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Original Investigation

Low Serum Bicarbonate and Kidney Function Decline: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: Among populations with established chronic kidney disease (CKD), metabolic acidosis is associated with more rapid progression of kidney disease. The association of serum bicarbonate concentrations with early declines in kidney function is less clear.

Study Design: Retrospective cohort study.

Setting & Participants: 5,810 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) with a baseline estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2 using the CKD-EPI (CKD Epidemiology Collaboration) creatinine−cystatin C equation.

Predictors: Serum bicarbonate concentrations.

Outcomes: Rapid kidney function decline (eGFR decline > 5% per year) and incident reduced eGFR (eGFR < 60 mL/min/1.73 m^2 with minimum rate of eGFR loss of 1 mL/min/1.73 m^2 per year).

Results: Average bicarbonate concentration was 23.2 ± 1.8 mEq/L. 1,730 (33%) participants had rapid kidney function decline, and 487 had incident reduced eGFR during follow-up. Each 1-SD lower baseline bicarbonate concentration was associated with 12% higher adjusted odds of rapid kidney function decline (95% CI, 6%-20%) and higher risk of incident reduced eGFR (adjusted incidence rate ratio, 1.11; 95% CI, 1.03-1.20) in models adjusting for demographics, baseline eGFR, albuminuria, and CKD risk factors. The OR for the associations of bicarbonate level < 21 mEq/L relative to 23-24 mEq/L was 1.35 (95% CI, 1.05-1.73) for rapid kidney function decline, and the incidence rate ratio was 1.16 (95% CI, 0.83-1.62) for incident reduced eGFR.

Limitations: Cause of metabolic acidosis cannot be determined in this study.

Conclusions: Lower serum bicarbonate concentrations are associated independently with rapid kidney function decline independent of eGFR or albuminuria in community-living persons with baseline eGFR > 60 mL/min/1.73 m^2. If confirmed, our findings suggest that metabolic acidosis may indicate either early kidney disease that is not captured by eGFR or albuminuria or may have a causal role in the development of eGFR < 60 mL/min/1.73 m^2.

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Patients with chronic kidney disease (CKD) often develop metabolic acidosis, which is reflected by a low serum bicarbonate level.[1,2] Acid-base regulation in the kidneys is maintained by renal tubular cells; thus, the pathogenesis of metabolic acidosis in patients with CKD is thought to be due in part to tubular dysfunction, causing decreased bicarbonate production in the kidney tubules.[2] In addition to marking tubule disease, metabolic acidosis might have a role in the pathogenesis of CKD by causing tubular damage by a compensatory increase in tubular

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ammonia production, resulting in complement activation and inflammation.[3] Metabolic acidosis also is associated with mortality risk.[4]

In the setting of established CKD, most have found that metabolic acidosis is associated with adverse kidney and mortality outcomes, including CKD progression, rapid kidney function decline, faster progression to end-stage renal disease, and all-cause mortality.[4-9] Additionally, in one hospital-based study, lower serum bicarbonate concentrations were associated with increased risk of kidney disease progression in individuals with relatively preserved kidney function (estimated glomerular filtration rate [eGFR] > 60 mL/min/1.73 m^2).[7]

The relationship between acid-base status and incidence of CKD has not been fully characterized. Therefore, we evaluated associations of serum bicarbonate concentrations with longitudinal change in kidney function in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. For kidney disease outcomes, we focused on individuals with eGFRs > 60 mL/min/1.73 m^2 to determine whether bicarbonate concentrations may predict incident reduced eGFR development and rapid declines in kidney function.

METHODS

Study Overview

MESA was designed to understand subclinical cardiovascular disease (CVD) and its progression to clinical CVD in a multiethnic cohort selected for the absence of clinical CVD at baseline. Details for recruitment and design have been published previously.[10] Briefly, from July 2000 through July 2002 (examination 1), MESA recruited 6,814 men and women aged 45-84 years who were free of clinical CVD and who self-identified as white, black, Hispanic, or Chinese. Participants were recruited from Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. After the baseline examination, participants returned for 3 additional visits: July 2002 to January 2004 (examination 2), January 2004 to July 2005 (examination 3), and July 2005 to July 2007 (examination 4). Repeat measurements of kidney function were obtained at examinations 3 and 4. The relevant institutional review boards at all participating centers approved the study.

Measurement of Serum Bicarbonate and Kidney Function

Total serum carbon dioxide (serum bicarbonate) was measured at MESA examination 1 in all participants at baseline using a pH rate-of-change method on a Beckman DxC automated clinical chemistry analyzer. Interassay imprecision across the study was determined to be 2.98%-3.19% (N = 84). Kidney function was assessed by creatinine and cystatin C concentrations. All assays were performed in frozen serum specimens that were stored at −70°C. Serum creatinine was measured by rate reflectance spectrophotometry using thin-film adaptation of the creatinine amidinohydrolase method on the VITROS analyzer (Johnson & Johnson Clinical Diagnostics Inc) at the Collaborative Studies Clinical Laboratory at Fairview−University of Minnesota Medical Center (Minneapolis, MN) and calibrated to the Cleveland Clinic. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Siemens) with a nephelometer (BNII; Siemens) and

corrected for assay drift. We used the CKD-EPI (CKD Epidemiology Collaboration) creatinine−cystatin C equation to estimate GFR.[11]

Outcomes

The primary outcomes were incident reduced eGFR and rapid kidney function decline. Incident reduced eGFR was defined as reaching eGFR < 60 mL/min/1.73 m^2 with a minimum rate of eGFR loss of 1 mL/min/1.73 m^2 per year. Rapid progression of kidney function decline was defined as a decline in eGFR > 5% per year, a rate of decline in eGFR that has been used in prior MESA reports.[12,13]

Candidate Covariates

Age, sex, race, income, education, past or current smoking, and alcohol use were ascertained by questionnaire at the baseline visit. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index was calculated as weight in kilograms divided by height in meters squared. Fasting blood was collected and stored at −70°C until needed for the appropriate assays, including high-density lipoprotein cholesterol, triglycerides, glucose, and C-reactive protein. Low-density lipoprotein cholesterol level was calculated using the Friedewald equation.[14] Diabetes was defined as use of insulin or oral hypoglycemic agents or fasting glucose level ≥ 126 mg/dL. At the baseline examination, usual dietary intake over the previous year was assessed with a modified block-style 120-item Block food frequency questionnaire (FFQ), which was patterned after the FFQ used in the Insulin Resistance Atherosclerosis Study.[15,16] Participants reported the size and frequency of consumption of specific beverages and foods, and these data were converted to approximate daily intake of nutrients using the Nutrition Data Systems for Research database (Nutrition Coordinating Center, University of Minnesota).[17] Dietary acid load was defined by the ratio of daily protein to potassium intake.[18] In order to accommodate the MESA population, the FFQ was modified to include Chinese foods and culinary practices.[19] Smoking was dichotomized as ever versus never smoking. Hypertension was defined as use of antihypertensive medications, self-report of hypertension, or blood pressure > 140/90 mm Hg at the baseline visit. Three blood pressure measurements were obtained 5 minutes apart in the seated position. The mean of the second 2 measurements was used for analysis. Diuretic use was assessed during clinic visits.

Statistical Analysis

Baseline characteristics of participants were compared across prespecified categories of bicarbonate concentration (<21, 21-22, 23-24, 25-26, and >27 mEq/L), based on the observed distribution of serum bicarbonate concentrations in MESA, using analysis of variance or χ^2 tests as appropriate. We further evaluated these associations of characteristics with baseline bicarbonate concentrations by conducting multivariable linear regression with bicarbonate level as the dependent variable. A priori, we planned analyses of bicarbonate categories with clinical outcomes and additionally stratified analyses based on urine albumin-creatinine ratio (ACR) >30 or <30 mg/g. For all outcomes, we also used spline functions to consider parametric nonlinear functions for serum bicarbonate concentration. Natural piecewise-cubic splines were used with the specified sequence of interior knots placed at the quartiles of distributions of serum bicarbonate. Multivariable logistic models were used to determine the association of serum bicarbonate categories with rapid kidney function decline, while Poisson regression was used to determine the association of serum bicarbonate categories with incident reduced eGFR. We initially adjusted for demographic covariates, then additionally adjusted for CVD risk factors, the ratio of daily protein to potassium intake, ACR, diuretic use, and baseline eGFR. Based on the MESA design, we repeated these analyses after stratification by race and with

bicarbonate dichotomized at < 23 mEq/L. Analyses were conducted using S-Plus (version 8.0; TIBCO Software Inc) and SPSS statistical software (version 15.0.1.1; SPSS Inc); $P < 0.05$ was considered statistically significant for all analyses including interaction terms.

RESULTS

Among the 5,810 participants with baseline eGFRs > 60 mL/min/1.73 m^2, mean age was 61 ± 10 (SD) years; 53% were women; the race/ethnicity distribution was 38% white, 27% black, 22% Hispanic, and 12% Chinese; and median follow-up was 4.75 (interquartile range [IQR], 4.52-4.97) years. Baseline eGFR was 84 ± 14 mL/min/1.73 m^2, and median urine ACR was 5.2 (IQR, 3.3-10.3) mg/g.

The distribution of baseline serum bicarbonate concentrations was approximately normal, with a mean level of 23 mEq/L (Fig 1). Participants with lower baseline serum bicarbonate concentrations were younger, were more likely to be Hispanic and to have smoked, and had a higher eGFR and higher dietary sodium intake than those with normal or high serum bicarbonate concentrations. The lowest bicarbonate category also had the lowest prevalence of hypertension and diuretic use. Other risk factors appeared similar across bicarbonate categories (Table 1). In adjusted linear regression analyses, independent correlates of lower bicarbonate concentrations included younger age, white race, lower educational attainment, diabetes mellitus, higher body mass index, higher eGFR, and higher daily dietary acid load (as defined
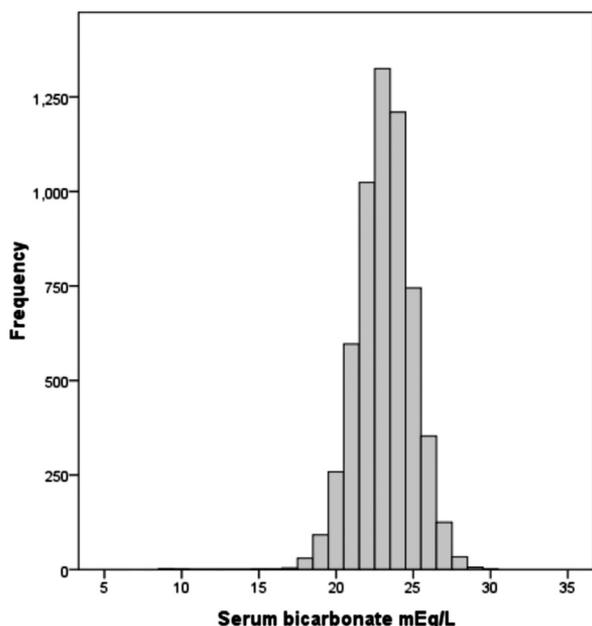
by a high dietary protein intake relative to potassium) and sodium intake (Table 2).[18]

Among the 5,810 with available bicarbonate concentrations at baseline, 5,165 had data on change in kidney function at follow-up examinations. Among these, spline analyses showed higher odds of rapid kidney function decline at lower serum bicarbonate concentrations and lower odds of rapid kidney function decline at higher bicarbonate concentrations (Fig 2A). The association between serum bicarbonate level and incident reduced eGFR was in the similar direction, but weaker at serum bicarbonate concentrations of 21-26 mEq/L (Fig 2B).

In both unadjusted and adjusted analyses, each 1.8-unit (SD) lower baseline bicarbonate concentration was associated with an approximately 10% higher odds for rapid kidney function decline and incident reduced eGFR. When serum bicarbonate level was analyzed as a categorical variable, concentrations < 21 mEq/L were associated with an approximately 35% higher odds of rapid kidney function decline in adjusted models relative to 23-24 mEq/L; bicarbonate concentrations > 25 mEq/L had similar associations with lower odds of rapid decline (Table 3). When we dichotomized the study population at the ACR cutoff of 30 mg/g, serum bicarbonate concentration < 23 mEq/L was associated with a 20% higher adjusted odds of rapid kidney function decline (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.06-1.37) in those with albuminuria, which was similar in those without albuminuria (OR, 1.24; 95% CI, 1.09-1.42). Dichotomizing by incident reduced eGFR, mean rates of annual decline were -6.9 ± 4.5 and -1.1 ± 3.7 mL/min/1.73 m^2 per year for participants with and without incident reduced eGFR, respectively. Additionally, mean rates of annual decline were -5.9 ± 3.0 and 0.5 ± 2.9 mL/min/1.73 m^2 per year for those with and without rapid kidney function decline, respectively.

Although directionally similar, serum bicarbonate categories were not associated significantly with adjusted risk of incident reduced eGFR (Table 3). Similar findings were observed for the dichotomized analysis of bicarbonate (<23 mEq/L vs higher: OR, 1.17; 95% CI, 0.99-1.39). Although there was no significant interaction detected across racial groups, the association was strongest and statistically significant for both outcomes among black participants (Table 4).

DISCUSSION

Low serum bicarbonate concentrations are associated with worsening CKD and its complications, including mortality, in populations with eGFRs < 60 mL/min/1.73 m^2,[4-7] but the relationship of serum bicarbonate concentrations with CKD progression in populations with eGFRs > 60 mL/min/1.73 m^2 is unknown. In this cohort of community-living individuals with baseline

Figure 1. Distribution of serum bicarbonate levels. The distribution of baseline serum bicarbonate concentrations (n = 5,810) was normal, with a mean level of 23 ± 1.8 (SD) mEq/L.

Table 1. Characteristics of MESA Participants by Baseline Serum Bicarbonate Categories

	<21 mEq/L	21-22 mEq/L	23-24 mEq/L	25-26 mEq/L	≥27 mEq/L	P
No. of participants	390	1,621	2,535	1,098	166	
Age (y)	58 ± 9	60 ± 10	61 ± 10	63 ± 10	65 ± 10	<0.001
Male sex	193 (50)	778 (48)	1,192 (47)	518 (47)	64 (39)	0.09
Race						<0.001
White	125 (32)	618 (38)	982 (39)	433 (39)	52 (31)	
Asian	41 (11)	210 (13)	323 (13)	125 (11)	17 (10)	
Black	90 (23)	361 (22)	693 (27)	377 (34)	75 (45)	
Hispanic	134 (34)	434 (27)	537 (21)	163 (15)	22 (13)	
Education						<0.001
<High school	73 (19)	296 (18)	459 (18)	160 (15)	35 (21)	
High school + some college	194 (50)	768 (48)	1,137 (45)	483 (44)	65 (39)	
≥College	123 (32)	550 (34)	930 (37)	453 (41)	66 (40)	
Diabetes mellitus	61 (16)	217 (13)	258 (10)	125 (11)	20 (12)	0.007
Glucose (mg/dL)	103 ± 40	99 ± 32	96 ± 27	95 ± 28	94 ± 18	<0.001
BMI (kg/m^2)	29.2 ± 5.2	28.6 ± 5.1	28.1 ± 5.5	27.5 ± 5.5	28.0 ± 6.6	<0.001
Smoking						<0.001
Never	165 (42)	779 (48)	1,310 (52)	569 (52)	89 (54)	
Ever	225 (58)	835 (52)	1,216 (48)	528 (48)	77 (46)	
HDL-C (mg/dL)	48 ± 14	50 ± 15	51 ± 15	54 ± 15	56 ± 16	<0.001
LDL-C (mg/dL)	117 ± 33	117 ± 32	117 ± 31	117 ± 31	113 ± 31	0.5
Triglycerides (mg/dL)	129 [84-187]	118 [82-171]	108 [76-158]	98 [71-137]	96 [73-140]	<0.001
Hypertension	127 (33)	607 (37)	1,042 (41)	544 (50)	109 (66)	<0.001
ACR (mg/g)	5.6 [3.4-12.0]	5.3 [3.3-10.2]	4.9 [3.2-9.8]	5.5 [3.4-10.8]	5.8 [3.7-10.9]	0.002
eGFR (mL/min/1.73 m^2)	90 ± 14	88 ± 15	87 ± 14	86 ± 14	83 ± 13	<0.001
Protein:K ratio	0.025 ± 0.006	0.024 ± 0.007	0.023 ± 0.006	0.023 ± 0.006	0.022 ± 0.006	<0.001
Dietary Na intake (mg)	2,248 ± 1,221	2,234 ± 1,312	2,154 ± 1,253	2,078 ± 1,198	1,851 ± 998	<0.001
Diuretic use	20 (5)	110 (7)	262 (10)	205 (19)	59 (36)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; HDL-C and LDL-C in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; MESA, Multi-Ethnic Study of Atherosclerosis.

eGFRs > 60 mL/min/1.73 m^2, lower serum bicarbonate concentrations were associated with rapid kidney function decline and incident reduced eGFR, independent of baseline eGFR and ACR. When stratifying these analyses by race, the association of low bicarbonate level with both outcomes was strongest among black participants.

Serum bicarbonate has been well studied as a predictor of progressive CKD in patients with established CKD. In a study of African Americans with baseline eGFRs of 20-65 mL/min/1.73 m^2, each 1-mmol/L higher serum bicarbonate level was associated with a significant reduction in a composite outcome of death, dialysis, or decline in kidney function.[5] In a cohort of patients in the Bronx, NY, low serum bicarbonate level was found to be associated with progression of kidney disease, irrespective of baseline eGFR.[7] However, another study in the MDRD (Modification of Diet in Renal Disease) Study cohort found that low

serum bicarbonate concentrations were not associated significantly with risk of kidney failure and all-cause mortality in nondiabetic patients with CKD stages 2-4.[9]

These findings are consistent with previous studies in individuals with relatively preserved kidney function (eGFR > 60 mL/min/1.73 m^2). A study of patients in New York City found that lower serum bicarbonate concentrations are associated with risk of kidney disease progression, including those with relatively preserved eGFRs (>60 mL/min/1.73 m^2).[7] Additionally, a small randomized trial found that bicarbonate supplementation slowed eGFR decline in patients with baseline eGFRs of 60-90 mL/min/1.73 m^2.[20]

The association between serum bicarbonate concentrations and kidney function decline in participants with eGFRs > 60 mL/min/1.73 m^2 has at least 2 potential biological explanations. The first possibility is that acidosis, as indicated by low serum bicarbonate concentrations, has a direct role in the pathogenesis of

Table 2. Associations of Demographic and Clinical Characteristics With Serum Bicarbonate Concentrations Using Multivariate Linear Regression

	β (95% CI)	P
Age, per-10 y older	0.21 (0.17 to 0.26)	<0.001
Male sex	−0.09 (−0.19 to 0.01)	0.05
Race		
White	0.00 (reference)	
Chinese	−0.05 (−0.20 to 0.11)	0.6
Black	0.29 (0.18 to 0.41)	<0.001
Hispanic	−0.47 (−0.59 to −0.35)	<0.001
Education		
<High school	−0.20 (−0.34 to −0.07)	0.003
High school + some college	−0.21 (−0.31 to −0.10)	<0.001
≥College	0.00 (reference)	
Diabetes	−0.23 (−0.38 to −0.09)	0.002
BMI category		
<18.5 kg/m^2	0.67 (0.16 to 1.17)	0.009
18.5-24.9 kg/m^2	0.00 (reference)	
25.0-29.9 kg/m^2	−0.38 (−0.50 to −0.27)	<0.001
≥30 kg/m^2	−0.43 (−0.55 to −0.31)	<0.001
Ever smoked	−0.19 (−0.28 to −0.09)	<0.001
HDL-C, per 5-mg/dL lower	−0.07 (−0.09 to −0.06)	<0.001
Hypertension	0.43 (0.34 to 0.52)	<0.001
ACR > 30 mg/g	−0.03 (−0.20 to 0.14)	0.8
eGFR, per 14 mL/min/1.73 m^2 lower[a]	0.17 (0.12 to 0.21)	<0.001
Asthma	0.01 (−0.09 to 0.11)	0.3
Dietary protein:K ratio, per 0.006 higher[a]	−0.17 (−0.22 to −0.12)	<0.001
Dietary Na, per 0.001 mg higher[a]	−0.11 (−0.16 to −0.06)	<0.001
Diuretic use	0.97 (0.82 to 1.11)	<0.001

Note: n = 5,810 participants with eGFR > 60 mL/min/1.73 m^2 in the Multi-Ethnic Study of Atherosclerosis.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; K, potassium; NA, sodium.

[a]Increment equivalent to 1 standard deviation.

CKD. Rat models of kidney disease have shown that increased ammonia production in response to metabolic acidosis can result in direct kidney injury through increased complement activation and inflammation.[3] Support for this hypothesis comes from findings that supplementation of serum bicarbonate concentrations slowed CKD progression in small randomized clinical trials in patients with and without CKD.[20,21] A second possibility is that lower serum bicarbonate level is a marker of kidney tubule dysfunction, rather than directly injurious to the kidney. Under this possibility, our data suggest that early losses of the kidney's acid-base regulatory capacity could precede losses of glomerular filtration, or at least may occur early enough in

the spectrum of CKD such that mild decrements in eGFR are not detectable using an eGFR equation combining both creatinine and cystatin C levels.

This study also produced novel observations regarding predictors of acid-base status in persons with preserved kidney function. What was especially surprising was the association of lower eGFRs with higher bicarbonate concentrations. In contrast to our findings, other studies, including a companion study in the Health, Aging, and Body Composition (Health ABC) cohort[22] have found that lower eGFR typically is associated with metabolic acidosis in cross-section, even in those with relatively preserved kidney function (eGFR > 60 mL/min/1.73 m^2), which is thought to be the result of a reduced number of functioning nephrons.[2,23-25] Our finding that Hispanics in MESA had lower adjusted bicarbonate concentrations than whites is similar to what has been shown in the Third National Health and Nutrition Examination Survey (NHANES III), although our finding that bicarbonate concentrations are higher in blacks is different from that in the NHANES III cohort, in which concentrations are similar between the 2 groups.[26] The other associations of education, diet, and diuretics with bicarbonate concentrations all suggest that environmental factors can influence acid-base status. Future studies are needed to confirm these observations.

Our findings ultimately may have clinical implications. First, serum bicarbonate is an inexpensive laboratory test that is present on standard clinical chemistry panels; it may have the potential to identify persons at risk of developing CKD, perhaps in combination with other biomarkers, which could inform more aggressive management of kidney disease risk factors. Additionally, previous studies have shown the potential for correction of serum bicarbonate levels through oral bicarbonate supplementation to slow kidney function decline and progression to end-stage renal disease in a population of patients with and without CKD.[20,21] This also could inform dietary counseling, such as substituting alkali-poor meats and cheeses with more alkali-rich fruits and vegetables.[27] If these findings are confirmed, correction of serum bicarbonate concentrations may hold the potential to either slow or prevent the progression to clinical CKD. Future intervention studies may be warranted to test this important question.

Strengths of our study include the large study population with baseline eGFRs > 60 mL/min/1.73 m^2, the multiethnic composition of the cohort, and the 5-year follow-up with measurements of creatinine and cystatin C. The study also has important limitations. These include the single measurement of bicarbonate and the lack of chronic obstructive pulmonary disease status reported in the cohort, although smoking and asthma status were recorded. Additionally, results in the analyses by race should be interpreted with caution
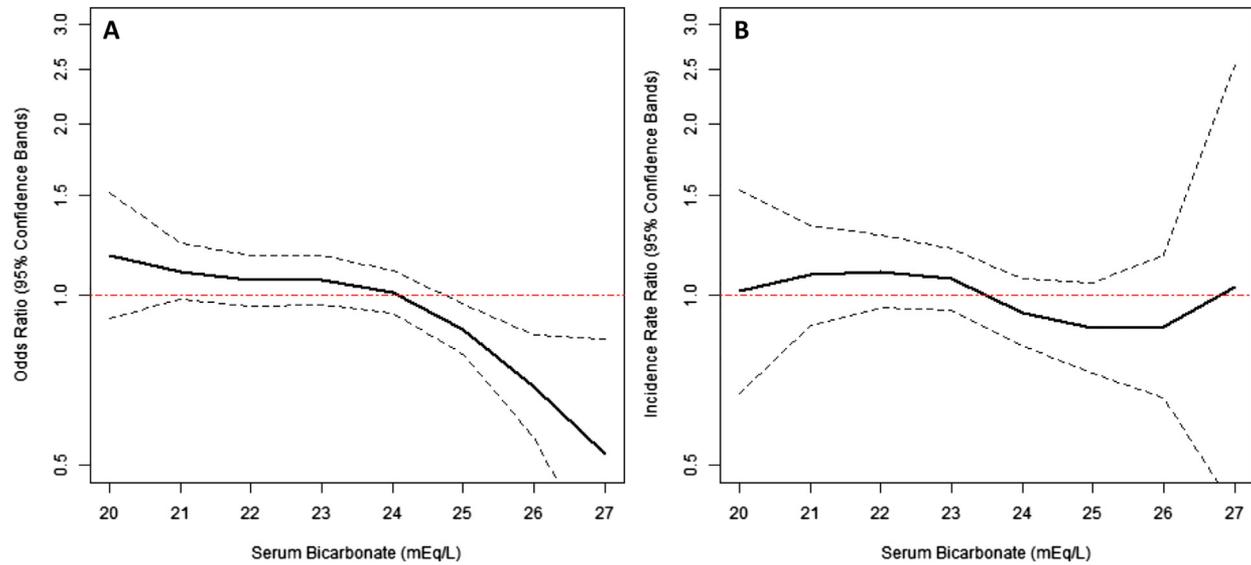
Figure 2. (A) Adjusted association of serum bicarbonate level with risk of (A) rapid kidney function decline and (B) incident reduced estimated glomerular filtration rate (eGFR) in MESA (Multi-Ethnic Study of Atherosclerosis). Spline analysis adjusted for age, race, sex, education, diabetes mellitus, hypertension, smoking, body mass index, high-density lipoprotein cholesterol level, eGFR, diuretic use, and albuminuria. Solid line represents the point estimate and dotted lines represent 95% confidence interval.

due to the small number of events in the lower bicarbonate categories.

Another important consideration is that bicarbonate levels in this study were measured from frozen samples as opposed to at the point of collection. Freezing and storing serum samples has been associated with ~4-mEq/L lower bicarbonate concentrations compared with measurements taken at the point of care in

Table 3. Associations of Serum Bicarbonate With Rapid Kidney Function Decline and Incident Reduced eGFR

Rapid Kidney Function Decline

Serum Bicarbonate	No.	No. With Rapid Decline	Demographic-Adjusted[a] OR (95% CI)	Fully Adjusted[b] OR (95% CI)
Continuous, per 1.8 mEq/L decrease[c]	5,165	1,730 (33)	1.15 (1.08-1.22)	1.12 (1.06-1.20)
Clinical category				
<21 mEq/L	340	136 (40)	1.46 (1.15-1.85)	1.35 (1.05-1.73)
21-22 mEq/L	1,436	493 (34)	1.10 (0.95-1.26)	1.06 (0.91-1.22)
23-24 mEq/L	2,271	756 (33)	1.00 (reference)	1.00 (reference)
25-26 mEq/L	974	297 (30)	0.84 (0.71-0.99)	0.82 (0.69-0.97)
≥27 mEq/L	144	48 (33)	0.86 (0.59-1.23)	0.85 (0.58-1.24)

Incident Reduced eGFR

Serum Bicarbonate	No.	No. With Incident Reduced eGFR	Demographic-Adjusted[a] IRR (95% CI)	Fully Adjusted[b] IRR (95% CI)
Continuous, per 1.8 mEq/L decrease[c]	5,165	487 (9)	1.11 (1.02-1.08)	1.12 (1.04-1.22)
Clinical category				
<21 mEq/L	340	30 (9)	1.33 (0.93-1.91)	1.18 (0.84-1.67)
21-22 mEq/L	1,436	142 (10)	1.20 (0.99-1.46)	1.15 (0.96-1.38)
23-24 mEq/L	2,271	205 (9)	1.00 (reference)	1.00 (reference)
25-26 mEq/L	974	93 (10)	0.97 (0.77-1.21)	0.84 (0.67-1.06)
≥27 mEq/L	144	17 (12)	0.98 (0.63-1.52)	0.83 (0.51-1.36)

Note: Number with event given as number or number (percentage).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; OR, odds ratio.
[a]Adjusted for age, sex, race, and education.
[b]Further adjusted for diabetes mellitus, hypertension, smoking, body mass index, high-density lipoprotein cholesterol level, eGFR, diuretic use, daily protein to potassium intake, and albuminuria.
[c]Increment equivalent to 1 standard deviation.

Table 4. Associations of Serum Bicarbonate With Rapid Kidney Function Decline and Incident Reduced eGFR, Stratified by Race

Rapid Kidney Function Decline

	No.	No. With Rapid Decline	Demographic-Adjusted[a] OR (95% CI)	Fully Adjusted[b] OR (95% CI)
White				
<23 mEq/L	674	209 (31)	1.19 (0.96-1.46)	1.11 (0.90-1.38)
≥23 mEq/L	1,356	397 (29)	1.00 (reference)	1.00 (reference)
Chinese				
<23 mEq/L	215	63 (29)	1.05 (0.73-1.52)	1.03 (0.70-1.52)
≥23 mEq/L	415	117 (28)	1.00 (reference)	1.00 (reference)
Black				
<23 mEq/L	384	169 (44)	1.42 (1.11-1.82)	1.33 (1.02-1.74)
≥23 mEq/L	992	363 (37)	1.00 (reference)	1.00 (reference)
Hispanic				
<23 mEq/L	503	188 (37)	1.18 (0.92-1.52)	1.16 (0.89-1.52)
≥23 mEq/L	626	224 (36)	1.00 (reference)	1.00 (reference)

Incident Reduced eGFR

	No.	No. With Incident Reduced eGFR	Demographic-Adjusted[a] IRR (95% CI)	Fully Adjusted[b] IRR (95% CI)
White				
<23 mEq/L	674	65 (10)	1.11 (0.95-1.29)	1.06 (0.91-1.24)
≥23 mEq/L	1,356	141 (10)	1.00 (reference)	1.00 (reference)
Chinese				
<23 mEq/L	215	12 (6)	0.93 (0.64-1.35)	0.89 (0.62-1.28)
≥23 mEq/L	415	26 (6)	1.00 (reference)	1.00 (reference)
Black				
<23 mEq/L	384	50 (13)	1.75 (1.45-2.09)	1.69 (1.41-2.03)
≥23 mEq/L	992	84 (9)	1.00 (reference)	1.00 (reference)
Hispanic				
<23 mEq/L	503	45 (9)	1.12 (0.92-1.36)	1.17 (0.96-1.43)
≥23 mEq/L	626	64 (10)	1.00 (reference)	1.00 (reference)

Note: Number with event given as number or number (percentage). *P* for bicarbonate-race interaction = 0.4 for rapid kidney function decline and 0.1 for incident reduced eGFR.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; OR, odds ratio.

[a]Adjusted for age, sex, race, and education.

[b]Further adjusted for diabetes mellitus, hypertension, smoking, body mass index, high-density lipoprotein cholesterol level, eGFR, diuretic use, and albuminuria.

prior studies, which likely is the result of volatile loss of carbon dioxide.[28] This discrepancy likely did not affect the observed associations of bicarbonate with kidney outcomes because a companion study in Health ABC, which measured bicarbonate at the point of care, had higher mean bicarbonate concentrations, but found similar associations with change in kidney function over time.[22]

Given the high prevalence of CKD in the United States and its strong associations with CVD events and mortality, the early identification of CKD holds the potential to inform risk management to either slow or prevent the onset of CKD and associated morbid consequences in a large proportion of the population. This study presents serum bicarbonate level as an early indicator of kidney function decline. Future studies in other cohorts are needed to confirm the association of

metabolic acidosis with early declines in kidney function and determine whether bicarbonate level is a modifiable risk factor for CKD in the general population or in targeted subgroups, such as the black population.

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