Bicarbonate Concentration, Acid-Base Status, and Mortality in the Health, Aging, and Body Composition Study

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Abstract

Background and objectives Low serum bicarbonate associates with mortality in CKD. This study investigated the associations of bicarbonate and acid-base status with mortality in healthy older individuals.

Design, setting, participants, & measurements We analyzed data from the Health, Aging, and Body Composition Study, a prospective study of well functioning black and white adults ages 70–79 years old from 1997. Participants with arterialized venous blood gas measurements (n=2287) were grouped into <23.0 mEq/L (low), 23.0–27.9 mEq/L (reference group), and ≥28.0 mEq/L (high) bicarbonate categories and according to acid-base status. Survival data were collected through February of 2014. Mortality hazard ratios (HRs; 95% confidence intervals [95% CIs]) in the low and high bicarbonate groups compared with the reference group were determined using Cox models adjusted for demographics, eGFR, albuminuria, chronic obstructive pulmonary disease, smoking, and systemic pH. Similarly adjusted Cox models were performed according to acid-base status.

Results The mean age was 76 years, 51% were women, and 38% were black. Mean pH was 7.41, mean bicarbonate was 25.1 mEq/L, 11% had low bicarbonate, and 10% had high bicarbonate. Mean eGFR was 82.1 ml/min per 1.73 m^2, and 12% had CKD. Over a mean follow-up of 10.3 years, 1326 (58%) participants died. Compared with the reference group, the mortality HRs were 1.24 (95% CI, 1.02 to 1.49) in the low bicarbonate and 1.03 (95% CI, 0.84 to 1.26) in the high bicarbonate categories. Compared with the normal acid-base group, the 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.

Conclusions In generally healthy older individuals, low serum bicarbonate associated with higher mortality independent of systemic pH and potential confounders. This association seemed to be present regardless of whether the cause of low bicarbonate was metabolic acidosis or respiratory alkalosis. Metabolic alkalosis also associated with higher mortality.

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Introduction

In CKD, low serum bicarbonate concentration is a risk factor for mortality and CKD progression (1–4). Low bicarbonate may also be a risk factor for eGFR decline and mortality in persons without CKD. In the non-CKD setting, the association between low bicarbonate and eGFR decline is more established (5–7). In the Health, Aging, and Body Composition (Health ABC) Study, participants with normal eGFR and bicarbonate <23.0 mEq/L had higher risk of incident CKD compared with those with normal bicarbonate (6). Shah *et al.* (7) reported a 54% higher risk of eGFR decline for those with bicarbonate ≤22 mEq/L compared with those with normal bicarbonate in a cohort of >5000 individuals, 91% of whom had normal eGFR at baseline. Regarding mortality, an analysis of the Third National Health and Nutrition Examination Survey (NHANES III) showed that participants with serum bicarbonate <22 mEq/L had 76% higher mortality than those with normal bicarbonate, and this association was not modified by CKD status (8). The association between bicarbonate and mortality has not been investigated in other cohorts with a low prevalence of CKD. Furthermore, a limitation of NHANES III is that systemic pH and P_{CO_2} were not measured, which is important, because low bicarbonate in persons with preserved eGFR may not necessarily reflect primary metabolic acidosis as it does in CKD.

Therefore, the goals of this study were to investigate the relationships between bicarbonate and acid-base status and all-cause mortality in a cohort with a low prevalence of CKD. To accomplish this, we examined data from participants in the Health ABC Study who

had arterialized venous blood gas (AVBG) measurements. Secondary analyses investigated the relationship between systemic pH and mortality and the associations between bicarbonate and cardiovascular and noncardiovascular mortality.

Materials and Methods

Study Population

The Health ABC Study enrolled 3075 black and white participants aged 70–79 years old from clinical sites in Memphis, Tennessee, and Pittsburgh, Pennsylvania from 1997 to 1998. Participants were eligible if they self-reported ability to walk one quarter of a mile, climb ten steps, perform basic activities of daily living without difficulty, and no life-threatening illnesses. Participants were evaluated at baseline, annually for the subsequent 5 years, and biannually thereafter. The Health ABC Study was overseen by institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh and performed under the principles embodied in the Declaration of Helsinki.

AVBG samples were obtained at the year 3 visit. Of 2921 participants who attended the year 3 visit, 2287 underwent AVBG sampling and were included in this analysis; the year 3 visit served as baseline.

Measurements

AVBG samples were obtained from a cannulated hand or wrist vein placed in a warmer set to 42°C for ≥15 minutes before blood sampling. Samples were obtained after ≥2 hours of fasting and analyzed on the day of phlebotomy. pH, P_{CO_2}, and P_{O_2} were measured in triplicate on a Radiometer ABL5 Blood Gas Analyzer (Radiometer, Brea, CA). Bicarbonate concentration was calculated using the Henderson–Hasselbalch equation. Average values of bicarbonate, pH, P_{CO_2}, and P_{O_2} for each participant were used.

Year 3 creatinine and cystatin C measurements were used to estimate GFR using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation (9). Creatinine was measured using a colorimetric assay calibrated to isotope dilution mass spectrometry–traceable standards. Cystatin C was measured using a particle–enhanced immunonephelometric assay (10). Urine albumin was measured using a particle–enhanced turbidimetric inhibition immunoassay. A modified Jaffe method measured urine creatinine. Serum albumin was measured using the bromocresol green method. Blood concentrations of TNF-α, IL-6, and C-reactive protein (CRP) were measured in duplicate as described (11). Urine albumin and creatinine, serum albumin, TNF-α, CRP, and IL-6 measurements were not measured at year 3; however, they were measured at baseline.

Protein intake was evaluated at the year 2 visit using food frequency questionnaires developed by Block Dietary Systems (Berkeley, CA). Trained interviewers administered questionnaires in person using three–dimensional food models. Body composition was measured at year 3 using fan–beam dual–energy x-ray absorptiometry (DXA; Hologic QDR-4500A; Hologic, Bedford, MA) as described (12). Total nonbone lean mass was calculated by subtracting bone mineral content from total lean mass obtained by DXA (13). Spirometry was performed at year 1 using a horizontal dry rolling seal HF6 Spirometer (Sensor Medics Corporation, Yorba Linda, CA) according to standard guidelines (14).

Definitions

Race (black or white) was self-reported. CKD was defined as eGFR<60 ml/min per 1.73 m^2. Participants were categorized as having low (<23.0 mEq/L), normal (23.0–27.9 mEq/L), or high (≥28.0 mEq/L) bicarbonate as previously performed in this cohort (6). Participants were categorized as having low (<7.39), normal (7.39–7.43), or high (>7.43) pH; normal pH was defined if the average pH was within 0.02 U of the median pH (7.41) in the cohort. Normal P_{CO_2} was defined if the average was within 2 mmHg of the median P_{CO_2} (40 mmHg) in the cohort. Participants were categorized into one of seven acid-base status categories as shown in Table 1. Normal acid-base status was defined if average pH, P_{CO_2}, and bicarbonate were each within the normal range. Remaining participants had at least one average value of pH, P_{CO_2}, or bicarbonate that was outside the normal range and were grouped into one of the abnormal acid-base categories as described in Table 1.

Cardiovascular disease (CVD) was defined as a history of coronary artery bypass graft surgery or angioplasty, carotid endarterectomy, lower extremity bypass or angioplasty, aneurysm repair, myocardial infarction, angina pectoris, transient ischemic attack, or cerebrovascular accident. Congestive heart failure (CHF) was defined if a physician diagnosed the participant with CHF. Chronic obstructive pulmonary disease (COPD) was defined as a forced expiratory volume in 1 second <70% of the forced vital capacity.

Ascertainment of Mortality Data

Mortality was ascertained from death certificates, hospital records, and interview with next of kin through February 24, 2014 (representing 14 years of follow-up). A central committee adjudicated all deaths, including cause of death. Cardiovascular deaths included those caused by atherosclerotic CVD, cerebrovascular disease, atherosclerotic disease at noncoronary/noncerebrovascular sites, and other CVD. Other deaths were considered noncardiovascular.

Statistical Analyses

Continuous variables are presented as means with SDs, unless otherwise specified. Categorical variables are presented as percentages. Significance tests were performed using ANOVA for continuous variables and chi-squared tests for dichotomous variables. Pearson correlation coefficients were calculated for bicarbonate, pH, P_{O_2}, and P_{CO_2}.

All–cause mortality hazard ratios (HRs) were determined using Cox proportional hazards models. The normal bicarbonate and pH categories served as the reference group in the corresponding Cox models. Model 1 was unadjusted. Model 2 was adjusted for demographics (age, sex, race, and clinical site). Model 3 included model 2 variables, eGFR, urinary albumin-to-creatinine ratio (ACR), COPD, and smoking, which were considered to be the

Table 1. Definitions of acid-base status and observed values of pH, bicarbonate, and P_{CO_2} in each category

Acid-Base Status	pH	Bicarbonate, mEq/L	P_{CO_2}, mmHg	*N*
Normal	7.39–7.43	23 to <28	38–42	
Observed mean (minimum–maximum)	7.41 (7.39–7.43)	25.0 (23.0–27.7)	40.0 (38.0–42.0)	758
Metabolic acidosis	≤7.41	<25.5	<40	
Observed mean (minimum–maximum)	7.39 (7.28–7.41)	21.8 (12.3–24.0)	36.9 (22.0–39.7)	211
Respiratory acidosis	≤7.41	≥25.5	≥40	
Observed mean (minimum–maximum)	7.39 (7.31–7.41)	27.2 (25.5–34.0)	45.7 (42.3–59.3)	418
Metabolic and respiratory acidosis	≤7.41	<25.5	≥40	
Observed mean (minimum–maximum)	7.38 (7.30–7.40)	24.2 (19.0–25.3)	42.2 (40.0–51.7)	213
Metabolic alkalosis	>7.41	≥25.5	≥40	
Observed mean (minimum–maximum)	7.43 (7.42–7.49)	28.1 (26.0–33.0)	43.0 (40.0–49.0)	215
Respiratory alkalosis	>7.41	<25.5	<40	
Observed mean (minimum–maximum)	7.44 (7.42–7.57)	23.4 (17.0–25.3)	35.5 (24.0–38.3)	372
Metabolic and respiratory alkalosis	>7.41	≥25.5	<40	
Observed mean (minimum–maximum)	7.45 (7.43–7.59)	26.3 (25.7–29)	38.3 (27.3–39.7)	100

major potential confounders. Model 4 included model 3 variables and systemic pH (when bicarbonate was the predictor variable) to determine if the relationship between bicarbonate and mortality was independent of systemic pH. When pH was the predictor variable, model 4 included model 3 variables and bicarbonate.

Interaction of the relationship between all-cause mortality and (*1*) bicarbonate or (*2*) pH by CKD status was investigated by including a multiplicative interaction term in model 4. A cubic spline regression analysis adjusted for model 4 variables was performed using bicarbonate as the predictor variable. Knots were placed at quartiles of bicarbonate concentration, and 25 mEq/L was the reference point. Proportional hazards assumptions were evaluated using a formal significance test on the basis of the unscaled and scaled Schoenfeld residuals and a graphical assessment of log-log survival curves. None of the variables violated proportional hazards assumptions.

The association between bicarbonate and (*1*) cardiovascular or (*2*) noncardiovascular mortality was explored using Cox models adjusted for model 4 variables.

Sensitivity analyses, using bicarbonate category as the predictor variable, were performed by adding to model 4 (*1*) CVD, CHF, systolic BP, and diabetes; (*2*) use of medications that can affect bicarbonate concentration (diuretics, angiotensin–converting enzyme inhibitors, or angiotensin receptor blockers) (15); (*3*) nutritional factors associated with bicarbonate concentration (body mass index, serum albumin concentration, and daily protein intake) (15,16); (*4*) height–adjusted total nonbone lean mass, because acidosis promotes muscle proteolysis in CKD (17); and (*5*) IL-6, CRP, and TNF-α concentrations, because low bicarbonate associates with greater inflammation (18). P_{O_2} was included in another sensitivity analysis, because pH, P_{CO_2}, and bicarbonate may have been affected by the degree of arterialization of the AVBG.

The association between acid-base status and mortality was investigated by adjusting for (*1*) model 3 variables and (*2*) model 3 variables plus all of the sensitivity analysis variables. Normal acid-base status served as the reference group.

Analyses were performed using Stata 11 (StataCorp., College Station, TX). *P* values <0.05 were considered statistically significant.

Results

Participant Characteristics

Table 2 presents characteristics of 2287 Health ABC Study participants with AVBG measurements. In general, there were higher percentages of men, whites, and chronic comorbidities in the low bicarbonate category compared with the other groups. Dietary protein intake was higher and diuretic use was lower in the low bicarbonate category compared with the other groups. pH was statistically different across the bicarbonate categories, although mean values were within the normal range. The percentage of participants with pH<7.39 was highest in the low bicarbonate category, and the percentage of participants with pH>7.43 was highest in the high bicarbonate category. Among participants in the normal bicarbonate category, pH was <7.39 in 20% and >7.43 in 16%.

Correlations of Bicarbonate, pH, P_{CO_2}, and P_{O_2}

Table 3 presents Pearson correlation coefficients for bicarbonate, pH, P_{CO_2}, and P_{O_2}. All correlations were statistically significant. However, correlation coefficients were low for all comparisons, except bicarbonate and P_{CO_2}, pH and P_{CO_2}, pH and P_{O_2}, and P_{O_2} and P_{CO_2}.

Association between Bicarbonate Concentration and All-Cause Mortality

The mean (SD) follow-up time was 10.3 (3.9) years (median, 12.1 years). During follow-up, 1326 (58%) participants died. The mortality rate was 56 (95% confidence interval [95% CI], 53 to 60) per 1000 person-years. Mortality rates in the low, normal, and high bicarbonate categories were 76 (95% CI, 65 to 88), 53 (95% CI, 50 to 57), and 61 (95% CI, 52 to 72) per 1000 person-years, respectively.

Figure 1 presents the unadjusted survival by bicarbonate category, and Table 4 presents unadjusted and adjusted all–cause mortality HRs using the normal

Table 2. Baseline characteristics

Characteristics	Entire Cohort (n=2287)	Serum Bicarbonate Category			P Value
		<23.0 mEq/L (n=246)	23.0–27.9 mEq/L (n=1804)	≥28.0 mEq/L (n=237)	
Demographics					
Age (yr), mean (SD)	76 (3)	76 (3)	76 (3)	76 (3)	0.25
Sex, no. (%)					
Women	1163 (51)	109 (44)	905 (50)	149 (63)	<0.001
Men	1124 (49)	137 (56)	899 (50)	88 (37)	
Race/ethnicity, no. (%)					
Black	869 (38)	96 (39)	653 (36)	120 (51)	<0.001
White	1418 (62)	150 (61)	1151 (64)	117 (49)	
Clinical characteristics					
Cardiovascular disease, no. (%)	569 (25)	87 (35)	430 (24)	52 (22)	<0.001
Congestive heart failure, no. (%)	52 (2)	9 (4)	34 (2)	9 (4)	0.05
Diabetes, no. (%)	326 (14)	50 (20)	242 (13)	34 (14)	0.02
Systolic BP (mmHg), mean (SD)	135.3 (20.3)	134.3 (22.4)	135.2 (20)	137.1 (21.0)	0.31
CKD,[a] no. (%)	242 (12)	61 (28)	160 (10)	21 (10)	<0.001
Chronic obstructive pulmonary disease,[b] no. (%)	456 (21)	68 (29)	341 (20)	47 (22)	<0.01
Current smoker, no. (%)	175 (8)	36 (15)	129 (7)	10 (4)	<0.001
Body mass index (kg/m^2), mean (SD)	27.3 (4.8)	27.1 (4.7)	27.3 (4.7)	27.2 (5.4)	0.77
ACE-I or ARB use, no. (%)	537 (23)	70 (28)	406 (23)	61 (26)	0.08
Diuretic use, no. (%)	662 (29)	45 (18)	485 (27)	132 (56)	<0.001
Protein intake (g/d), mean (SD)	66.9 (28.9)	68.3 (32.9)	67.4 (28.6)	62.1 (25.2)	0.02
Laboratory data					
eGFR (ml/min per 1.73 m^2), mean (SD)	82.1 (18.3)	73.0 (20.9)	83.2 (17.7)	82.7 (17.8)	<0.001
Urine ACR (mg/g), median (IQR)	8.1 (4.4–19.3)	10.7 (5.6–27.5)	7.7 (4.2–18.4)	9.5 (5.2–22.8)	<0.001
Serum albumin (g/dl), mean (SD)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	0.27
Arterialized venous pH, mean (SD)	7.41 (0.03)	7.40 (0.04)	7.41 (0.02)	7.41 (0.03)	<0.001
pH<7.39, no. (%)	502 (22.0)	94 (38.2)	360 (20.0)	48 (20.3)	<0.001
pH=7.39–7.43, no. (%)	1400 (61.2)	111 (45.1)	1155 (64.0)	134 (56.5)	
pH>7.43, no. (%)	385 (16.8)	41 (16.7)	289 (16.0)	55 (23.2)	
Arterialized venous P_{CO_2} (mmHg), mean (SD)	40.4 (3.9)	35.4 (3.3)	40.4 (3.0)	46.0 (3.6)	<0.001
Arterialized venous P_{O_2} (mmHg), mean (SD)	53.2 (10.9)	55.0 (11.9)	53.5 (10.6)	49.0 (11.6)	<0.001

ACE-I, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACR, albumin-to-creatinine ratio; IQR, interquartile range.

[a]Defined as eGFR<60 ml/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation (9). eGFR was available in 219, 1645, and 221 participants in the low, normal, and high bicarbonate categories (total with eGFR=2085).

[b]Defined as forced expiratory volume in 1 second <70% of the forced vital capacity. Spirometry was performed in 236, 1700, and 215 participants in the low, normal, and high bicarbonate categories (total with spirometry =2151).

bicarbonate category as the reference group. After adjusting for demographics, eGFR, ACR, COPD, and smoking (model 3), mortality was 22% higher in the low bicarbonate category compared with the reference group. Mortality in the high bicarbonate category was similar to the reference group. Adding pH (model 4) did not substantially change the results in the low (HR, 1.24; 95% CI, 1.02 to 1.49) or (HR, 1.03; 95% CI, 0.84 to 1.26) high bicarbonate groups. There was no evidence that the association between bicarbonate categories and mortality varied by CKD status (interaction P=0.74).

Table 3. Pearson correlation coefficients for bicarbonate, pH, P_{O_2}, and P_{CO_2}

Variable	Bicarbonate, mEq/L	pH	P_{O_2}, mmHg	P_{CO_2}, mmHg
Bicarbonate, mEq/L	1.00			
pH	0.16	1.00		
P_{O_2}, mmHg	−0.17	0.41	1.00	
P_{CO_2}, mmHg	0.77	−0.49	−0.42	1.00

$P<0.01$ for all correlations.

Figure 2 presents the cubic spline regression results adjusted for model 4 variables. Mortality was lowest at bicarbonate concentration approximately 26 mEq/L. Mortality was higher at <26 mEq/L, peaked at approximately 23 mEq/L, and remained flat below this. Mortality was also higher at >26 mEq/L and reached statistical significance at approximately 32 mEq/L.

In sensitivity analyses, the all–cause mortality HRs were not substantially different after CVD, CHF, systolic BP, diabetes, medications, nutritional factors, total nonbone mass, inflammatory markers, and P_{O_2} were added to model 4. A final sensitivity analysis, which added all of these variables to model 4, did not meaningfully alter the results (Table 4).

Associations between Bicarbonate Concentration and Cardiovascular and Noncardiovascular Mortality

There were 372 cardiovascular deaths, 866 noncardiovascular deaths, and 88 unclassified deaths. Cardiovascular mortality rates in the low, normal, and high bicarbonate categories were 19 (95% CI, 15 to 26), 15 (95% CI, 14 to 17), and 16 (95% CI, 12 to 22) per 1000 person-years, respectively. Noncardiovascular mortality rates in the low, normal, and high bicarbonate categories were 51 (95% CI, 42 to 61), 35 (95% CI, 32 to 37), and 41 (95% CI, 34 to 51) per 1000 person-years, respectively.

In the low bicarbonate category, the adjusted cardiovascular mortality HR was 1.23 (95% CI, 0.86 to 1.75), and the adjusted noncardiovascular mortality HR was 1.15 (95% CI, 0.91 to 1.46). In the high bicarbonate category, the adjusted cardiovascular mortality HR was 1.09 (95% CI, 0.75 to 1.59), and the adjusted noncardiovascular mortality HR was 1.03 (95% CI, 0.80 to 1.32).

Association between pH and All-Cause Mortality

Table 5 presents unadjusted and adjusted all–cause mortality HR using the normal pH category as the reference. There was no statistically significant association between pH and mortality after adjusting for demographics, eGFR, ACR, COPD, and smoking (model 3). The results were the same after including bicarbonate in the model. The *P* value for interaction by CKD status was not significant.

Association between Acid-Base Status and All-Cause Mortality

Table 1 presents the mean, minimum, and maximum values for pH, P_{CO_2}, and bicarbonate and the number of participants in each acid-base category. Table 6 presents the adjusted Cox model results. Mortality was higher for both metabolic acidosis and respiratory alkalosis compared with those with normal acid-base status, although this did not reach statistical significance in the metabolic acidosis group. Metabolic alkalosis but not respiratory acidosis associated with higher mortality. Combined

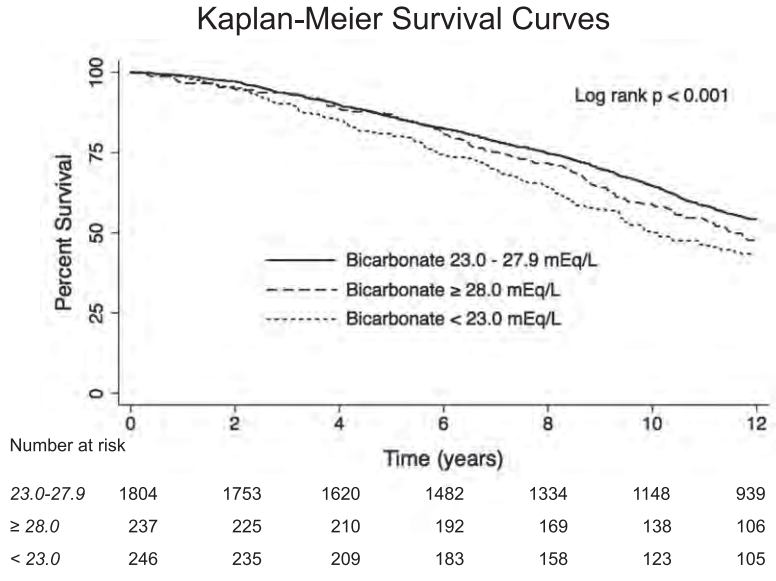

Figure 1. | Unadjusted survival in the study population according to bicarbonate category.

Table 4. Cox model results showing the all–cause mortality hazard ratios and 95% confidence intervals by serum bicarbonate category in the Health, Aging, and Body Composition Study

All-Cause Mortality	Bicarbonate Categories HR (95% CI)		
	<23.0 mEq/L	23.0–27.9 mEq/L	≥28.0 mEq/L
Model 1	1.48 (1.26 to 1.73)	Reference	1.14 (0.96 to 1.36)
Model 2	1.41 (1.20 to 1.66)	Reference	1.10 (0.92 to 1.31)
Model 3	1.22 (1.01 to 1.47)	Reference	1.04 (0.85 to 1.27)
Model 4[a]	1.24 (1.02 to 1.49)	Reference	1.03 (0.84 to 1.26)
Model 4 + CVD, CHF, diabetes, and SBP	1.22 (1.01 to 1.47)	Reference	1.03 (0.84 to 1.26)
Model 4 + diuretics, ACE-I, and ARB	1.26 (1.04 to 1.52)	Reference	1.00 (0.81 to 1.23)
Model 4 + serum albumin, BMI, and daily protein intake	1.22 (1.00 to 1.48)	Reference	1.04 (0.84 to 1.27)
Model 4 + nonbone lean mass	1.23 (1.01 to 1.48)	Reference	1.03 (0.84 to 1.26)
Model 4 + IL-6, TNF-α, and CRP	1.26 (1.03 to 1.54)	Reference	0.97 (0.78 to 1.21)
Model 4 + Po_2	1.26 (1.04 to 1.53)	Reference	0.98 (0.80 to 1.21)
Model 4 + all variables[b]	1.26 (1.02 to 1.56)	Reference	0.95 (0.76 to 1.19)

Model 1: unadjusted. Model 2: adjusted for age, sex, race, and clinical site. Model 3: adjusted for model 2 variables, eGFR, urinary albumin-to-creatinine ratio, chronic obstructive pulmonary disease, and smoking. Model 4: adjusted for model 3 variables and systemic pH. HR, hazard ratio; 95% CI, 95% confidence interval; CVD, cardiovascular disease; CHF, congestive heart failure; SBP, systolic BP; ACE-I, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein.
[a]P=0.74 for interaction between bicarbonate categories and mortality by CKD status.
[b]Additional variables were CVD, CHF, diabetes, SBP, use of diuretics, ACE-Is, or ARBs, serum albumin, BMI, daily protein intake, nonbone lean mass, IL-6, TNF-α, CRP, and Po_2.

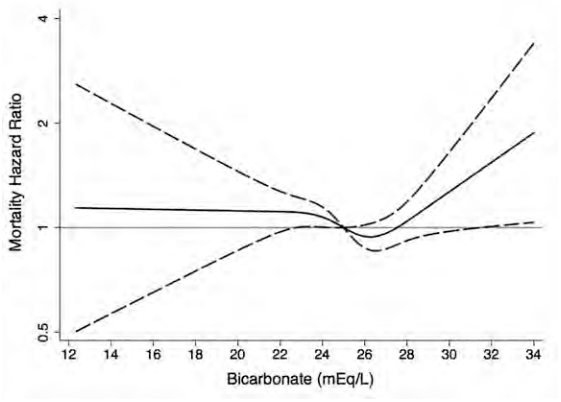

Figure 2. | Cubic spline regression analysis of the relationship between serum bicarbonate and mortality. Adjusted for age, sex, race, clinical site, eGFR, urinary albumin-to-creatinine ratio, chronic obstructive pulmonary disease, smoking, and pH. The line represents the hazard ratio point estimate, and the dashed lines represent the 95% confidence limits. Serum bicarbonate concentration of 25 mEq/L was the reference.

metabolic and respiratory disorders did not associate with mortality.

Discussion

In this cohort of generally healthy older individuals with a low prevalence of CKD, participants with low bicarbonate had 24% higher risk of all-cause mortality than those with normal bicarbonate, and CKD status did not modify this association. These results are consistent with the findings in the NHANES III (8) and support the notion that low bicarbonate concentration is a risk factor for poor outcomes (5–7) in persons with preserved renal function. The blood gas measurements in the Health ABC Study allowed us to address a limitation of prior research in this area, and we make the novel contribution of determining that the association between low bicarbonate and mortality was independent of systemic pH, suggesting that low bicarbonate associated with mortality, regardless of whether the underlying acid-base disorder was metabolic acidosis or respiratory alkalosis. This was reinforced by the higher HR for those with metabolic acidosis and respiratory alkalosis compared with the normal acid-base group.

Although metabolic acidosis did not have a statistically significant association with mortality in this cohort, metabolic acidosis contributes to several negative consequences. These include tubulointerstitial fibrosis (19–21), bone demineralization (22), protein catabolism and sarcopenia (23), inflammation (24), stimulation of the renin-angiotensin system (25) and adrenocortiocotrophic hormone (26), and resistance to growth hormone and IGF (27). However, including some of these factors in the Cox models did not attenuate the association between low bicarbonate and mortality. Nevertheless, correction of metabolic acidosis with alkali seems to ameliorate many of these effects (28–31), although it is uncertain if it improves survival.

With respect to respiratory alkalosis, hypoxemia is a strong stimulus and could explain the association with mortality. However, adjusting for common hypoxemic conditions (CHF and COPD) did not attenuate the results. Respiratory alkalosis can result from pain, which could increase mortality by promoting autonomic dysfunction

Table 5. Cox model results showing the all–cause mortality hazard ratios and 95% confidence intervals by pH category in the Health, Aging, and Body Composition Study

All-Cause Mortality	pH Categories HR (95% CI)		
	<7.39	7.39–7.43	>7.43
Model 1	1.19 (1.05 to 1.36)	Reference	1.02 (0.88 to 1.19)
Model 2	1.10 (0.97 to 1.26)	Reference	1.05 (0.90 to 1.22)
Model 3	0.97 (0.83 to 1.13)	Reference	1.05 (0.89 to 1.25)
Model 4	0.97 (0.83 to 1.13)	Reference	1.05 (0.89 to 1.25)

Model 1: unadjusted. Model 2: adjusted for age, sex, race, and clinical site. Model 3: adjusted for model 2 variables, eGFR, urinary albumin-to-creatinine ratio, chronic obstructive pulmonary disease, and smoking. Model 4: adjusted for model 3 variables and systemic pH. P=0.35 for interaction between pH categories and mortality by CKD status. HR, hazard ratio; 95% CI, 95% confidence interval.

Table 6. Cox model results showing the all–cause mortality hazard ratios and 95% confidence intervals by acid-base status

Acid-Base Status	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Normal	Reference	Reference
Metabolic acidosis	1.17 (0.94 to 1.47)	1.25 (0.98 to 1.61)
Respiratory acidosis	1.10 (0.91 to 1.32)	1.12 (0.90 to 1.39)
Metabolic and respiratory acidosis	1.05 (0.84 to 1.32)	1.13 (0.87 to 1.45)
Metabolic alkalosis	1.35 (1.08 to 1.69)	1.38 (1.06 to 1.78)
Respiratory alkalosis	1.21 (1.01 to 1.46)	1.29 (1.05 to 1.59)
Metabolic and respiratory alkalosis	0.88 (0.62 to 1.25)	0.93 (0.62 to 1.39)

Model 1: adjusted for age, sex, race, clinical site, eGFR, urinary albumin-to-creatinine ratio, chronic obstructive pulmonary disease, and smoking. Model 2: adjusted for model 1 variables, cardiovascular disease, congestive heart failure, diabetes, systolic BP, use of diuretics, angiotensin–converting enzyme inhibitors, or angiotensin receptor blockers, serum albumin, body mass index, daily protein intake, nonbone lean mass, IL-6, TNF-α, C-reactive protein, and P_{O_2}. HR, hazard ratio; 95% CI, 95% confidence interval.

(32,33), and anxiety, which associates with higher cardiovascular mortality in women (34). The mortality associated with respiratory alkalosis may relate to the tendency toward alkalemia, because metabolic alkalosis also associated with mortality in this cohort. In critically ill patients, mortality is higher with higher pH (35), and displacement of the hemoglobin-oxygen dissociation curve (36) and ionized hypocalcemia are likely mediators. Chronic metabolic alkalosis may increase mortality by inducing vascular calcification (37). These associations between acid-base status and mortality are intriguing and should be confirmed and further investigated.

To broadly elucidate potential causes of death associated with bicarbonate concentration, we explored the relationship between bicarbonate and cardiovascular and noncardiovascular mortality. Individuals in the low bicarbonate category had 23% higher risk of cardiovascular death and 15% higher risk of noncardiovascular death than those with normal bicarbonate, although these were not statistically significant for either outcome. These data suggest that low bicarbonate associates with both cardiovascular and noncardiovascular mortality; however, this requires additional exploration.

Several interventional studies have investigated and are investigating the potential benefits of normalizing low bicarbonate with alkaline therapy in patients with CKD (28,38–40). This has not been evaluated in persons without CKD. However, results from studies in healthy individuals not known to have low bicarbonate suggest that oral potassium bicarbonate supplementation raises bicarbonate concentration and maintains bone health and muscle mass (41–44). The results from this study suggest that raising low serum bicarbonate may improve clinical outcomes in persons with preserved eGFR. However, the results also caution against raising bicarbonate too high, because this might raise mortality risk if metabolic alkalosis develops. The results presented in Figure 2 suggest that targeting a serum bicarbonate concentration of approximately 26 mEq/L is reasonable.

The blood gas measurements are a significant strength of this study. Another is that bicarbonate was measured at the point of care, which is important, because measurement delays can result in falsely low values (45). Also, mortality event rates were high in this cohort. Creatinine and cystatin C were used to estimate GFR, which is more accurate in individuals with normal eGFR and helped minimize residual confounding by CKD (9). The Health ABC Study also collected valuable data, such as DXA and systemic inflammatory markers, which allowed us to explore whether nonbone lean mass, a surrogate of skeletal muscle mass, and inflammation attenuated the relationship between bicarbonate and mortality. Despite these strengths and others, this study also has limitations. AVBG measurements were performed once, and certain measurements, such as urinary albumin and spirometry, were not performed contemporaneously with the AVBG. GFR was not measured, and residual confounding remains possible. Total CO_2 is usually measured in clinical practice; hence, the bicarbonate concentrations in this study underestimated total CO_2.

In summary, the association between low bicarbonate and mortality in healthy older individuals was independent of pH, suggesting that this relationship did not depend on whether metabolic acidosis or respiratory alkalosis was the underlying disorder. Analyses by acid-base status reinforced this notion. Bicarbonate >32 mEq/L and metabolic alkalosis also associated with mortality.

Although alkaline therapy is a promising strategy to improve clinical outcomes, high serum bicarbonate and metabolic alkalosis should probably be avoided.

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Disclosures

None.

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