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

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Contributions: Research idea and study design: data acquisition: MJS, MGS; data analysis/interpretation: LG, THD, LF, DEF, KVP, RHY, TBH, SBK, ABN, MJS, MGS, JHI; statistical analysis: LG, JHI. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LG and JHI take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary Material

Table S1: Baseline characteristics of participants with and without available data for analysis.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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Abstract

Background—In populations with prevalent chronic kidney disease (CKD), lower serum bicarbonate is associated with more rapid CKD progression, but whether lower bicarbonate is also associated with risk of incident estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 and 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 measured at the time of collection by arterialized venous blood sample using an arterial blood gas analyzer.

Outcomes—Change in eGFR, and new eGFR < 60 ml/min/1.73m^2 and loss of ≥1 ml/min/1.73m^2 per year at follow-up.

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

Results—At baseline, mean eGFR was 84±16 (SD) mL/min/1.73m^2, and serum bicarbonate was 25.2±1.9 mmol/L. Compared to 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/1.73m^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 eGFR>60 mL/min/1.73m^2, 252 (25%) developed incident eGFR <60 mL/min/1.73m^2 at follow-up. Adjusting for the same covariates, participants with bicarbonate concentrations < 23 mmol/L had nearly 2-fold greater odds of incident eGFR <60 mL/min/1.73m^2 (OR, 1.72; 95% CI, 0.97–3.07) compared to those with higher bicarbonate concentrations.

Limitations—Only two measurements of kidney function separated by seven years and loss to follow up due to intervening mortality in this elderly population.

Conclusions—Lower serum bicarbonate concentrations are independently associated with decline in eGFR and incident eGFR <60 mL/min/1.73m^2 in community-living older persons. If confirmed, serum bicarbonate levels may give insights into kidney tubule health among persons

with preserved eGFR and suggest a possible new target for intervention to prevent CKD development.

Keywords

Acidosis; alkalosis; kidney disease; aging; risk factor; renal disease; disease progression; kidney disease trajectory

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 CKD, the kidney's ability to regulate acid-base homeostasis is impaired, frequently resulting in metabolic acidosis.[1, 2] The degree of acidosis may informrenal prognosis above and beyond established glomerular markers of kidney function such as estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (ACR). Among populations with prevalent CKD, lower serum bicarbonate concentrations have been associated with CKD progression, incident 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 are observed in some individuals with mild reductions in kidney function.[10, 11] Whether lower serum bicarbonate concentrations may precede development of—and identify risk for—incident eGFR <60 mL/min/1.73m^2 is unknown. If so, then serum bicarbonate concentrations, a readily available clinical test, may allow identification of individuals at higher risk for incident eGFR <60 mL/min/1.73m^2. Acidosis may also 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 concentrations with rate of change in eGFR and incident development of eGFR<60 mL/min/1.73m^2 among a cohort of community-living elderly persons with seven 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 eGFR and incident development of eGFR <60 mL/min/1.73m^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 two clinical sites in Memphis, Tennessee and Pittsburgh, Pennsylvania 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 two weeks later that included physiological 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 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 as it was the only visit at which serum bicarbonate concentrations were determined. Among 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. Among 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 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 Pco2 on an ABL5 blood gas analyzer (Radiometer, Copenhagen, Denmark). The pH and Pco2 were analyzed potentiometrically using a glass membrane and glass/silver/silver chloride electrode, respectively. Serum bicarbonate 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 Ektachem 700 Analyzer (Vitols 950 Analyzer, Johnson & Johnson, New Brunswick, NJ) using a colorimetric assay and were calibrated to IDMS-traceable standards.[13] Cystatin C was analyzed on a BNII nephelometer (Dade Behring Inc, Deerfield, IL) using a particle-enhanced immunonephelometric assay.[14] Demographics, creatinine, and cystatin C were combined to estimate glomerular filtration rate 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, Newark, DE). Urine creatinine was measured by a modified Jaffe method on a clinical chemistry analyzer (Siemens, Newark, DE).[16] Intra-assay and interassay coefficients of variation (CVs) were 2% and 6% for albumin and 0.6% and 1% for creatinine, respectively.

Other Measurements—Age, sex, race, and smoking status were determined by self-report. Height was measured to the nearest millimeter by using a Harpenden stadiometer (Holtain Ltd, Crosswell, Wales, UK) without shoes. Weight was measured to the nearest 0.1 kg using a balance beam scale with the participant wearing lightweight clothing.[17] Body mass index was calculated in kg/m^2. Diabetes was defined by use of hypoglycemic agents, self-reported history, fasting plasma glucose ≥ 126 mg/dl, or a 2-hour oral glucose tolerance test ≥ 200 mg/dl. Systolic and diastolic blood pressures were obtained by trained and certified clinical staff from the right arm using a conventional mercury sphygmomanometer with the participant in a seated position. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications and a self-reported physician's diagnosis of hypertension. Obstructive lung disease was determined based on spirometry at the year-1 visit using a horizontal dry rolling seal spirometer (SensorMedics Corporation, Yorba Linda, CA).[18] Participants' medications brought to the study visits were recorded by study personnel and categorized using the Iowa Drug Information System into major therapeutic groups based on the ingredients in the medications.

Statistical Analysis—We began by calculating annualized change in eGFR as the difference between the year-3 and year-10 eGFR measurements and dividing by the number of intervening years to provide annual change in eGFR in $ml/min/1.73m^2$ per year. To explore the functional form of the relationship of interest, we used linear regression with change in eGFR as the dependent variable, and evaluated bicarbonate categories (each 1 mmol/L defining a category), age, sex, race, and baseline eGFR as independent variables. This exploratory analysis suggested that participants with bicarbonate concentrations < 23.0 and > 28.0 mmol/L had more rapid change in eGFR than individuals within the intermediate categories. Thus, the intermediate categories (5 categories within 23.0–28.0 mmol/L) were collapsed and three bicarbonate categories (< 23.0, 23.0–28.0, and > 28.0 mmol/L) were used in subsequent analysis. The 23.0–28.0 mmol/L bicarbonate category was set as the referent.

We compared the distribution of demographics, baseline kidney function, and kidney disease risk factors across the three bicarbonate categories using ANOVA for continuous variables (or Kruskal-Wallis for skewed variables), and the chi square test (or Fisher's exact test) for categorical variables, as appropriate. Next, we used linear regression to determine the association of baseline bicarbonate category with change in eGFR. An initial model adjusted for age, sex, race, clinical site, baseline eGFR, and ACR. A subsequent model additionally adjusted for diabetes (yes/no), systolic blood pressure (continuous), obstructive lung disease (yes/no), smoking (current, former, never), renin-angiotensin-aldosterone system (RAAS) inhibitor use (yes/no), and diuretic use (yes/no). Next, we defined a binary outcome of "rapid kidney function decline", defined as an annual decline in eGFR ≥ 3 $ml/min/1.73m^2$ per year. This definition has been used in prior studies in older adults and is known to be associated with adverse outcomes.[19] We used logistic regression to evaluate the association of baseline bicarbonate categories with rapid kidney function decline adjusting for the same series of covariates as for the continuous change in eGFR outcome. Last, to determine whether baseline bicarbonate concentrations are associated with incident

development of eGFR <60 mL/min/1.73m^2, we excluded individuals with eGFR <60 ml/min/1.73m^2 at baseline. Among the remaining participants, we defined incident eGFR <60 ml/min/1.73m^2 as an eGFR < 60 ml/min/1.73m^2 and a decline of at least 7 ml/min/1.73m^2 (corresponding to a loss of at least 1 ml/min/1.73m^2 per year) at the follow-up examination. We evaluated the association of baseline bicarbonate categories with the incident eGFR<60 mL/min/1.73 m^2 outcome using logistic regression using the aforementioned series of adjusted models.

All analyses were conducted using Stata SE version 11 (StataCorp LP, College Station, TX). P-values < 0.05 were considered statistically significant for all analyses.

RESULTS

By necessity, we excluded individuals who presented to baseline examination but ultimately did not have sufficient data for analysis due to death or missing follow-up kidney function data. Compared to those with available data, those without were older, more frequently black, more likely to be current smokers, had higher ACR, had more diabetes and obstructive lung disease, and had higher systolic blood pressures. Other variables including baseline eGFR were similar (Table S1, available as online supplementary material).

Among the 1,073 study participants included in this analysis, the mean age was 75.2 ± 2.8 (standard deviation) years, 52% were women, and 33% were black. The mean baseline eGFR was 84.2 ± 15.8 ml/min/1.73m^2, and 7.8% had a baseline eGFR <60 ml/min/1.73m^2. The mean rate of change in eGFR during follow-up was −2.1 ± 2.0 ml/min/1.73m^2 per year. Compared to participants with bicarbonate levels of 23–28 mmol/L, those with lower bicarbonate concentrations were more likely to be white, male, to use RAAS inhibitors and to smoke, while they were less likely to use diuretics or have obstructive lung disease (Table 1). Established CKD risk factors including age, diabetes, and blood pressure did not differ significantly across bicarbonate categories. Baseline eGFR was lower and ACR was higher in the low bicarbonate category.

In models adjusted for age, sex, race, and baseline eGFR, the relationship of serum bicarbonate with annual change in eGFR was U-shaped; both persons with bicarbonate < 23.0 and > 28.0 mmol/L had more rapid longitudinal decline in eGFR than those in intermediate categories (Figure 1). When the 23.0–28.0 mmol/L bicarbonate categories were collapsed and set as the referent, participants with lower bicarbonate concentrations lost eGFR approximately 0.5 ml/min/1.73m^2 per year faster during follow-up in unadjusted analysis (Table 2). This association was essentially unaltered when adjusted for age, gender, race, clinical site, baseline eGFR, and ACR, and in the final model with additional adjustment for diabetes, systolic blood pressure, obstructive lung disease, smoking, RAAS inhibitor, and diuretic use. Compared to persons in the serum bicarbonate 23.0–28.0 mmol/L reference category, those with higher bicarbonate concentrations had eGFR loss approximately 0.3 ml/min/1.73m^2 per year faster, but this association was not statistically significant across the sequence of models.

Next, we evaluated the association of baseline serum bicarbonate concentration with a binary outcome of rapid kidney function decline, defined as eGFR loss greater than 3 ml/min/1.73m^2 per year (Table 3). Compared to participants with bicarbonate values in the 23.0–28.0 mmol/L category, those with lower bicarbonate had approximately 50%–60% greater odds of rapid kidney function decline across the sequence of models, although this association failed to reach statistical significance in any model.

We then excluded the 84 individuals with eGFR < 60 ml/min/1.73m^2 at baseline and examined the association of serum bicarbonate concentrations with incident development of eGFR <60 mL/min/1.73m^2 during follow-up among the remaining 989 participants. Among these, 252 (25%) developed incident eGFR <60 mL/min/1.73m^2 at follow-up 7 years later. Compared to participants with bicarbonate concentrations of 23.0–28.0 mmol/L, those with lower serum bicarbonate were at approximately two-fold greater odds for incident eGFR <60 mL/min/1.73m^2 in unadjusted models (Table 4). The association was slightly attenuated in the final model but remained significantly associated with a 1.8-fold greater odds of incident eGFR <60 mL/min/1.73m^2.

DISCUSSION

Among well-functioning community-living elders predominantly with preserved kidney function at baseline, we found that lower serum bicarbonate concentrations were associated with more rapid loss of kidney function over time. Within the subset of persons with eGFR >60 mL/min/1.73m^2 at baseline, lower serum bicarbonate concentrations were associated with development of incident eGFR <60 mL/min/1.73m^2 during follow-up. These associations became apparent in individuals with baseline serum bicarbonate concentrations < 23 mmol/L, and were independent of baseline eGFR, urine ACR, demographics, and established CKD risk factors.

Kidney tubule cells are integral for maintenance of acid-base homeostasis, and metabolic acidosis is well established as a hallmark of advanced CKD. Several prior studies conducted in populations with established CKD have demonstrated that lower serum bicarbonate concentrations are associated with more rapid progression of CKD, incident development of ESRD, and all-cause mortality.[3–9] Some have shown that lower bicarbonate concentrations are associated with ESRD independent of iothalamate-measured GFR.[6] Small clinical trials suggest that treating metabolic acidosis with oral bicarbonate can slow progression of CKD.[20–22] Collectively, these studies suggest that the associations of lower serum bicarbonate with CKD progression may not merely reflect residual confounding by GFR. However, most prior studies evaluated populations with prevalent CKD.[3–9] Thus, the contribution of this study is in demonstrating that lower serum bicarbonate concentrations predict CKD progression and, for the first time, incident development of eGFR <60 mL/min/1.73m^2 in individuals with normal or near-normal GFR living in the general population.

Prior studies have demonstrated a fairly linear relationship between CKD stage and the prevalence of metabolic acidosis; approximately 5% of patients with CKD stages 2–3 have a serum bicarbonate concentration < 22 mmol/L whereas the prevalence increases to approximately 18% in CKD stage 4.[10, 11] While metabolic acidosis and lower eGFR are

linked processes, these studies also highlight marked inter-individual heterogeneity; despite severe CKD, the majority of patients with CKD stage 4 maintain serum bicarbonate concentrations ≥ 23 mmol/L. Alternatively, and shown again in our analysis, some individuals with much less severe CKD may have low serum bicarbonate concentrations. However, whether lower serum bicarbonate serves simply as a marker of kidney tubule dysfunction or may be causally linked to CKD progression is uncertain.

Metabolic acidosis in CKD reflects a decrease in total renal ammoniagenesis resulting from a diminished number of functioning tubules. At the same time, the remaining functioning tubules can increase the single nephron ammonia generation in an effort to compensate for the diminished functioning tubule number.[23] In animal models, an increase in ammoniagenesis leads to complement activation and tubulointerstitial injury.[24] Treatment with bicarbonate is believed to decrease ammoniagenesis and potentially decrease associated kidney injury. Indeed, a clinical trial in a CKD population suggested that alkali therapy may slow CKD progression over time.[21] Furthermore, at least one small clinical trial in a population with relatively preserved eGFR also demonstrated a trend toward preservation of kidney function.[20] Our results support the intriguing possibility that initiation of alkali therapy in persons with normal or near-normal kidney function may decrease CKD incidence. This hypothesis will require testing in future intervention studies.

A second possibility is that acidosis is not causal but is rather a marker of tubular dysfunction. It is well established that the degree of renal tubule atrophy and tubulointerstitial fibrosis on kidney biopsy are strong risk markers for progression of CKD,[25–27] but this fibrosis is not well captured by standard clinical measures of kidney function including eGFR, iothalamate GFR, and urine ACR. For example, a recent study evaluated the correlates of nephrosclerosis in kidney biopsy specimens among 1,203 healthy kidney donor candidates. The authors found that nephrosclerosis ranged from 3% in the 20- to 29-year age group to 73% in those aged 70–79 years. However, the nephrosclerosis on biopsy had no relationship with iothalamate-measured GFR after adjusting for age.[28] Because the kidney tubule is responsible for acid-base regulation, we hypothesize that individuals with lower serum bicarbonate concentrations in our study may have had more severe renal tubulointerstitial disease, and thus associations with longitudinal decline in kidney function may be because serum bicarbonate is providing information on non-glomerular aspects of renal tubulointerstitial disease. Future studies with concurrent kidney biopsy data will be required to investigate this hypothesis.

Recent findings suggest that non-glomerular markers of kidney tubule dysfunction and injury may inform CKD prognosis independent of eGFR and urine ACR. For example, several urine markers of kidney tubule injury such as kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have been studied primarily within the context of hospitalized acute kidney injury. Recently, several studies have demonstrated that these markers may inform prognosis in community-living individuals without acute kidney injury. Peralta and colleagues demonstrated that higher urine KIM-1 concentrations were associated with incident development of CKD and more rapid loss of eGFR independent of baseline eGFR or ACR in the Multi-Ethnic Study of Atherosclerosis (MESA).[29] Bahvsar and colleagues made similar observations evaluating urine NGAL concentrations in the

ARIC (Atherosclerosis Risk in Communities) study.[30] Serum bicarbonate could be another readily available marker of tubular function providing prognosis independent of eGFR and albuminuria.

A third possibility is that lower serum bicarbonate concentrations may reflect non-renal processes. For example, studies in patients with advanced CKD demonstrate that intake of diets high in fruits and vegetables may increase serum bicarbonate concentrations.[31] Conversely, high protein consumption will reduce serum bicarbonate concentrations. This may have direct deleterious effects on kidney function through non–bicarbonate-mediated mechanisms. If similar results were to generalize to healthy community-living older individuals without advanced CKD, then low serum bicarbonate may reflect differences in diet intake instead of tubulointerstitial kidney disease. Differences in dietary choices, in turn, may be linked with other lifestyle factors and health habits. However, if our results are confirmed, low serum bicarbonate may still serve as a useful marker of risk of CKD progression even if not causally related.

In a companion paper appearing in this issue of *AJKD*, the association of serum bicarbonate concentrations and decline in kidney function and incident CKD was evaluated in the MESA cohort.[32] The authors also found associations of lower serum bicarbonate with CKD progression and incident CKD. This confirmation is important considering differences between methods and study populations between the two studies. The MESA cohort was younger (mean age, 61 vs. years) and excluded participants with cardiovascular disease. The mean serum bicarbonate level was also lower in MESA (23 vs. 25 mmol/L). Bicarbonate was measured in serum samples from long-term storage that had been shipped to the central laboratory in MESA, whereas it was measured on an arterial blood gas machine at the point of care in Health ABC. Thus, the lower mean bicarbonate level in MESA may reflect loss of carbon dioxide through specimen processing.[33] Nonetheless, the associations with outcomes were similar. Finally, the Health ABC cohort includes pulmonary function data and demonstrates that the association remains robust even after adjusting for obstructive lung disease.

Strengths of this study include the availability of creatinine and cystatin C measurements at both baseline and follow-up 7 years later, as well as ACR and serum bicarbonate concentrations at baseline in a relatively large sample of community-living elders. Participants represented both genders, white and black race, and were recruited from the community in multiple sites, increasing generalizability. Serum bicarbonate concentrations were measured in triplicate and averaged, decreasing measurement error. Information on potential confounders including demographics, medication use, and lung disease, were available for adjustment. The study also has important limitations. Kidney function measures were available only at baseline and again 7 years later without intervening measurements. Repeat measurement of eGFR was required to define a trajectory of change in eGFR and incident eGFR <60 mL/min/1.73m^2. Because we evaluated an older cohort, some individuals died prior to repeat eGFR assessment. Those who remained alive but did not return to provide repeat eGFR measurement were likely older and of poorer health status than those retained in the analysis. The companion paper had more frequent assessment of kidney function over time and confirms our findings.[32] Study participants were all aged 70

years or older at baseline and of white or black race. Whether results generalize to younger persons or other races/ethnicities is uncertain. We lacked gold standard measures of GFR, and residual confounding by GFR cannot be excluded. Prior intervention trials suggest causal relationships of metabolic acidosis with CKD progression.[20–22] This observational study cannot assess causality. Nonetheless, we believe our findings may assist in assessing CKD prognosis above and beyond the baseline eGFR and ACR irrespective of whether bicarbonate serves as a marker or is causally related to CKD progression.

In conclusion, lower serum bicarbonate concentrations are associated with more rapid loss of eGFR over time and incident development of eGFR <60 mL/min/1.73m^2 in well-functioning community-living elders. These relationships are independent of the baseline eGFR and urine ACR level. Future studies with concurrent availability of serum bicarbonate concentrations and kidney biopsy data are required to determine whether lower serum bicarbonate concentrations may mark the presence or severity of tubulointerstitial atrophy and fibrosis, and whether serum bicarbonate concentrations may improve CKD risk prognostication by marking non-glomerular aspects of kidney damage. If our findings are confirmed, future intervention trials would be warranted to assess whether alkali therapy may prevent incident eGFR<60 mL/min/1.73m^2 development in high risk individuals with preserved kidney function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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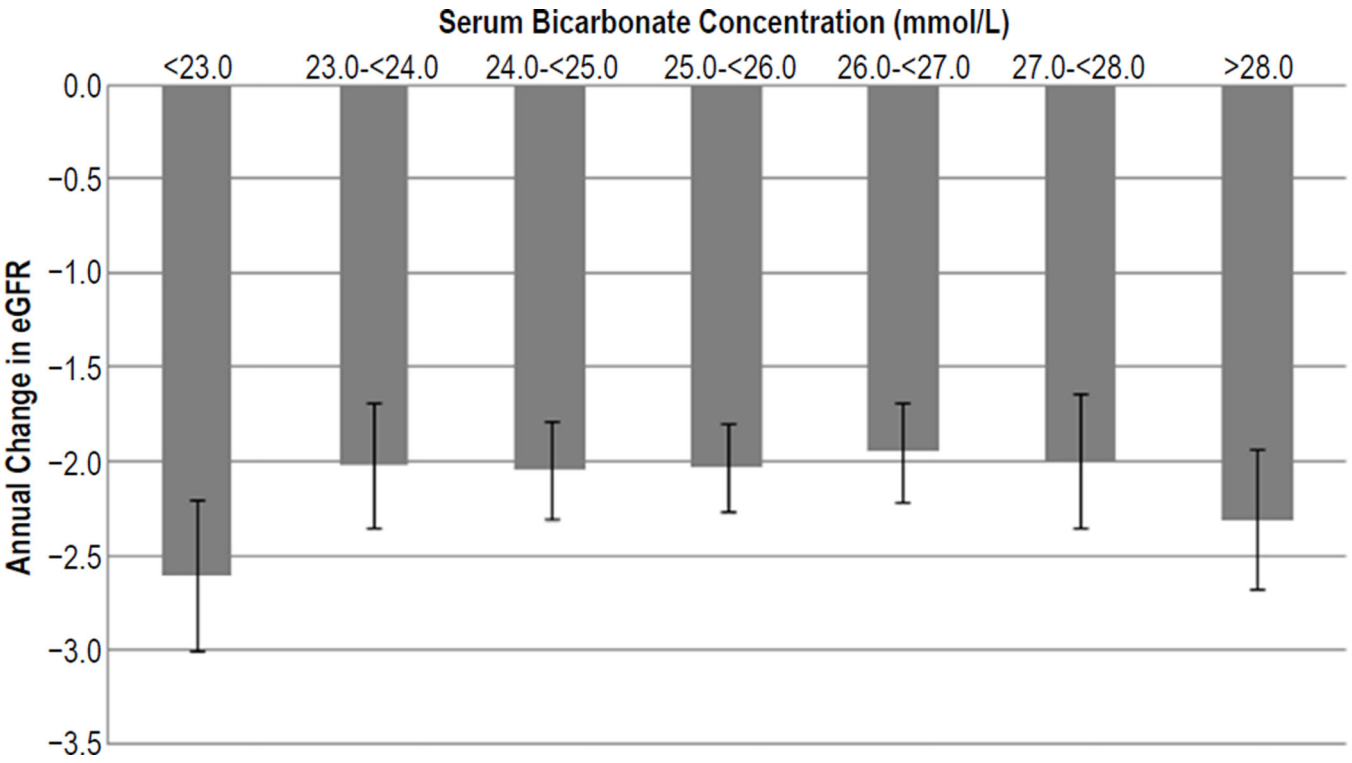

Figure 1. Association of Serum Bicarbonate Concentrations with Annual Change in eGFR

Figure shows the adjusted association of baseline serum bicarbonate concentration with annual change in eGFR in community-living elders. The model is adjusted for age, gender, race, and baseline eGFR. The X-axis shows serum bicarbonate categories. The Y-axis shows the annualized rate of change in eGFR. Error bars reflect 95% confidence intervals.

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Table 1

Baseline characteristics by serum bicarbonate categories

	Total	< 23.0 mmol/L	23.0–28.0 mmol/L	>28.0 mmol/L	p-value
No. of participants	1073	85 (8%)	887 (83%)	101 (9%)	
Serum Bicarbonate (mmol/L)	25.2 (1.9)	21.4 (1)	25.1 (1.2)	28.8 (1.0)	
Age (y)	75.2 (2.8)	75.2 (3)	75.2 (2.8)	75.6 (2.8)	0.4
Black	358 (33.4)	25 (29)	286 (32.2)	47 (46.5)	0.01
Female sex	559 (52.1)	41 (48)	452 (51.0)	66 (65.4)	0.02
eGFR (ml/min/1.73m^2)	84 (16)	76 (19)	84 (15)	86 (16)	<0.001
eGFR < 60 ml/min/1.73m^2	84 (7.8)	16 (19)	62 (7.0)	6 (6.0)	< 0.001
ACR (mg/g)	7.2 [4.0–15.2]	10.2 [5.3–27.0]	7.1 [3.9–14.8]	6.9 [4.8–14.7]	0.02
BMI (kg/m^2)	27.4 (4.7)	26.8 (4)	27.5 (4.6)	26.7 (5.2)	0.1
Diabetes	188 (17.5)	20 (24)	148 (16.7)	20 (19.8)	0.2
Systolic BP (mmHg)	134.1 (19.8)	130.8 (18)	134.3 (19.9)	134.9 (19.9)	0.3
Diastolic BP (mmHg)	71.2 (10.4)	71.6 (13)	71.2 (10.2)	70.9 (9.6)	0.9
Obstructive lung disease	43 (4.0)	0 (0)	35 (4.0)	8 (7.9)	0.02
Smoking history					0.03
Never	514 (47.9)	34 (40)	421 (47.5)	59 (58.4)	
Former	503 (46.9)	42 (49)	423 (47.7)	38 (37.6)	
Current	56 (5.2)	9 (11)	43 (4.9)	4 (4.0)	
RAAS inhibitor use	242 (22.6)	27 (32)	197 (22.2)	18 (17.8)	0.06
Diuretic use	284 (26.5)	13 (15)	212 (23.9)	59 (58.4)	<0.001
β blocker use	175 (16.3)	9 (11)	147 (16.6)	19 (18.8)	0.3
pH	7.41 (0.03)	7.40 (0.04)	7.41 (0.02)	7.41 (0.03)	0.002

Note: Values for categorical variables are given as number or number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].

eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; BMI, body mass index; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system

Table 2

Association of Baseline Bicarbonate Category with Annual Change in eGFR

	< 23.0 mmol/L	23.0–28.0 mmol/L	> 28.0 mmol/L
No. of participants (%)	85 (8%)	887 (83%)	101 (9%)
Annual change in eGFR			
Unadjusted	−0.436 (−0.870 to −0.003); 0.05	(referent group)	−0.337 (−0.735 to −0.067); 0.1
Model 1*	−0.552 (−0.974 to −0.131); 0.01	(referent group)	−0.270 (−0.658 to 0.118); 0.2
Model 2**	−0.543 (−0.965 to −0.121); 0.01	(referent group)	−0.245 (−0.640 to 0.150); 0.2

Note: Annual change in eGFR is expressed as mL/min/1.73 m^2 per year. Unless otherwise indicated, values are given as Δ (95% confidence interval); p-value.

eGFR, estimated glomerular filtration rate

* Adjusted for age, race, gender, clinical site, baseline eGFR, urine albumin-creatinine ratio.

** Adjusted for Model 1 variables plus diabetes, systolic blood pressure, obstructive lung disease, smoking, renin-angiotensin-aldosterone system inhibitor use, and diuretic use.

Table 3

Association of Baseline Bicarbonate Category with Rapid Kidney Function Loss

	< 23.0 mmol/L	23.0–28.0 mmol/L	> 28.0 mmol/L
No. of participants (%)	85 (8%)	887 (83%)	101 (9%)
OR for Rapid Kidney Function Loss			
Unadjusted	1.53 (0.96 −2.45); 0.08	1.00 (reference)	1.49 (0.96 −2.30); 0.07
Model 1*	1.60 (0.98 −2.61); 0.06	1.00 (reference)	1.41 (0.90 −2.21); 0.1
Model 2**	1.57 (0.94 −2.61); 0.08	1.00 (reference)	1.31 (0.81 −2.10); 0.3

Note: Rapid kidney function loss is defined as >3 mL/min/1.73 m^2 per year. Unless otherwise indicated, values are given as odds ratio (95% confidence interval); p-value.

eGFR, estimated glomerular filtration rate

* Adjusted for age, race, gender, clinical site, baseline eGFR, urine albumin-creatinine ratio.

** Adjusted for Model 1 variables plus diabetes, systolic blood pressure, obstructive lung disease, smoking, renin-angiotensin-aldosterone system inhibitor use, and diuretic use.

Table 4

Association of Baseline Bicarbonate Categories with Incident eGFR<60 mL/min/1.73m^2

	< 23.0 mmol/L	23.0–28.0 mmol/L	> 28.0 mmol/L
No. of participants (%)	69 (7%)	825 (83%)	95 (10%)
OR for incident eGFR < 60			
Unadjusted	2.05 (1.23 −3.41); 0.006	1.00 (reference)	1.33 (0.83 −2.13); 0.2
Model 1*	1.72 (0.97 −3.07); 0.06	1.00 (reference)	1.32 (0.78 −2.24); 0.3
Model 2**	1.81 (1.01 −3.27); 0.05	1.00 (reference)	1.10 (0.63 −1.93); 0.7

Note: Unless otherwise indicated, values are given as odds ratio (95% confidence interval); p-value.

eGFR, estimated glomerular filtration rate

*Adjusted for age, race, gender, clinical site, baseline eGFR, urine albumin/creatinine ratio

**Adjusted for Model 1 variables plus diabetes, systolic blood pressure, obstructive lung disease, smoking, renin-angiotensin-aldosterone system inhibitor use, and diuretic use.