum bicarbonate level with change in eGFR and incident eGFR < 60 mL/min/1.73 m^2.

Results: At baseline, mean eGFR was 84 ± 16 (SD) mL/min/1.73 m^2, and serum bicarbonate level was 25.2 ± 1.9 mmol/L. Compared with participants with higher bicarbonate concentrations (23.0-28.0 mmol/L), those with bicarbonate concentrations < 23 mmol/L ($n = 85$ [8%]) lost eGFR 0.55 (95% CI, 0.13-0.97) mL/min/1.73 m^2 per year faster in models adjusted for demographics, CKD risk factors, baseline eGFR, and urine albumin-creatinine ratio. Among the 989 (92%) participants with baseline eGFRs > 60 mL/min/1.73 m^2, 252 (25%) developed incident eGFRs < 60 mL/min/1.73 m^2 at follow-up. Adjusting for the same covariates, participants with bicarbonate concentrations < 23 mmol/L had nearly 2-fold greater odds of incident eGFRs < 60 mL/min/1.73 m^2 (OR, 1.72; 95% CI, 0.97-3.07) compared with those with higher bicarbonate concentrations.

Limitations: Only 2 measurements of kidney function separated by 7 years and loss to follow-up due to intervening mortality in this elderly population.

Conclusions: Lower serum bicarbonate concentrations are associated independently with decline in eGFR and incident eGFR < 60 mL/min/1.73 m^2 in community-living older persons. If confirmed, serum bicarbonate levels may give insight into kidney tubule health in persons with preserved eGFRs and suggest a possible new target for intervention to prevent CKD development.

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**A list of the Health ABC Study principal investigators and coordinators appears in the Acknowledgements.*

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The kidney plays a central role in maintenance of acid-base homeostasis. Proximal tubule and collecting duct cells are responsible for bicarbonate reclamation from the urinary filtrate and ammoniagenesis and jointly contribute to renal acid-base regulation. In advanced chronic kidney disease (CKD), the kidney's ability to regulate acid-base homeostasis is impaired, frequently resulting in metabolic acidosis.[1,2] The degree of acidosis may inform renal prognosis above and beyond established glomerular markers of kidney function, such as estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (ACR). In populations with prevalent CKD, lower serum bicarbonate concentrations have been associated with CKD progression, incident end-stage renal disease (ESRD), and mortality in prior studies.[3-9] In all but one of these,[4] the association remained statistically significant when adjusted for baseline eGFR or iothalamate GFR.

On average, overt acidosis is observed in relatively advanced CKD. However, there is considerable heterogeneity, and modest decrements in serum bicarbonate levels are observed in some individuals with mild reductions in kidney function.[10,11] Whether lower serum bicarbonate concentrations may precede the development of and identify the risk for incident eGFRs < 60 mL/min/1.73 m^2 is unknown. If so, then serum bicarbonate concentration, a readily available clinical test, may allow identification of individuals at higher risk for incident eGFRs < 60 mL/min/1.73 m^2. Acidosis also may contribute to progression of kidney disease[12] and alkali therapy may be a preventive strategy in populations at high risk for CKD progression. Thus, our objective was to determine the association of serum bicarbonate concentration with rate of change in eGFR and incident development of eGFR < 60 mL/min/1.73 m^2 in a cohort of community-living elderly persons with 7 years' follow-up in the Health, Aging, and Body Composition (Health ABC) Study. A priori, we hypothesized that lower serum bicarbonate concentrations would be associated with more rapid rate of change in eGFRs and incident development of eGFRs < 60 mL/min/1.73 m^2 independent of baseline eGFR, ACR, and CKD risk factors.

METHODS

Study Population

The Health ABC cohort enrolled 3,075 well-functioning men and women aged 70-79 years from 2 clinical sites in Memphis, TN, and Pittsburgh, PA, from April 1997 through June 1998. Participant eligibility required self-reported ability to walk a quarter mile, climb 10 steps, perform basic activities of daily living without difficulty, the absence of life-threatening illness, and plans to remain in the geographic area for at least 3 years. Participants underwent a baseline evaluation that included a medical history taken in the home and a clinic visit about 2 weeks later that included physiologic tests, physical activity assessment, and radiographic tests. Venous blood and spot urine specimens were obtained. Participants returned for repeat evaluation annually for the subsequent 5 years and biannually thereafter. The study was approved by the institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh. In addition, the present study was approved by the Institutional Review Board at the University of California, San Diego.

We evaluated participants who attended the year-3 Health ABC clinic evaluation, which served as the baseline visit for this study because it was the only visit at which serum bicarbonate concentrations were determined. Of the 2,921 participants who participated in the year-3 visit, we excluded 634 with missing serum bicarbonate measurements, 202 for missing baseline eGFR measurements at year 3, and 919 who either did not return to the year-10 visit or did not provide repeat measurement of eGFR. Of these 919 participants, 467 had died in the intervening period. Of the remaining participants, we excluded 93 due to missing covariate information, resulting in a final analytic sample size of 1,073 individuals for this analysis.

Measurements

Serum Bicarbonate

Serum bicarbonate level was determined through analysis of arterialized venous blood gas samples obtained from a cannulated hand or wrist vein subsequently placed in a warmer set to 42°C and warmed for a minimum of 15 minutes prior to blood sampling. Samples were obtained after at least 2 hours of fasting and analyzed on site on the day of phlebotomy. Each sample was measured for pH and P_{CO_2} on an ABL5 blood gas analyzer (Radiometer). pH and P_{CO_2} were analyzed potentiometrically using a glass membrane and glass/silver/silver chloride electrode, respectively. Serum bicarbonate level was calculated using the Henderson-Hasselbalch equation. Each sample was measured 3 times and results were averaged.

Kidney Function

Kidney function was determined using identical methods at the year-3 and year-10 visits. There were no assessments of kidney function in the intervening years. Blood samples were obtained after an overnight fast. Creatinine was measured in a central laboratory using an Vitros 950 Analyzer (Johnson & Johnson) using a colorimetric assay and were calibrated to isotope-dilution mass spectrometry–traceable standards.[13] Cystatin C was analyzed on a BNII nephelometer (Dade Behring Inc) using a particle-enhanced immunonephelometric assay.[14] Demographics, creatinine level, and cystatin C level were combined to estimate GFR using the CKD-EPI (CKD Epidemiology Collaboration) creatinine−cystatin C equation.[15]

Urine ACR measurements were not available at the year-3 examination; however, they were measured at baseline. Thus, we used the baseline measurements and carried them forward to the year-3 examination. Urine albumin was measured using a particle-enhanced turbidimetric inhibition immunoassay allowing for direct albumin quantification (Siemens). Urine creatinine was measured by a modified Jaffé method on a clinical chemistry analyzer (Siemens).[16] Intra- and interassay coefficients of variation were 2% and 6% for albumin and 0.6% and 1% for creatinine, respectively.