Association between Serum Bicarbonate and Death in Hemodialysis Patients: Is It Better to Be Acidotic or Alkalotic?

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The optimal acid-base status for survival in maintenance hemodialysis (MHD) patients remains controversial. According to recent reports, acidosis is associated with improved survival in MHD patients. It was hypothesized that this inverse association is due to a confounding effect of the malnutrition-inflammation complex syndrome (MICS). Associations between baseline (first 3 mo averaged) predialysis serum bicarbonate (HCO_3^-) and 2-yr mortality were examined in 56,385 MHD patients who were treated in virtually all DaVita dialysis clinics across the United States. The range of HCO_3^- was divided into 12 categories (<17, ≥27, and 10 groups in between). Three sets of Cox regression models were evaluated to estimate hazard ratios of all-cause and cardiovascular death in both incident and prevalent patients: (*1*) Unadjusted, (*2*) multivariate case mix adjusted (which also included dialysate HCO_3^- and Kt/V), and (*3*) adjusted for case mix and nine markers of MICS (body mass index; erythropoietin dose; protein intake; serum albumin; creatinine; phosphorus; calcium; ferritin and total iron binding capacity; and blood hemoglobin, WBC, and lymphocytes). There were significant inverse associations between serum HCO_3^- and serum phosphorus and estimated protein intake. The lowest unadjusted mortality was associated with predialysis HCO_3^- in the 17- to 23-mEq/L range, whereas values ≥23 mEq/L were associated with progressively higher all-cause and cardiovascular death rates. This association, however, reversed after case-mix and MICS multivariate adjustment, so that HCO_3^- values >22 mEq/L had lower death risk. Although previous epidemiologic studies indicated an association between high serum HCO_3^- and increased mortality in MHD patients, this effect seems to be due substantially to the effect of MICS on survival.

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There are abundant data from short-term metabolic studies in patients with chronic kidney disease (CKD) indicating that metabolic acidosis, a common condition in renal insufficiency, may engender or worsen protein-energy malnutrition, inflammation, and bone disease (1–6). Hence, two separate sets of guidelines within the Kidney Disease Outcome Quality Initiatives (K/DOQI)—Nutrition (7) and Bone Disease guidelines (8)—as well as the European guidelines (9) recommend a serum bicarbonate level >22 mEq/L. In patients with CKD, protein-energy malnutrition and inflammation are closely associated and together are referred to as malnutrition-inflammation complex syndrome (MICS) (10). Because MICS has been implicated as a major cause of poor clinical outcome in patients with CKD, the hypothesis has been advanced that metabolic acidosis, by engendering both malnutrition and negative nitrogen balance (11–13) and inflammation (14,15), may play a major role in increased mortality in this population. However, in contradistinction to most metabolic studies of small populations, which indicate a deleterious effect of acidosis on clinical outcome, the majority of epidemiologic studies in maintenance dialysis patients have indicated an inverse association between small decreases in serum bicarbonate (HCO_3^-) and improved markers of MICS and also survival (5,16,17). In fact the Dialysis Outcome Practice Pattern Study (DOPPS) (18) recently showed that moderate predialysis acidosis was associated with better nutritional status and lower relative risk for mortality and hospitalization in approximately 7000 maintenance dialysis patients. Hence, the association between metabolic acidosis and survival in dialysis patients has led to confusion pertaining to the effects of metabolic acidosis in this patient population (19). Moreover, interventional studies have yielded inconsistent results in different subgroups of patients with CKD; although in chronic peritoneal dialysis patients mitigating acidemia seems more consistently to improve nutritional status and reduce hospitalizations, the results in maintenance hemodialysis (MHD) patients are mixed (5,16).

We hypothesized that there is an overwhelming effect of the MICS that substantially alters the association between acidosis and survival in these patients. We sought to re-examine the

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underlying association between metabolic acidosis and alkalosis *versus* survival that maybe influenced by clinical conditions or other dominating characteristics. We therefore examined these associations using a series of multivariate models in a large sample of MHD patients across the United States.

Materials and Methods

Database Creation

The database used in this study has been described previously (20–22). In summary, the data warehouse of DaVita, Inc., the second largest dialysis care provider in the United States with >500 dialysis facilities and 40,000 maintenance dialysis patients across the country at any given time, includes comprehensive information on virtually all of its patients. A 24-mo cohort (July 1, 2001, through June 30, 2003) of these patients was studied. This period was selected because comprehensive clinical, demographic, and laboratory values during each thrice-weekly hemodialysis session began to be registered electronically in great detail during early to middle 2001. All repeated measures of every relevant variable for each patient within the entry quarter (during the first 13 wk upon the start of observation) were averaged to obtain one quarterly mean value for that variable. The study was approved by Institutional Review Committees of Harbor-UCLA and DaVita.

Cohort Time, Dialysis Vintage, and Death

Cohort time included the number of days a patient participated in the cohort and could vary from 1 to 731 d. Dialysis vintage was defined as the duration of time elapsed between the first day of dialysis treatment and the first day that the patient entered the cohort. The entry quarter was defined as the first quarter in which a patient's dialysis vintage was >3 mo for at least half the duration of the quarter. By implementing this criterion, any patient who had not maintained in the cohort beyond the first 3 mo of MHD was excluded.

Laboratory Data

Blood samples were predialysis except for the postdialysis serum urea nitrogen obtained to calculate urea kinetics. Blood samples were drawn using uniform techniques in all dialysis facilities across the nation and were transported to the Central DaVita Laboratory in Deland, FL, within 24 h. All laboratory values were measured *via* automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of bicarbonate (HCO_3^-), urea nitrogen, albumin, creatinine, phosphorus, potassium, and total iron binding capacity (TIBC), were measured at least monthly. Serum ferritin was measured quarterly. Hemoglobin was measured weekly to biweekly in most patients. Single pool Kt/V, a reflection of dialysis dose, and normalized protein nitrogen appearance (nPNA), also known as normalized protein catabolic rate, an estimation of daily protein intake, were calculated monthly in DaVita central laboratory according to Daugirdas *et al.* (23) using urea kinetic modeling software.

The entire HCO_3^- range was divided into 12 categories (<17, ≥27, and 10 increments of 1 mEq/L in between). Ten laboratory variables were also selected to ascertain the patient's nutritional and/or inflammatory status, together referred to as MICS (10), especially because each of these variables is associated with morbidity and mortality in MHD patients: (*1*) Serum albumin, which has strong associations with inflammation and comorbid conditions in MHD patients (24–26); (*2*) nPNA as a marker of daily protein intake; (*3*) serum TIBC, which is associated with subjective global assessment of nutrition (27); (*4*) serum ferritin, a possible indicator of inflammation (28); (*5*) serum creatinine, a marker of muscle mass and meat intake (29); (*6*) serum calcium, which correlates with coronary calcification (30); (*7*) serum phosphorus, which correlates with protein intake (30); (*8*) peripheral white blood cell (WBC) count, which may correlate with serum C-reactive protein (31); (*9*) percentage of lymphocytes in the WBC, a potential nutritional marker that was shown recently to have independent associations with mortality in MHD patients (32); and (*10*) blood hemoglobin (33).

Statistical Analyses

Because the dialysis population is a dynamic cohort with a high turnover rate, a nonconcurrent cohort was formed to include all existing MHD patients of the first quarter of observation (q1) and all MHD patients of the subsequent quarters (q2 through q8) of the 24-mo study. A baseline value was created for each measure by left-truncating the first available 3-mo averaged value of the entry quarter for each patient.

In addition to standard descriptive statistics, the Cox proportional hazard regression for truncated and censored data were used to determine whether the 24-mo survival was associated with baseline categories of serum HCO_3^-. The reference category (with which the death risk in other categories is compared) was the serum HCO_3^- range between 22 and 22.9 mEq/L. This range of serum HCO_3^- was chosen as the reference because it was adjacent to and had sample size similar to the modal category, had the highest numbers of death cases, and allowed for the most precise comparison with other HCO_3^- categories.

For each analysis, three models were examined on the basis of the level of multivariate adjustment: (*1*) Unadjusted models, which included HCO_3^- categories, entry quarter, and mortality data; (2) case-mix and dialysis dose models, which were adjusted for age, gender, race and ethnicity, diabetes, vintage categories, primary insurance (Medicare, Medicaid, private, and others), marriage status (married, single, divorced, widowed, and others), standardized mortality ratio of the dialysis clinic during entry quarter as reported by the United States Renal Data System (34), residual renal function during the entry quarter, the Kt/V (single pool), and dialysate bath bicarbonate concentration; and (3) case-mix plus MICS adjusted models, which included all of the above-mentioned covariates as well as 12 indicators of nutritional status and inflammation, including prescribed erythropoietin (EPO) dose (or EPO resistance index, *i.e.*, EPO dose divided by averaged hemoglobin [35]), protein intake (nPNA), serum phosphorus, calcium, albumin, TIBC, ferritin and creatinine, WBC count, lymphocyte percentage, hemoglobin level, and body mass index (BMI; postdialysis dry weight [kg] divided by height squared [m^2] [36,37]). Missing covariate data (<5%) were imputed by the mean or median of the existing values, whichever was appropriate. The only exception was the bath bicarbonate, which had approximately 25% missing data; hence, a dummy variable that also included an additional category for the missing bath bicarbonate value was created. All descriptive and multivariate statistics were carried out by the Stata, version 7.0 (College Station, TX).

Results

The original 2-yr national database of all DaVita MHD patients included 69,819 patients. After implementing the above-mentioned selection criteria, including deleting patients who did not receive MHD treatment for <3 mo (after exclusion of incident patients) or who had missing data, the resulting cohort included 56,385 MHD patients, 36,289 (64%) of whom originated from the first quarter (q1) and 20,096 (36%) of whom originated during the subsequent quarters (q2 through q8). Table 1 shows baseline demographic, clinical, and laboratory characteristics of the entire 56,386 patient cohort. Serum

Table 1. Baseline data of the nonconcurrent (left truncated) cohort of 56,385 MHD patients[a]

Variable	Incident Patients (n = 23,089)	Prevalent Patients (n = 33,296)
Age (yr)	61.4 ± 15.6	60.2 ± 15.4
>65 yr old (%)	46	42
Gender (% women)[b]	46	47
Diabetes (%)	47	44
Race and ethnicity (%)		
white	42	35
black	27	36
Asian[c]	4	4
Hispanic[c]	17	18
Vintage (%)		
<6 mo	100	0
6 to 24 mo	0	37
2 to 5 yr	0	41
>5 yr	0	22
Cohort time (d)	339 ± 221	542 ± 245
Post-HD weight (kg)[c]	73.9 ± 20.2	73.6 ± 19.6
BMI (kg/m^2)[c]	26.1 ± 6.3	26.1 ± 6.1
Kt/V (single pool)	1.51 ± 0.34	1.55 ± 0.30
nPCR or nPNA (g/kg per d)	0.98 ± 0.25	1.01 ± 0.24
Serum albumin (g/dl)	3.64 ± 0.45	3.82 ± 0.37
HCO_3^- (mEq/L)	21.7 ± 2.9	21.9 ± 2.8
Phosphorus (mg/dl)	5.6 ± 1.5	5.8 ± 1.6
Calcium (mg/dl)	9.1 ± 0.7	9.3 ± 0.7
Urea nitrogen (mg/dl)	58 ± 17	60 ± 17
Creatinine (mg/dl)	7.8 ± 3.1	9.9 ± 3.2
Potassium (mEq/L)	4.7 ± 0.7	4.9 ± 0.7
Ferritin (ng/ml)	450 ± 416	725 ± 496
TIBC (mg/dl)	209 ± 44	197 ± 40
Blood hemoglobin (g/dl)	12.2 ± 1.3	11.8 ± 1.2
WBC (1000 per fl)	7.5 ± 2.4	7.2 ± 2.3
Lymphocyte (% of total WBC)	21 ± 8	21 ± 8
Administered rHuEPO dose (units/wk)	21,880 ± 23,514	18,748 ± 22,044

[a]The cohort includes 36,289 (64%) patients from the first quarter (q1) and 20,096 (36%) from the subsequent quarters (q2 through q8). Patients are divided into two groups of incident (vintage < 6 mo) and prevalent (vintage > 6 mo). The P value for the difference between incident and prevalent patients for each variable is <0.001 unless specified otherwise. HD, hemodialysis; BMI, body mass index; HCO_3^-, serum bicarbonate; nPCR, normalized protein catabolic rate; nPNA, normalized protein nitrogen appearance; TIBC, total iron binding capacity; WBC, white blood cells; rHuEPO, recombinant human erythropoietin.

[b]P value between 0.05 and 0.001.

[c]$P > 0.05$.

HCO_3^- mean (±SD) was 21.8 ± 2.8 mEq/L (median 22.0 mEq/L; interquartile range 20.0 to 23.7 mEq/L). Among the reported fresh dialysate bicarbonate concentrations that were used in DaVita MHD patients during the first 3 mo of the cohort, they were mostly 35 mEq/L (76%), 40 mEq/L (20%), and 30 mEq/L (3%).

Table 2 shows both unadjusted and case-mix and MICS (fully) adjusted correlation coefficients between serum HCO_3^- and several pertinent clinical and laboratory variables. Serum phosphorus has one of the strongest correlations and an inverse relation with serum HCO_3^-, indicating that hyperphosphatemic MHD patients tend to have a lower serum HCO_3^- level. Similar inverse but weaker associations were also observed for serum urea nitrogen and potassium as well as the urea kinetics estimated protein intake.

Table 3 shows the 12 selected serum HCO_3^- categories. Serum phosphorus and albumin concentrations and protein intake as well as all-cause and cardiovascular mortality rates are listed for each HCO_3^- group. As depicted in Figure 1A, serum phosphorus was progressively lower in the groups with progressively higher serum HCO_3^-, corresponding to the same inverse associations mentioned above (see Table 2). Figure 1B displays serum albumin concentrations in incremental HCO_3^- groups, indicating the inverted J-shaped association between

Table 2. Correlations between HCO_3^- and relevant clinical and laboratory variables[a]

Variable	Unadjusted (Pearson) Correlation *r*	Multivariate (Partial) Correlation
Age	0.15	0.08
Dialysis dose: Kt/V (single pool)	0.08	0.02
Dialysis vintage	0.04	0.04
BMI	−0.04	0.03
Protein intake: nPNA or nPCR	**−0.22**	**−0.20**
Serum albumin	−0.11	−0.04
phosphorus	**−0.35**	**−0.25**
calcium	0.15	0.18
potassium	**−0.22**	−0.14
urea nitrogen	**−0.33**	−0.19
creatinine	−0.16	−0.10
TIBC	−0.12	−0.05
ferritin	0.04	0.02
Blood hemoglobin	−0.11	−0.09
WBC	−0.09	−0.09
lymphocyte percentage	0.03	0.03

[a]Unadjusted and multivariate adjusted case-mix plus MICS models were used (see Materials and Methods). All *P* values are <0.001 due to large sample size. Correlation coefficients of ±0.20 or stronger are in bold.

the two laboratory markers with the lowest serum albumin levels observed in the hyperbicarbonatemic MHD patients. However, a strictly downgoing association was observed for the 3-mo averaged urea kinetic indicator of protein intake (nPNA or normalized protein catabolic rate); patients with progressively lower serum HCO_3^- levels had the highest protein intake, and *vice versa* (Table 3, Figure 1C). Finally, the high serum HCO_3^- categories had the greatest 24-mo mortality rates, as demonstrated in Table 3 and Figure 1D, whereas mortality tended to be reduced in lower HCO_3^- groups.

To examine the adjusted associations between serum HCO_3^- and prospective mortality in 56,386 MHD patients, we examined Cox proportional hazard models. Figure 2 demonstrates the hazard ratios of all-cause (left) and cardiovascular (right) mortality. The HCO_3^- category of 22 to <23 mEq/L was the reference group in all models. The lowest unadjusted mortality was associated with a predialysis HCO_3^- in the 17 to 23 mEq/L range, whereas values ≥23 mEq/L were associated with progressively higher death rates, a J-shaped association. After adjustment for case mix and dialysis dose variables, a U-shaped association was noticed with increased mortality at both ends of the HCO_3^- spectrum (<17 and >27 mEq/L). After additional multivariate adjustment for 12 potential markers of the MICS, the association transformed into a reversed J-shaped relationship, so a HCO_3^- concentration of ≥22 mEq/L was associated with less risk for death, whereas HCO_3^- levels <22 mEq/L were associated with the highest death risk. Similar trends in associations between serum HCO_3^- and mortality were also observed when the cohort was divided into two subcohorts of incident (vintage <6 mo) and prevalent (vintage ≥6 mo) MHD patients (Figure 3); however, the associations and transitions across death risk of adjacent HCO_3^- groups and among three levels of adjustment were less smooth. This maybe due to mitigated statistical power and increased background noise caused by a 50% reduction in the number of deaths and sample sizes studied in each group. Figure 4 gives a schematic illustration of the change in the magnitude and the direction of

Table 3. The entire range of HCO_3^- in 56,386 MHD patients, divided into 12 incremental categories: <17, ≥27, and 10 groups in between[a]

Serum HCO_3^- Group (mEq/L)	Group Size (Absolute Number of Patients [%])	Serum Phosphorus (mg/dl)	nPNA (nPCR; g/kg per d)	Serum Albumin (g/dl)	Two-Year All-Cause Death (%)	Two-Year Cardiovascular Death (%)
<17	2061 (4)	7.1 ± 1.9	1.12 ± 0.28	3.78 ± 0.44	22	10
17 to <18	2108 (4)	6.7 ± 1.6	1.10 ± 0.26	3.80 ± 0.40	22	9
18 to <19	3520 (6)	6.4 ± 1.6	1.07 ± 0.25	3.80 ± 0.40	21	9
19 to <20	5274 (9)	6.2 ± 1.6	1.05 ± 0.25	3.79 ± 0.39	23	11
20 to <21	6968 (12)	6.0 ± 1.5	1.03 ± 0.24	3.77 ± 0.40	24	11
21 to <22	8042 (14)	5.8 ± 1.4	1.01 ± 0.23	3.77 ± 0.39	24	11
22 to <23 (base)	7997 (14)	5.6 ± 1.4	0.98 ± 0.23	3.75 ± 0.40	25	11
23 to <24	7155 (13)	5.4 ± 1.3	0.96 ± 0.23	3.73 ± 0.40	26	12
24 to <25	5374 (10)	5.2 ± 1.3	0.95 ± 0.23	3.72 ± 0.42	27	12
25 to <26	3548 (6)	5.1 ± 1.3	0.92 ± 0.22	3.68 ± 0.43	28	13
26 to <27	2132 (4)	5.0 ± 1.3	0.92 ± 0.23	3.65 ± 0.48	29	12
≥27	2207 (4)	4.7 ± 1.3	0.90 ± 0.22	3.56 ± 0.42	32	14
All patients	56,386 (100)	5.7 ± 1.5	1.00 ± 0.24	3.74 ± 0.41	25	11

[a]Estimated protein intake (*via* urea kinetics), serum levels of phosphorus and albumin, and 24-mo prospective mortality (both all-cause and cardiovascular) are shown for each HCO_3^- category (data for continuous values are mean ± SD).

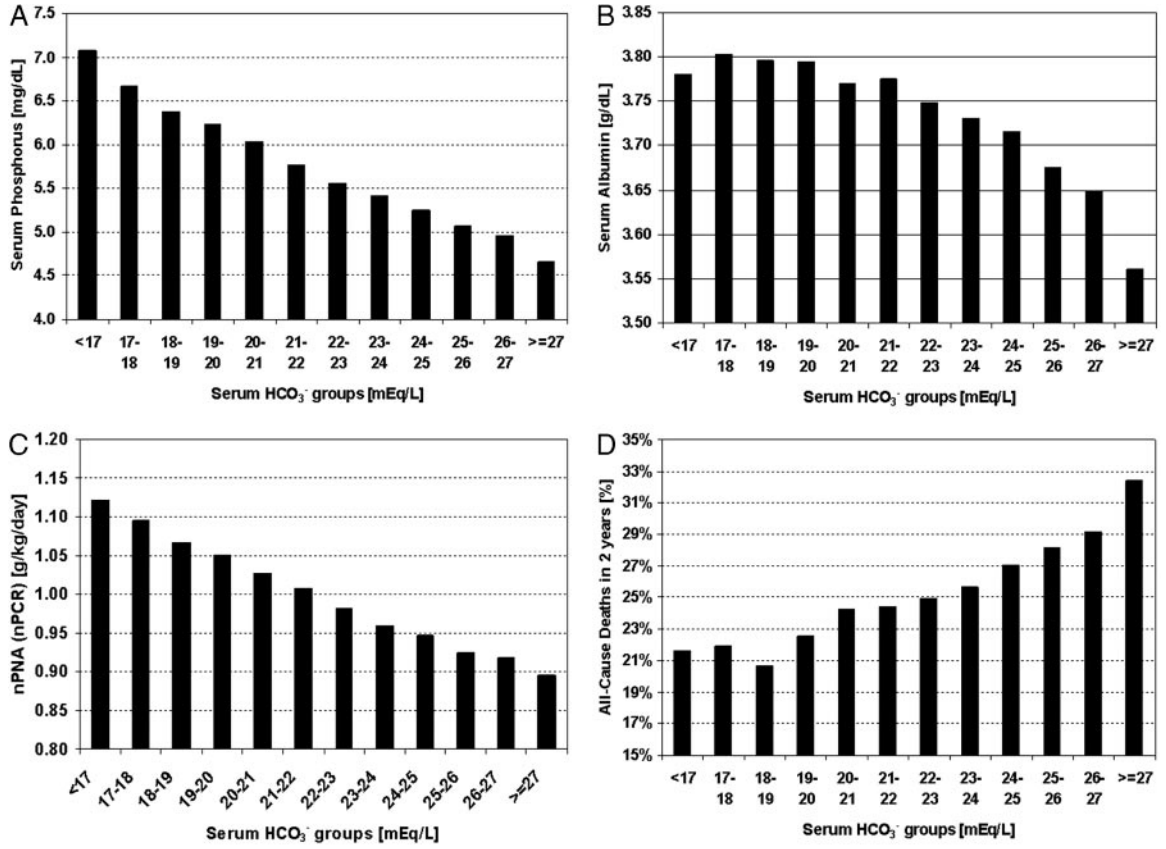

Figure 1. Relevant measures in 12 categories of serum bicarbonate (HCO_3^-) in 56,367 maintenance hemodialysis (MHD) patients. (A) Serum phosphorus concentrations in 12 categories of HCO_3^- in 56,367 MHD patients. (B) Serum albumin concentration in 12 categories of HCO_3^- in 56,386 MHD patients. (C) Urea kinetic estimated protein intake (normalized protein nitrogen appearance or normalized protein catabolic rate) in 12 categories of HCO_3^- in 56,386 MHD patients. (D) Two-year all-cause mortality rate in each of the 12 categories of HCO_3^- in 56,386 MHD patients (unadjusted data).

the associations at the three above-mentioned multivariate adjustment levels.

Sensitivity analyses, which included constructing the same multivariate models using the subcohort of 36,289 (64%) patients from q1 or only patients with the two longest vintage (>2 yr) resulted in similar hazard ratios and trends. Further subgroup analyses indicated similar patterns for both patients with and without diabetes and for MHD patients in different age and race groups, dialysis dose ranges, and serum albumin categories (data not shown). Stepwise addition of some of the case-mix and MICS covariates to the unadjusted model showed that the age and nPNA contributed substantially to the observed differences among the three models. Inclusion of serum potassium in the fully adjusted model did not substantially change the magnitude or direction of the associations. Relevant interactions, such as those between serum HCO_3^- and albumin, phosphorus, or nPNA, did not account for the differences observed among the three levels of adjustment. Addition of EPO resistance index in lieu of EPO dose did not change the associations (data not show).

Discussion

Studying a large national dialysis database, we found inverse associations between 3-mo averaged predialysis serum HCO_3^- and several nutritional indicators, including serum phosphorus, potassium, and urea levels as well as nPNA, an indicator of protein intake, in >56,000 MHD patients. These findings may indicate that a high protein intake may lead to a low serum HCO_3^- level at the start of the subsequent dialysis treatment. Moreover, we initially found improved survival rates in the acidotic range of serum HCO_3^-, whereas normal to alkalotic HCO_3^- levels seemed to be associated with higher all-cause and cardiovascular mortality. These associations, however, reversed almost entirely after multivariate adjustment for case mix and markers of malnutrition and inflammation, together also known as MICS. This striking reversal may indicate that the associations described between serum HCO_3^- and mortality by others (17,18) and also found in our unadjusted models are essentially due to the confounding effect of MICS. Moreover, because the reversal of these associations was not altered with the inclusion of serum phosphorus in the multivariate models, the role of the commonly used acidogenic phosphorus binder sevelamer hydrochloride in causing hypobicarbonatemia and its related adverse effects seems relatively immaterial. Our findings may have significant implications for the clinical treatment of >300,000 maintenance dialysis patients in the United States and many more in other countries.

Metabolic acidosis occurs commonly in patients with CKD

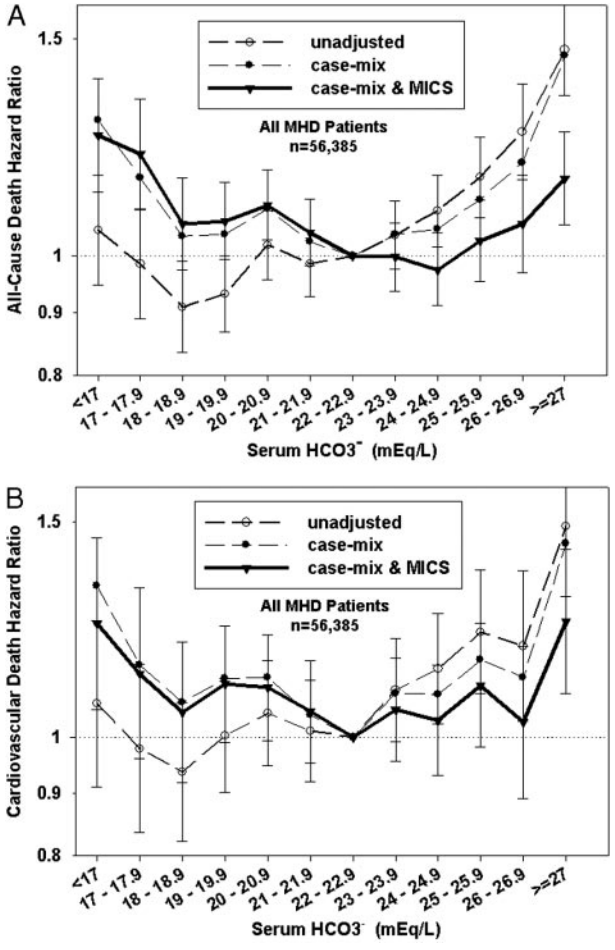

Figure 2. Hazard ratio 2-yr all-cause (right) and cardiovascular (left) mortality in each of the 12 categories of HCO_3^- in 56,385 MHD patients. Error bars indicate 95% confidence intervals for unadjusted and fully adjusted (case mix and malnutrition-inflammation complex syndrome [MICS]) models. See text for the list of covariates.

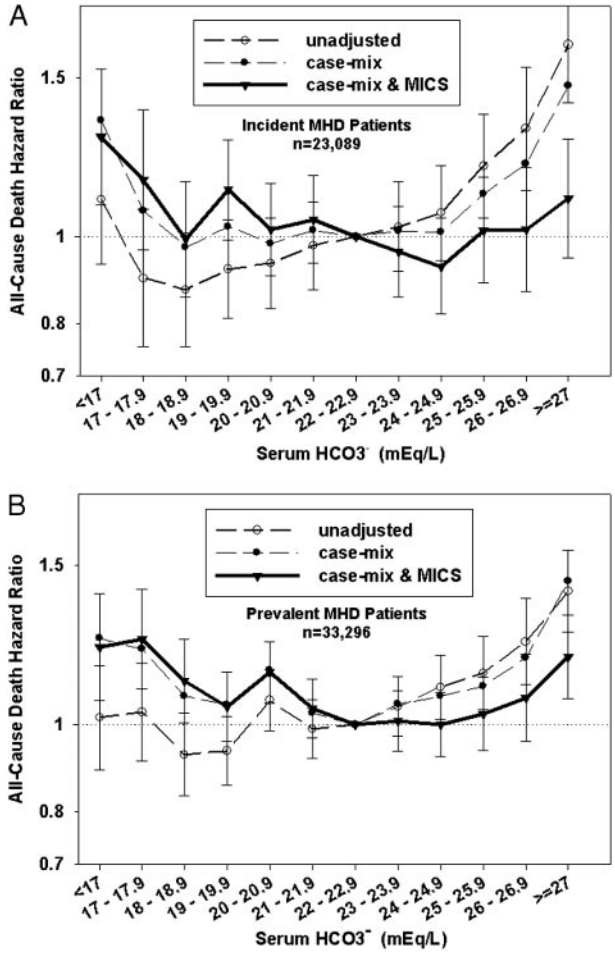

Figure 3. Hazard ratio 2-yr mortality in incident (vintage <6 mo; right) and prevalent (vintage >6 mo; left) MHD patients for the 12 categories of HCO_3^-. Error bars indicate 95% confidence intervals for unadjusted and fully adjusted (case mix and MICS) models. See text for the list of covariates.

(3,4,38,39). Acidemia is believed to be an important cause of morbidity and many adverse consequences in patients with CKD and ESRD (2,5,38,40,41). The acidosis of renal failure may contribute to protein-energy malnutrition, another common condition and a risk factor for poor outcome (41–44). Moreover, a chronic state of inflammation is commonly observed in renal failure and may predispose to both protein-energy malnutrition and increased rate of cardiovascular and atherosclerotic disease in this population (24,26). MICS is a common condition in patients with stages 4 and 5 CKD. Several mechanisms may contribute to the development of malnutrition from metabolic acidosis in patients with CKD: (*1*) Increased protein catabolism, (*2*) decreased protein synthesis, (*3*) endocrine abnormalities including insulin resistance, (*4*) reduction in serum leptin levels, and (*5*) inflammation *per se* (3–5,16,44,45).

Despite that much research indicates a catabolic response to metabolic acidosis, including subnormal levels of essential branched-chain amino acids, increased protein breakdown, and abnormalities in bone metabolism and hormonal responses (46–48), the vast majority of recent epidemiologic studies in maintenance dialysis patients have shown an inverse relationship between metabolic acidosis and nutritional status (14,18,49–55). Uribarri (50) reported a significant inverse relationship between serum HCO_3^- and nPNA and found that MHD patients with a $HCO_3^- \leq 21$ mEq/L (*versus* those ≥25 mEq/L) had a higher predialysis serum creatinine and urea level. Dumler *et al.* (51) reported a higher serum albumin, creatinine, and nPNA in MHD patients with metabolic acidosis. Gao *et al.* (52) found an inverse association between predialysis serum HCO_3^- and serum urea, phosphorus, and uric acid in 50 MHD patients. Lin *et al.* (14) reported a higher BMI, triceps skinfold thickness, dietary protein intake, nPNA, and serum potassium in acidemic MHD patients. Finally, two epidemiologic studies with large sample sizes reported by Leavey *et al.* (53) ($n = 3891$) and Chauveau *et al.* (54) ($n = 7123$) found significant inverse relationships between predialysis HCO_3^- and serum albumin as well as serum prealbumin, nPNA, and BMI, respectively. An epidemiologic analysis of a large cohort of MHD patients by Lowrie *et al.* (17) showed that the associ-

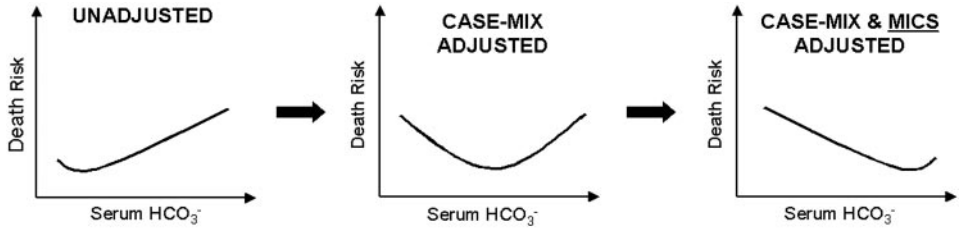

Figure 4. Schematic representation of the association between serum bicarbonate and death risk at different levels of multivariate adjustment. (Left) Unadjusted (J-shaped). (Middle) Case-mix adjusted (U-shaped). (Right) Case-mix and MICS adjusted (reverse J-shaped).

ation between the baseline serum HCO_3^- and prospective mortality was J-shaped, in that the risk for death was higher when serum HCO_3^- was either <17.5 or >25 mEq/L. This inverse association was confirmed recently by DOPPS investigators (18), who concluded that moderate predialysis acidosis seems to be associated with better nutritional status and lower relative risk for mortality or hospitalization. Although Lowrie *et al.* (56–59) discussed the possibility that confounding factors might alter or blunt the risks associated with acidemic dialysis patients, to our knowledge, our study is the first to seek to pinpoint the substantial impact of elements of MICS that lead to the alterations of the unadjusted associations.

It was shown recently that subjective reported appetite is a strong predictor of survival in MHD patients (60). A higher protein intake, as indicated by an increased nPNA, is associated with decreased mortality and hospitalization (61). This relationship seems to confound the underlying association between low serum HCO_3^- levels and increased protein catabolism with subsequent wasting and poor outcomes. Hence, it is possible but not shown unequivocally previously that MICS-adjusted associations differ substantially from unadjusted ones. With regard to correlations with outcome, our study, hence, is one of the first to suggest the plausibility of the foregoing hypothesis.

Some calcium-free phosphate binders may be implicated as a cause of metabolic acidosis and its adverse effects in MHD patients (5). Until late 1990s, most MHD patients were treated exclusively with aluminum- and calcium-based phosphate binders, which are alkaline. In the past several years, including during the studied cohort (2001 to 2003), sevelamer hydrochloride has increasingly become the primary phosphorus binders in patients with CKD because of the concerns related both to aluminum toxicity and to coronary artery calcification as a result of higher calcium intake (62,63). Each sevelamer capsule also includes some amount of nitrogen and chloride, which may lead to some decrease in HCO_3^- levels and some increase in the calculated nPNA, respectively. This might result in the reverse association between serum HCO_3^- and both serum phosphorus and nPNA, assuming that hyperphosphatemic patients received higher than average doses of sevelamer. However, given the small amount of change in nPNA as a result of intake of nitrogen contained in sevelamer, it is highly unlikely that the difference between the two ends of the HCO_3^- spectrum found in our study is the result of sevelamer intake. Hence, we believe that the association between high serum phosphorus and low serum HCO_3^- found in our study as well as by DOPPS investigators (18) is merely a reflection of increased protein intake, which will also lead to hyperphosphatemia.

A limitation of our study is lack of information on outpatient medications such as phosphorus binders and lack of explicit laboratory markers of inflammation such as C-reactive protein. However, we did use data on serum albumin, ferritin, and TIBC and WBC count and lymphocyte percentage, which also tend to reflect the presence or absence of inflammation (27,28,31). Another limitation of our analysis is that there is no proven steady state that is required for accurate calculation for nPNA equation. However, the 3-mo averaging of the nPNA values along with large sample size should mitigate this inherent limitation of this particular MICS surrogate. Our study is based on only a 24-mo follow-up, rather than longer periods of observation, so the results may not apply to long-term survival. Nonetheless, two thirds of MHD patients die within the first 5 yr of initiation of dialysis (34). The narrow time window of our study ensures that confounding by changes in practice or technology is minimal. Our study by far has the largest sample size to date, and our data originate from one dialysis care provider that has uniform patient treatment practices when compared with DOPPS data (18); all laboratory measurements are performed in one single facility, and most data are 3-mo means of several measures. Hence, measurement variability is minimized. However, we agree that there are serious problems with the accuracy of the measurement of serum bicarbonate in large-scale studies (64). Moreover, epidemiologic analyses can identify only associations; causal relationships need to be demonstrated by clinical trials. Hence, the results of epidemiologic data analyses should be considered with caution.

Conclusions

Our study provides further evidence that the MICS may be the substantial contributor to the counterintuitive associations between serum HCO_3^- and mortality, which is similar to what has been described as risk-factor paradox or reverse epidemiology in this patient population (19). On the basis of our findings, the data presented by Bommer *et al.* (18) indicating that moderate predialysis acidosis is associated with lower relative risk for mortality or hospitalization may be viewed at a different angle. Although the MICS-adjusted associations between

serum HCO_3^- and mortality are in the opposite direction of the original association, it is important to appreciate that physicians usually treat a patient on the basis of his or her unadjusted data. A low serum HCO_3^- level indeed is a marker of prolonged survival, probably because it reflects higher protein intake in MHD patients. If this concept indeed is true, then the results of this study provide further support for the need for increased attention to malnutrition, inflammation, low appetite, and inadequate food intake in MHD patients.

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