Dialysis Modality and Correction of Uremic Metabolic Acidosis: Relationship with All-Cause and Cause-Specific Mortality

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Summary

Background and objectives Uremic metabolic acidosis is only partially corrected in many hemodialysis patients, and low serum bicarbonate predicts higher death risk. This study determined the comparative efficacy of peritoneal dialysis in correcting uremic metabolic acidosis and the association of serum bicarbonate and death risk with the two therapies.

Design, setting, participants, & measurements Data were obtained from 121,351 prevalent ESRD patients (peritoneal dialysis, 10,400; hemodialysis, 110,951) treated in DaVita facilities between July 1, 2001 and June 30, 2006, with follow-up through June of 2007.

Results Serum bicarbonate was <22 mEq/L in 25% and 40% of peritoneal dialysis and hemodialysis patients, respectively. Thus, peritoneal dialysis patients were substantially less likely to have lower serum bicarbonate (adjusted odds ratio<20 mEq/L, 0.45 [0.42, 0.49]; <22 mEq/L, 0.41 [0.39, 0.43]). Time-averaged serum bicarbonate<19 mEq/L was associated with an 18% and 25% higher risk for all-cause and cardiovascular mortality, respectively, in prevalent peritoneal dialysis patients (reference group: serum bicarbonate between 24 and <25 mEq/L). In analyses using the entire cohort of peritoneal dialysis and hemodialysis patients, the adjusted risk for all-cause mortality was higher in most subgroups with serum bicarbonate<22 mEq/L, irrespective of dialysis modality.

Conclusions The measured bicarbonate is significantly higher in peritoneal dialysis patients, suggesting that the therapy provides a more complete correction of metabolic acidosis than intermittent hemodialysis. Survival data suggest maintaining serum bicarbonate>22 mEq/L for all ESRD patients, irrespective of dialysis modality.

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Introduction

Correction of metabolic acidosis, a cardinal manifestation of late stage CKD, is one of the goals of effective dialysis. In patients with CKD, uncorrected metabolic acidosis leads to clinically significant consequences like protein energy wasting and bone disease, and in hemodialysis (HD) patients, it is associated with higher death risk (1–7). Clinical trials have shown that correction of metabolic acidosis results in improvements in protein energy wasting and reduction of hospitalizations of peritoneal dialysis (PD) patients (8,9). Furthermore, high–normal arterial pH is associated with more positive nitrogen balances than low–normal pH in PD patients (10). Animal studies have also indicated that metabolic acidosis is associated with development or worsening of proteinuria and exacerbation of tubulointerstitial injury, and in humans with CKD in a randomized controlled clinical trial, correction of metabolic acidosis was shown to attenuate the rate of decline in renal function (11–13). These data may be applicable to ESRD, because residual renal function is an important predictor of survival of HD and PD patients (14,15).

Despite the risks associated with uncorrected metabolic acidosis and the demonstrable benefits with its treatment, almost one-half of HD patients evaluated in a large study had suboptimal correction of metabolic acidosis (7). To our knowledge, there are no data comparing the effectiveness of PD with HD in the correction of metabolic acidosis. Furthermore, there is no consensus whether the therapeutic targets for serum bicarbonate should differ by dialysis modality (16–20). We undertook this study to test the hypothesis that PD provides a more complete correction of metabolic acidosis and that the serum bicarbonate level below which the death risk is increased in patients does not vary by dialysis modality.

Materials and Methods

Data Source

This observational cohort study uses data from maintenance dialysis patients treated in DaVita facilities between July 1, 2001 and June 30, 2006 who were followed through June of 2007, and it is linked to the data from the US Renal Data System (USRDS). Data from DaVita were used to determine subjects' age,

sex, diabetes status, body weight, height, and dialysis modality. The USRDS data were used to determine the day of first dialysis, race/ethnicity, marital status, primary insurance, eight comorbid conditions at start of dialysis therapy, and date and cause of death.

The initial study cohort consisted of 164,801 patients. Patients were assigned to the dialysis modality used at the time of entry into the cohort. The following patients were excluded: patients with unknown or missing data on dialysis modality and patients who died, underwent renal transplantation, were lost to follow-up by day 90 from the first dialysis treatment (n=13,711), and were at extremes of age (≤16 or ≥99 years; n=7588). Furthermore, data for baseline serum bicarbonate were missing for 22,151 patients (PD: 1,658, 14%; HD: 20,493, 16%). Hence, the final cohort consisted of 121,351 subjects (PD=10,400; HD=110,951). Supplemental Table 1 summarizes the differences in characteristics of the study cohort from those patients with missing baseline bicarbonate levels stratified by dialysis modality.

Data on dialysate bicarbonate were available for 76,415 of 110,951 HD patients; there were an additional 842 subjects with values<30 or >40 mEq/L. Thus, analysis of the

Table 1. Baseline data of study cohort stratified by modality

Variable	All Patients (n=121,351)	
	PD (n=10,400)	HD (n=110,951)
Age (yr)	56±15	61±15
>65 yr old (%)	31	45
Sex (% female)	47	45
Diabetes mellitus (%)	48	58
Race/ethnicity (%)		
Asian	4	3
Black	24	32
Hispanic	13	15
White	52	42
Other	7	6
Vintage (median; mo)	34 (15, 64)	27 (11, 53)
Primary insurance (%)		
Medicare	59	61
Medicaid	3	6
Private	13	11
Others	14	12
Marital status (%)		
Single	19	22
Married	45	37
Widow	7	13
Divorced	6	7
Comorbid conditions (%)		
Atherosclerotic heart disease	15	21
Congestive heart failure	16	28
Other cardiac diseases	4	6
Cerebrovascular disease	5	8
Peripheral vascular disease	8	12
Chronic obstructive pulmonary disease	3	6
Cancer	4	4
Current smoker[a]	5	5
Weight (kg)	74±19	75±21
Body mass index (kg/m^2)	26±6	27±7
Serum albumin (g/dl)	3.6±0.5	3.7±0.5
Serum creatinine (mg/dl)	8.6±3.7	8.0±3.3
Serum ferritin (ng/ml)	277 (122, 584)	380 (180, 712)
Serum total iron binding capacity (mg/dl)	229±54	209±46
Serum calcium (mg/dl)	9.2±0.8	9.2±0.7
Serum phosphorus (mg/dl)	5.4±1.5	5.6±1.5
Serum parathyroid hormone (pg/ml)	286 (158, 524)	245 (143, 418)
Serum alkaline phosphatase (U/L)	97 (75, 131)	98 (77, 131)
Blood hemoglobin (g/dl)[a]	12.0±1.5	12.0±1.4
White blood cell count ($\times 10^3/\mu$l)	7.5±2.6	7.5±2.5
Percent lymphocyte	19.6±8	20.5±8

Data are presented as mean ± SD, median and interquartile range, or percentage. The differences in each variable were statistically significantly different between the two dialysis modalities except as indicated.
[a]The differences in each variable were not statistically significantly different between the two dialysis modalities.

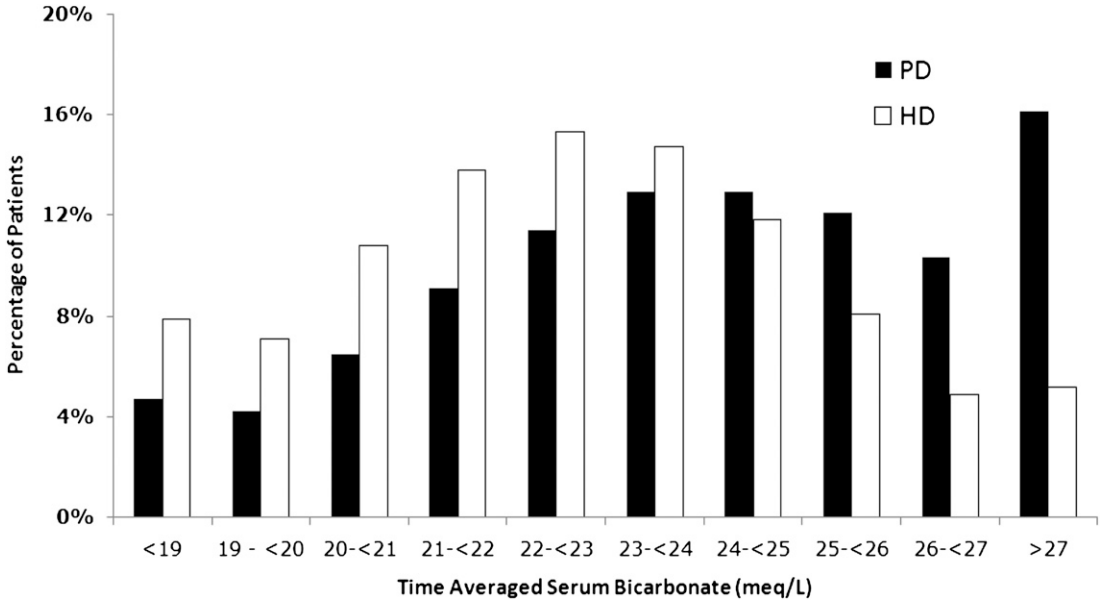

Figure 1. | **Distribution of time-averaged serum bicarbonate levels in patients treated with peritoneal dialysis (*n*=10,400) and hemodialysis (*n*=110,951).**

Table 2. Odds ratio of peritoneal dialysis patients having time-averaged serum bicarbonate values below clinically relevant thresholds using hemodialysis patients as references (95% confidence interval; peritoneal dialysis *n*=10,400; hemodialysis *n*=110,951)

Time-Averaged Serum Bicarbonate (mEq/L)	Unadjusted	Case Mix-Adjusted[a]	Case Mix and Laboratory Data-Adjusted[b]
<20	0.55 (0.51, 0.59)	0.43 (0.40, 0.46)	0.45 (0.42, 0.49)
<22	0.49 (0.46, 0.51)	0.39 (0.37, 0.41)	0.41 (0.39, 0.43)
<24	0.40 (0.39, 0.42)	0.32 (0.30, 0.33)	0.35 (0.33, 0.36)

[a]Age, sex, diabetes, race/ethnicity, primary insurance, marital status, vintage category (<6 months, 6 months to 2 years, 2–5 years, and >5 years), atherosclerotic heart disease, congestive heart failure, other cardiac diseases, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, and tobacco smoking.
[b]Case mix variables plus body mass index, serum albumin, creatinine, ferritin, total iron binding capacity, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percent lymphocyte.

relationship of time-averaged dialysate and serum bicarbonate levels was restricted to 75,573 HD patients (68%; mean ± SD of serum bicarbonate levels of patients included versus patients excluded: 22.4±2.5 versus 23.1±2.8 mEq/L).

All samples were shipped to a single central laboratory in Deland, Florida. The first studied quarter for each patient was the first calendar-quarter in which the patient's vintage was longer than 90 days. Quarterly averages were calculated for each laboratory variable using all measurements made during that 3-month period. In HD patients, the serum bicarbonate was measured in samples obtained immediately before an HD session (pre-HD). Baseline serum bicarbonate was the average value for the calendar-quarter of entry into the cohort. Time-averaged serum bicarbonate was defined as the average value of pre-HD and steady state measurements in HD and PD patients, respectively, from up to 20 calendar quarters (mean=6.8±5.6). Subjects were divided *a priori* into 10 categories based on time-averaged serum bicarbonate (<19, 19 to <20, 20 to <21, 21 to <22, 22 to <23, 23 to <24, 24 to <25, 25 to <26, 26 to <27, and ≥27 mEq/L).

The study was approved by the Institutional Review Board of Los Angeles Biomedical Research Institute at Harbor–University of California at Los Angeles as exempt from informed consent.

Statistical Methods

Complete data were available for age, sex, race, and diabetes. Data for comorbidities were missing for 5%. Insurance status was missing for 9%, marital status was missing for 21%, body mass index was missing for 7%, parathyroid hormone was missing for 12%, serum total iron binding capacity, ferritin, and creatinine, and lymphocyte percentage were missing for 1%–2%, and serum albumin, calcium, phosphorus, and alkaline phosphatase, and white blood cell count and hemoglobin were missing for <1%. The frequency of missing data was similar for both dialysis modalities, except for body mass index (missing: PD=41%; HD=3%). Missing data were imputed for the continuous variables using median, comorbid conditions using mean, and other categorical data using prevalence among individuals with complete data.

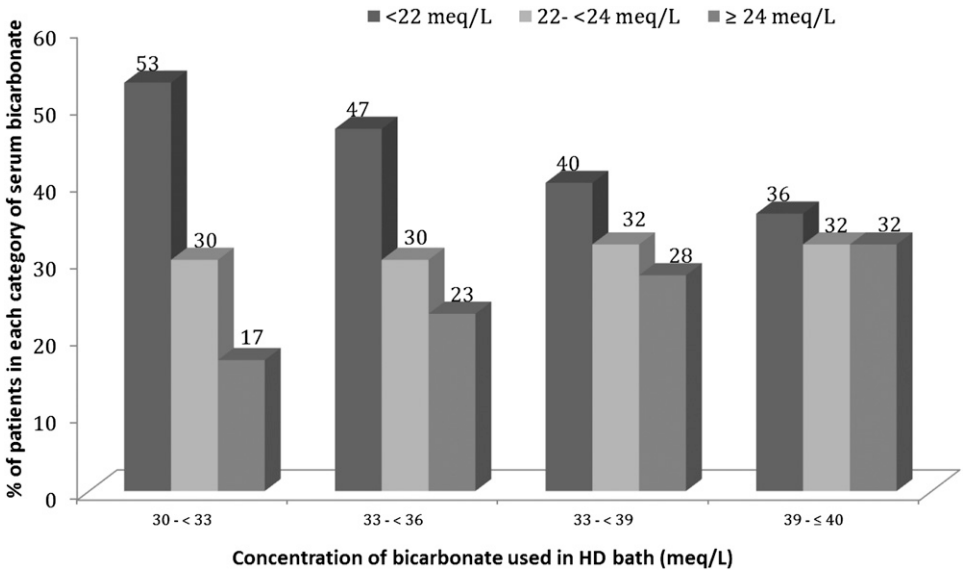

Figure 2. | Distribution of time-averaged serum bicarbonate stratified by the range of time-averaged dialysate bicarbonate concentration in 75,573 patients treated with hemodialysis.

Logistic regression analysis was used to compare the odds of having serum bicarbonate below three different thresholds (<20, <22, and <24 mEq/L) for PD patients using HD as reference. Survival analyses using Cox proportional hazard regression were performed to determine the relationship between time-averaged serum bicarbonate with all-cause, cardiovascular, and infection-related mortality in (*1*) PD patients and (*2*) the combined PD–HD cohort. The outcomes were assigned to the dialysis modality at time of entry into the study cohort. For each regression analysis, three levels of adjustment were examined: (*1*) unadjusted; (*2*) case mix-adjusted, including age, sex, race/ethnicity, presence of diabetes, eight comorbid conditions, four categories of dialysis vintage, primary insurance status, and marital status as additional covariates; and (*3*) case mix and laboratory data-adjusted with body mass index, serum total iron binding capacity, ferritin, creatinine, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, albumin, white blood cell count, lymphocyte percentage, and hemoglobin as additional covariates. The population-attributable risk of death caused by time-averaged serum bicarbonate<22 mEq/L in PD and HD patients was calculated as $P_e \times (RR - 1)/RR$, where P_e is the prevalence of low serum bicarbonate among all who died and RR is the relative risk of death (21).

All analyses were carried out using STATA, version 10.1 (StataCorp LP, College Station, TX; www.stata.com).

Results

Patient Characteristics

Baseline characteristics of the cohort stratified by dialysis modality are listed in Table 1. PD patients were younger, were more likely to be white, were less likely to have diabetes and other comorbid conditions, had higher serum creatinine, total iron binding capacity, and parathyroid hormone levels, and had lower serum ferritin level.

Distribution of Serum Bicarbonate by Dialysis Modality

Figure 1 depicts the distribution of time-averaged serum bicarbonate by dialysis modality. Serum bicarbonate was <22 mEq/L in 25% of PD patients and 40% of HD patients. The adjusted odds ratios for PD patients to have serum bicarbonate below 20, 22, and 24 mEq/L were 0.45 (0.42, 0.49), 0.41 (0.39, 0.43), and 0.35 (0.33, 0.36), respectively, compared with HD patients (Table 2). Serum potassium level was progressively higher with lower serum bicarbonate levels (serum potassium with bicarbonate<19 mEq/L: PD=5.0±0.6, HD=4.9±0.5; serum potassium with serum bicarbonate≥27 mEq/L: PD=4.0±0.5, HD=4.4±0.6). Thus, there was a progressive increase in proportion of patients with time-averaged serum potassium>5.5 mEq/L with declining serum bicarbonate levels (for serum bicarbonate<19 mEq/L, PD=10% and HD=15%; for serum bicarbonate≥27 mEq/L, PD=0.5% and HD=3%).

Completeness of correction of metabolic acidosis in HD patients was associated with the dialysate bicarbonate levels (Supplemental Table 2). Although 53% of patients dialyzed against a time-averaged bath bicarbonate concentration of 30 to <33 mEq/L had serum bicarbonate<22 mEq/L, 36% of patients dialyzed against a bath concentration of 39 to ≤40 mEq/L had that level (Figure 2). For each strata of serum and dialysate bicarbonate, the mean single-pool Kt/V_{urea} was significantly higher than the minimum value considered an adequate dialysis dose (Supplemental Table 3).

Serum Bicarbonate and Death Risk in PD Patients

With increasing time-averaged serum bicarbonate, PD patients were older, were more likely to be diabetic and have cardiovascular comorbidities, had shorter dialysis vintage, and had lower serum creatinine, ferritin, phosphorus, and parathyroid hormone levels (Table 3).

On follow-up of the 10,400 PD patients, 2912 (28%) patients received a kidney transplant, and 4710 (45%) patients died

Table 3. Baseline characteristics of patients treated with peritoneal dialysis at time of entry into cohort stratified by time-averaged serum bicarbonate

	Time-Averaged Serum Bicarbonate (mEq/L; Number of Subjects)									
	<19 (*n*=484)	19 to <20 (*n*=441)	20 to <21 (*n*=677)	21 to <22 (*n*=940)	22 to <23 (*n*=1181)	23 to <24 (*n*=1340)	24 to <25 (*n*=1341)	25 to <26 (*n*=1255)	26 to <27 (*n*=1072)	≥27 (*n*=1669)
Age (yr)	51±14	50±15	52±15	52±15	54±15	55±15	56±15	58±15	58±15	61±15
>65 yr old (%)	17	17	21	22	27	29	32	37	39	47
Sex (% female)	53	51	52	49	46	48	45	47	44	46
Diabetes mellitus (%)	42	43	47	46	47	47	50	49	51	55
Race/ethnicity (%)										
Asian	5	2	3	4	4	4	5	5	5	5
Black	19	23	23	26	27	26	23	22	23	23
Hispanic	13	16	14	14	11	12	14	12	14	13
White	50	52	52	49	50	49	51	54	52	54
Other	11	7	7	5	7	8	6	5	4	4
Vintage (median; mo)	53 (24, 94)	55 (30, 92)	51 (25, 87)	48 (24, 86)	42 (20, 72)	37 (17, 68)	31 (15, 56)	28 (13, 52)	26 (12, 49)	21 (9, 44)
Primary insurance (%)										
Medicare	66	60	61	58	59	59	58	56	59	62
Medicaid	5	3	3	3	3	3	3	2	3	2
Private	11	15	14	15	14	14	13	13	11	8
Other	8	9	11	12	12	14	14	18	17	17
Marital status (%)										
Single	23	23	21	24	20	20	17	17	18	15
Married	39	37	40	40	42	44	46	49	49	53
Widow	6	4	6	5	6	6	6	8	6	11
Divorced	8	9	8	6	6	7	6	7	6	5
Comorbid conditions (%)										
Atherosclerotic heart disease	11	13	13	14	14	15	15	15	17	20
Congestive heart failure	13	12	15	15	13	16	17	14	19	20
Other cardiac diseases	2	2	3	3	4	3	4	5	5	6
Cerebrovascular disease	4	2	4	4	4	4	5	6	6	6
Peripheral vascular disease	6	6	5	7	7	9	8	8	8	10
COPD	4	3	3	3	3	3	3	3	3	4
Cancer	2	1	3	3	3	3	4	5	5	4
Current smoker	7	6	7	6	5	5	4	5	6	4
Weight (kg)	72±20	74±19	74±19	73±19	74±19	75±19	75±18	74±18	72±17	71±17
Body mass index (kg/m^2)	26±6	26±6	27±6	26±6	26±6	26±6	27±6	26±6	25±5	25±5
Serum albumin (g/dl)	3.7±0.5	3.7±0.5	3.7±0.5	3.7±0.5	3.6±0.5	3.6±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.4±0.5

Table 3. (Continued)

	Time-Averaged Serum Bicarbonate (mEq/L; Number of Subjects)								
	<19 (*n*=484)	19 to <20 (*n*=441)	20 to <21 (*n*=677)	21 to <22 (*n*=940)	22 to <23 (*n*=1181)	23 to <24 (*n*=1340)	24 to <25 (*n*=1341)	25 to <26 (*n*=1255)	26 to <27 (*n*=1072)	≥27 (*n*=1669)
Serum creatinine (mg/dl)	10.1±3.7	9.9±3.7	9.5±3.6	9.4±3.4	9.1±3.5	8.8±3.6	8.5±3.5	8.0±3.4	7.9±3.5	7.0±3.4
Serum ferritin (ng/ml)	398 (171, 748)	381 (166, 741)	359 (146, 699)	344 (153, 677)	314 (138, 647)	291 (130, 602)	254 (115, 531)	229 (108, 488)	241 (102, 470)	228 (104, 467)
Serum total iron binding capacity (mg/dl)	215±45	214±52	218±53	222±56	223±55	228±55	233±52	237±55	235±54	237±51
Serum calcium (mg/dl)	9.1±0.9	9.2±0.9	9.2±0.8	9.2±0.9	9.2±0.8	9.2±0.8	9.1±0.8	9.2±0.7	9.2±0.8	9.1±0.7
Serum phosphorus (mg/dl)	6.6±1.9	6.3±1.7	6.0±1.6	5.9±1.6	5.6±1.5	5.5±1.4	5.3±1.4	5.0±1.3	4.9±1.2	4.6±1.2
Serum parathyroid hormone (pg/ml)	333 (188, 684)	277 (157, 588)	308 (168, 544)	342 (172, 619)	298 (170, 579)	315 (176, 315)	287 (162, 531)	282 (158, 499)	268 (138, 476)	240 (136, 413)
Alkaline phosphatase (U/L)	97 (75, 131)	106 (79, 149)	101 (77, 146)	101 (76, 138)	97 (74, 130)	96 (75, 127)	96 (75, 131)	96 (75, 128)	94 (74, 124)	95 (74, 122)
Blood hemoglobin (g/dl)	11.7±1.5	11.8±1.5	11.9±1.5	11.8±1.5	11.8±1.5	11.9±1.5	12.0±1.5	12.1±1.5	12.1±1.5	12.1±1.5
WBC count ($\times 10^3/\mu l$)	8.0±2.6	7.6±2.5	7.7±2.5	7.5±2.4	7.6±2.7	7.5±2.6	7.6±3.3	7.3±2.4	7.4±2.5	7.2±2.2
Percent lymphocyte	19.1±7.9	20.1±8.1	19.5±8.5	19.6±7.9	19.9±7.8	19.7±7.8	19.5±7.9	19.6±7.6	19.2±7.5	19.3±7.8

Data are presented as mean ± SD, median and interquartile range, or percentage. COPD, chronic obstructive pulmonary disease; WBC, white blood cell count.

(cardiovascular=1964; infection-related=948). PD patients with time-averaged serum bicarbonate levels<19 mEq/L had an adjusted hazards ratio for all-cause mortality of 1.18 (1.01–1.37) and an adjusted hazards ratio for cardiovascular mortality of 1.25 (1.00–1.57; reference group: time-averaged serum bicarbonate=24 to <25 mEq/L) (Figure 3 and Table 4). However, there was no association between serum bicarbonate levels and infection-related mortality. Inclusion of serum potassium as a covariate attenuated the hazards ratio for all-cause and cardiovascular mortality in PD patients with time-averaged serum bicarbonate levels<19 mEq/L, but it had no meaningful effect in other subgroups.

Comparison of Association of Serum Bicarbonate with Death Risk in PD and HD Patients

On follow-up of the 110,951 HD patients, 13,540 (12%) patients received a kidney transplant, and 60,087 (54%) patients died (cardiovascular=24,695; infection-related=10,628). For this analysis, HD patients with time-averaged pre-HD serum bicarbonate of 24 to <25 mEq/L were used as the reference group. The adjusted risk for all-cause mortality was higher in most subgroups with serum bicarbonate<22 mEq/L, irrespective of the dialysis modality (Figure 4 and Table 5). Although there was no graded relationship between serum bicarbonate and cardiovascular or infection-related mortality in PD patients, a higher risk was seen in HD patients with serum bicarbonate of <24 and <22 mEq/L, respectively (Figure 4 and Table 5). Inclusion of serum potassium as a covariate had no meaningful effect on hazards ratio for any of the outcomes in any of the subgroups examined. The population-attributable risks for all-cause mortality with time-averaged serum bicarbonate<22 mEq/L in PD and HD patients were 2.3% (0.07, 4.6) and 5.6% (4.6, 6.7), respectively.

Sensitivity Analyses

Three sets of sensitivity analyses were performed. In the first analysis, only individuals with complete data for all variables were included (PD=3050; HD=60,589). The same qualitative trends were observed with a few exceptions—unlike the primary analysis, infection-related mortality was higher in PD patients with time-average serum bicarbonate≥27 mEq/L (Supplemental Table 4). Furthermore, in the analysis using the combined PD and HD cohort, cardiovascular mortality was also higher with time-averaged serum bicarbonate<19 mEq/L in PD patients (Supplemental Table 4). In the second sensitivity analysis, models were built after excluding marital status and body mass index—covariates with the highest proportion of missing data. All-cause and cardiovascular mortality was higher in both PD patients and the entire PD–HD cohort with time-averaged serum bicarbonate<20 and <22 mEq/L, respectively (Supplemental Tables 5 and 6). In the third sensitivity analysis, 3 mEq/L was added to the measured predialysis serum bicarbonate of HD patients to yield an adjusted bicarbonate value to account for the interdialytic variation in the control of metabolic acidosis. Survival analyses were repeated in the PD–HD cohort, with HD patients with adjusted serum bicarbonate=26 to <27 as reference. The general trend of higher all-cause and cardiovascular mortality with higher death risk was

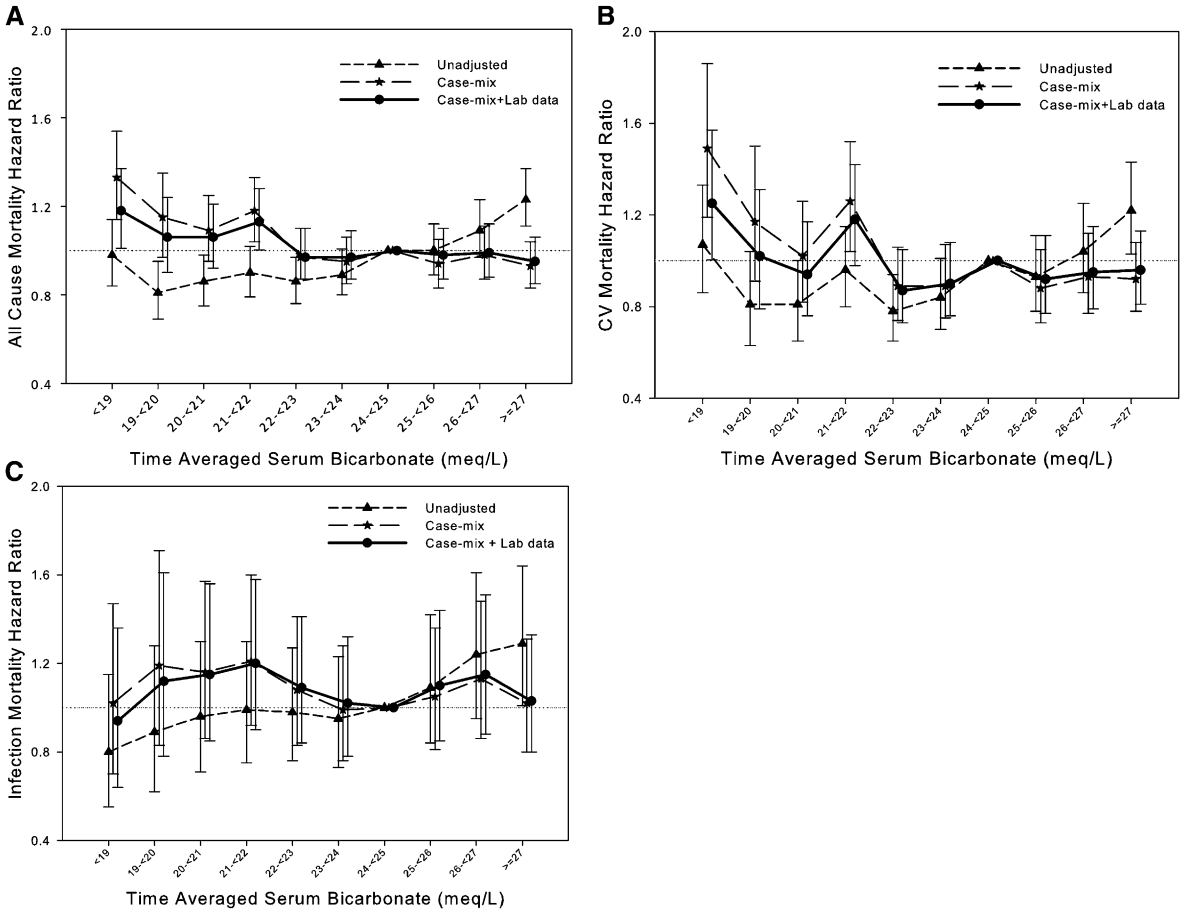

Figure 3. | Association of time-averaged serum bicarbonate concentration with mortality in patients undergoing peritoneal dialysis (*n*=10,400). (A) All-cause mortality. (B) Cardiovascular mortality. (C) Infection-related mortality. Reference group: peritoneal dialysis patients with time-averaged serum bicarbonate levels from 24 to <25 mEq/L.

Table 4. Association of time-averaged serum bicarbonate with all-cause, cardiovascular, and infection-related mortality in patients treated with peritoneal dialysis (*n*=10,400)

Time-Averaged Serum Bicarbonate (mEq/L)	Population (%)	Adjusted Hazards Ratio (95% Confidence Interval)		
		All-Cause	Cardiovascular	Infection-Related
<19	5	1.18 (1.01–1.37)	1.25 (1.00–1.57)	0.94 (0.64–1.36)
19 to <20	4	1.06 (0.90–1.24)	1.02 (0.79–1.31)	1.12 (0.78–1.61)
20 to <21	7	1.06 (0.92–1.21)	0.94 (0.76–1.17)	1.15 (0.85–1.56)
21 to <22	9	1.13 (1.00–1.28)	1.18 (0.98–1.42)	1.20 (0.90–1.58)
22 to <23	11	0.97 (0.87–1.10)	0.87 (0.73–1.05)	1.09 (0.84–1.41)
23 to <24	13	0.97 (0.87–1.09)	0.90 (0.76–1.08)	1.02 (0.78–1.32)
24 to <25	13	Reference	Reference	Reference
25 to <26	12	0.98 (0.87–1.10)	0.92 (0.77–1.11)	1.10 (0.85–1.44)
26 to <27	10	0.99 (0.88–1.12)	0.95 (0.79–1.15)	1.15 (0.88–1.51)
≥27	16	0.95 (0.85–1.06)	0.96 (0.81–1.13)	1.03 (0.80–1.33)

Data adjusted for age, sex, race and/or ethnicity, diabetes, dialysis vintage (<6 months, 6 months to 2 years, 2–5 years, and >5 years), primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, body mass index, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count.

Table 5. Association of time-averaged serum bicarbonate and all-cause, cardiovascular, and infection-related mortality in patients treated with peritoneal dialysis (*n*=10,400) and hemodialysis (*n*=110,951)

Time-Averaged Serum Bicarbonate (mEq/L)	Population (%)		Adjusted Hazards Ratio (95% Confidence Interval)					
			All-Cause Mortality		Cardiovascular Mortality		Infection-Related Mortality	
	PD	HD	PD	HD	PD	HD	PD	HD
<19	5	8	1.18 (1.04–1.35)	1.35 (1.30–1.41)	1.41 (1.17–1.71)	1.46 (1.37–1.54)	1.08 (0.78–1.50)	1.53 (1.40–1.68)
19 to <20	4	7	1.09 (0.95–1.26)	1.18 (1.13–1.22)	1.17 (0.94–1.46)	1.21 (1.13–1.28)	1.33 (0.97–1.82)	1.31 (1.19–1.44)
20 to <21	7	11	1.12 (1.00–1.25)	1.14 (1.10–1.18)	1.28 (0.94–1.34)	1.19 (1.13–1.26)	1.38 (1.07–1.77)	1.24 (1.14–1.34)
21 to <22	9	14	1.15 (1.04–1.26)	1.10 (1.06–1.13)	1.33 (1.15–1.54)	1.13 (1.08–1.19)	1.38 (1.11–1.71)	1.13 (1.05–1.22)
22 to <23	11	15	0.99 (0.91–1.09)	1.03 (1.01–1.07)	0.99 (0.86–1.14)	1.07 (1.01–1.12)	1.26 (1.03–1.53)	1.04 (0.97–1.13)
23 to <24	13	15	1.01 (0.93–1.10)	1.01 (0.98–1.04)	1.05 (0.91–1.20)	1.05 (1.00–1.10)	1.20 (0.99–1.46)	1.02 (0.94–1.10)
24 to <25	13	12	1.03 (0.95–1.12)	Reference	1.14 (1.01–1.29)	Reference	1.16 (0.95–1.40)	Reference
25 to <26	12	8	1.01 (0.92–1.10)	0.97 (0.93–1.01)	1.06 (0.92–1.21)	0.94 (0.89–1.01)	1.27 (1.05–1.55)	1.01 (0.93–1.11)
26 to <27	10	5	1.02 (0.93–1.12)	0.95 (0.91–0.99)	1.09 (0.94–1.26)	0.93 (0.86–0.99)	1.33 (1.09–1.64)	0.91 (0.81–1.01)
≥27	16	5	0.97 (0.90–1.05)	1.04 (1.00–1.09)	1.10 (0.99–1.25)	1.03 (0.96–1.10)	1.18 (0.99–1.40)	0.97 (0.87–1.08)

Data adjusted for age, sex, race and/or ethnicity, diabetes, dialysis vintage (<6 months, 6 months to 2 years, 2–5 years, and >5 years), primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, body mass index, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count. HD, hemodialysis; PD, peritoneal dialysis.

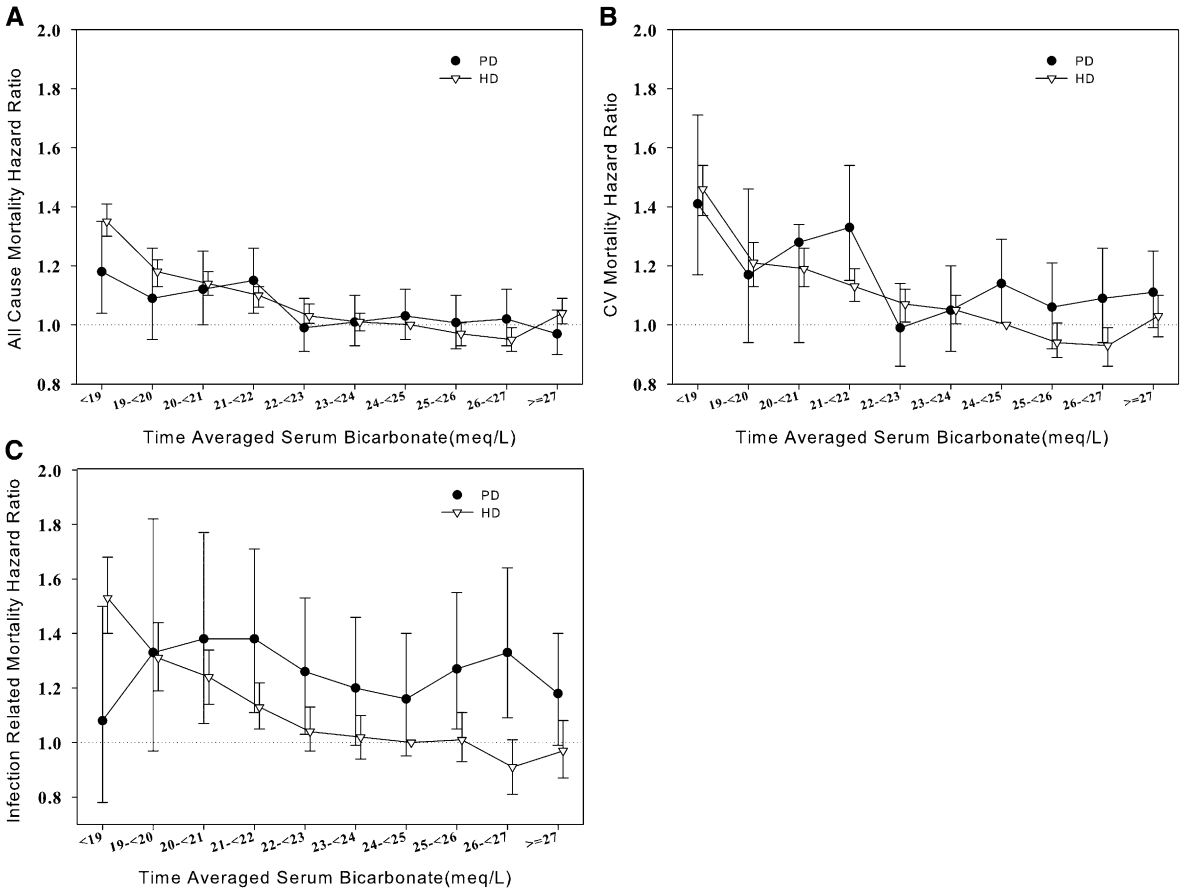

Figure 4. | Association of time-averaged serum bicarbonate concentration with outcomes in patients undergoing peritoneal dialysis (*n*=10,400) and hemodialysis (*n*=110,951). (A) All-cause mortality. (B) Cardiovascular mortality. (C) Infection related mortality. Reference group: hemodialysis patients with serum bicarbonate levels from 24 to <25 mEq/L.

observed, albeit with different thresholds for each dialysis modality (Supplemental Table 7).

Discussion

Our study allows us to make a few key observations. First, between 2001 and 2006, a substantial proportion of maintenance dialysis patients in the United States had an inadequate correction of uremic metabolic acidosis; complete correction was more likely with PD (PD=75%; HD=60%). Second, this study is the first to report an association between serum bicarbonate and death risk in PD patients and shows that the threshold below which death risk is higher is the same irrespective of dialysis modality (<22 mEq/L).

The present study is the largest evaluation of the adequacy of correction of metabolic acidosis, and to our knowledge, it is the first comprehensive comparison of PD and HD patients. There was a large difference in the proportion of PD and HD patients with time-averaged serum bicarbonate<22 mEq/L—25% and 40%, respectively. The previous studies that had evaluated the distribution of serum bicarbonate levels in PD patients were limited, because they were derived from a single center and/or had small sample sizes. In two single-center studies, serum bicarbonate was <22 mEq/L in 21% and 16% of patients, respectively (*n*=43 and *n*=79, respectively) (22,23). In contrast, a larger study reported a lower prevalence of uncorrected metabolic acidosis in PD patients (*n*=252; serum bicarbonate<22 mEq/L=10%–12%) (24). The significantly higher prevalence of serum bicarbonate levels<22 mEq/L in HD patients is similar to earlier reports. Thus, a previous analysis reported that 49% of the HD patients had serum bicarbonate<22 mEq/L at an earlier time period (7). Similarly, two other studies have shown that one-third to one-half of HD patients have inadequate correction of metabolic acidosis (*n*=7123 and 1000, respectively) (25,26).

One of the reasons for the higher prevalence of low serum bicarbonate levels in our study may be that the measurements were made in samples shipped overnight to a central laboratory; this practice has been shown to result in lower serum bicarbonate levels (27). Nevertheless, almost 80% of dialysis patients in the United States are treated in facilities owned by large dialysis organizations (28); all laboratory specimens in these facilities are shipped overnight to a central laboratory. Hence, our findings have substantial external validity in the United States. Moreover, the effect is unlikely to vary by dialysis modality, and thus, our finding of differential correction of metabolic acidosis by modality remains robust.

Several explanations for the large differences observed by dialysis modality can be considered. First, the measured

serum bicarbonate in PD patients is an equilibrated value. In contrast, HD is an intermittent therapy, with a saw-tooth pattern of metabolic control, and the pre-HD serum bicarbonate is the lowest value for the patient. Second, notwithstanding the timing of measurement, it is conceivable that PD may be more effective in correcting metabolic acidosis because of the continuous nature of the therapy. Third, differences may, in part, be caused by differences in concentrations of the buffer in the dialysate. Although the peritoneal dialysate contains 40 mEq/L lactate, most HD patients are dialyzed against bath bicarbonate with ≤35 mEq/L.

To our knowledge, this study is the first to show an increased death risk with low serum bicarbonate in PD patients. The results of at least three previous studies that have examined this question in HD patients have been inconsistent; our study builds on these previous findings. In a landmark study of prognostic predictors for HD patients, the work by Lowrie and Lew (5) reported an increased death risk with serum bicarbonate<17.5 or >25 mEq/L. However, the study reported only univariate associations (5). Analysis of data from the Dialysis Outcomes and Practice Patterns also showed a higher adjusted death risk for HD patients with predialysis bicarbonate<17 or >27 mEq/L, with the lowest mortality in patients with serum bicarbonate of 20.1–21.0 mEq/L (6). In the largest study to have examined this issue before our current analysis, a reverse J-shaped pattern between serum bicarbonate and mortality was noted, with lower death risk with serum bicarbonate>22 mEq/L (7). These findings are consistent with our observation of a higher death risk with time-averaged bicarbonate levels<22 mEq/L. The use of time-averaged values in this study provides a more robust association with death risk than has been reported thus far.

The mechanisms whereby uncorrected metabolic acidosis may increase the death risk of dialysis patients are unclear. Low arterial pH is associated with hyperkalemia from a transcellular shift of potassium, a significant predictor of death risk (29,30). In our cohort, the likelihood of significant hyperkalemia increased with decrease in serum bicarbonate. Acidosis also induces protein energy wasting through increased protein catabolism, decreased protein synthesis, and increased insulin resistance (1–4). Other potential mechanisms include systemic inflammation and a more rapid loss of residual renal function (11–13,31–35). Furthermore, metabolic acidosis leads to a net calcium efflux from the bone, which in turn, can lead to fragility fractures and is associated with a higher death risk in HD patients (36,37).

Although there are no clinical trials that show that correction of metabolic acidosis tangibly improves any hard outcomes in dialysis patients, our study lends support to the argument for a more aggressive approach to the problem. Correction of metabolic acidosis has been associated with improvements in important intermediate measures in PD patients or patients at earlier stages of CKD. Thus, in a clinical trial using peritoneal dialysate with 35 versus 40 mEq/L lactate, at the end of 12 months, patients treated with the latter had higher increase in body weight, greater mid-arm circumference, and fewer hospitalizations (9). In another clinical trial, PD patients treated with oral sodium bicarbonate to achieve a serum bicarbonate level of 26–28 mEq/L had better subjective global assessment scores, higher normalized protein catabolic rates, and fewer hospitalizations (8). Consistent with these findings, an arterial pH of 7.45 was associated with more positive nitrogen balances in seven of eight PD patients compared with a pH of 7.37 (10). Finally, correction of metabolic acidosis has been shown to slow the rate of decline of renal function (11–13).

To date, there has been no consensus among expert groups whether the target serum bicarbonate levels should vary by dialysis modality. Clinical practice guidelines from the National Kidney Foundation Disease Outcomes Quality Initiative recommend serum bicarbonate levels≥22 mEq/L, irrespective of dialysis modality (16,17). In contrast, the United Kingdom Renal Association recommends serum bicarbonate to be within the normal range for PD patients but provides greater latitude for HD patients (target predialysis values=18–24 mEq/L) (18,19). Similarly, the European Best Practice Guidelines recommend achieving bicarbonate levels≥25 mEq/L for PD patients but 20–22 mEq/L for HD patients (20). To our knowledge, this study provides the first comparison of the level of serum bicarbonate below which death risk goes up in HD and PD patients using values as they are measured in clinical practice. Given that death risk increased with serum bicarbonate levels<22 mEq/L in both HD and PD patients, our study suggests that the targets should not vary by dialysis modality.

Our study is not without limitations. First, there were some variables for which information was not available for all patients. We undertook several sensitivity analyses to determine the impact of this limitation, each of which produced similar findings. Second, information on some potential confounders, like serum C-reactive protein or residual renal function, was missing. We attempted to overcome this limitation by adjusting for surrogates for inflammation and dialysis vintage, respectively. Third, data on adherence to dialysis regimen and information about PD prescription modality (continuous ambulatory or automated PD), solute clearances, or peritoneal transport rate were unavailable. Fourth, although information on small solute clearances was available for HD patients, it was not available for PD patients. The overwhelming majority of dialysis patients in the United States achieves the recommended targets for dialysis adequacy. Indeed, in 2005, 93% each of PD and HD patients had a weekly Kt/V_{urea}≥1.7 or per-session single-pool Kt/V_{urea}≥1.2 (38). Fifth, this study reports data from 2001 to 2006, and practices may have changed since that time. Finally, data on comorbidity were obtained from the time of start of dialysis, and the use of Medical Evidence Form 2728 may have led us to underestimate the prevalence of different comorbid conditions (39).

In conclusion, our study shows that uncorrected metabolic acidosis is more likely to be present in HD than PD patients. Given the consistent association of low bicarbonate levels with higher death risk and the absence of an adequately powered clinical trial, all attempts should be made to correct uremic metabolic acidosis.

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References

1. Mehrotra R, Kopple JD, Wolfson M: Metabolic acidosis in maintenance dialysis patients: Clinical considerations. *Kidney Int Suppl* 88: S13–S25, 2003
2. Chiu YW, Mehrotra R: What should define optimal correction of metabolic acidosis in chronic kidney disease? *Semin Dial* 23: 411–414, 2010
3. Bailey JL, Wang X, England BK, Price SR, Ding X, Mitch WE: The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. *J Clin Invest* 97: 1447–1453, 1996
4. May RC, Bailey JL, Mitch WE, Masud T, England BK: Glucocorticoids and acidosis stimulate protein and amino acid catabolism in vivo. *Kidney Int* 49: 679–683, 1996
5. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15: 458–482, 1990
6. Bommer J, Locatelli F, Satayathum S, Keen ML, Goodkin DA, Saito A, Akiba T, Port FK, Young EW: Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 44: 661–671, 2004
7. Wu DY, Shinaberger CS, Regidor DL, McAllister CJ, Kopple JD, Kalantar-Zadeh K: Association between serum bicarbonate and death in hemodialysis patients: Is it better to be acidotic or alkalotic? *Clin J Am Soc Nephrol* 1: 70–78, 2006
8. Szeto CC, Lai KN: Metabolic acidosis and nutritional status of patients receiving continuous ambulatory peritoneal dialysis (CAPD). *Int J Artif Organs* 21: 192–195, 1998
9. Stein A, Moorhouse J, Iles-Smith H, Baker F, Johnstone J, James G, Troughton J, Bircher G, Walls J: Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int* 52: 1089–1095, 1997
10. Mehrotra R, Bross R, Wang H, Appell M, Tso L, Kopple JD: Effect of high-normal compared with low-normal arterial pH on protein balances in automated peritoneal dialysis patients. *Am J Clin Nutr* 90: 1532–1540, 2009
11. Gadola L, Noboa O, Márquez MN, Rodriguez MJ, Nin N, Boggia J, Ferreiro A, García S, Ortega V, Musto ML, Ponte P, Sesser P, Pizarrosa C, Ravaglio S, Vallega A: Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int* 65: 1224–1230, 2004
12. Nath KA, Hostetter MK, Hostetter TH: Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 76: 667–675, 1985
13. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM: Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 20: 2075–2084, 2009
14. Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: A reanalysis of the CANUSA study. *J Am Soc Nephrol* 12: 2158–2162, 2001
15. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT; NECOSAD Study Group: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 15: 1061–1070, 2004
16. K/DOQI, National Kidney Foundation: Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 35 [Suppl 2]: S1–S140, 2000
17. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42 [Suppl 3]: S1–S201, 2003
18. Davies S: Clinical Practice Guidelines Module 3b: Peritoneal Dialysis, 2008. Available at: www.renal.org. Accessed April 9, 2012
19. Mactier R: Clinical Practice Guidelines: Hemodialysis, 2008. Available at: www.renal.org. Accessed April 9, 2012
20. Fouque D, Vennegoor M, ter Wee P, Wanner C, Basci A, Canaud B, Haage P, Konner K, Kooman J, Martin-Malo A, Pedrini L, Pizzarelli F, Tattersall J, Tordoir J, Vanholder R: EBPG guideline on nutrition. *Nephrol Dial Transplant* 22 [Suppl 2]: ii45–ii87, 2007
21. Greenland S: Applications of stratified analysis methods. In: *Modern Epidemiology*, 2nd Ed., edited by Rothman K, Greenland S, Philadelphia, Lipincott-Raven, 1998
22. Kung SC, Morse SA, Bloom E, Raja RM: Acid-base balance and nutrition in peritoneal dialysis. *Adv Perit Dial* 17: 235–237, 2001
23. Dumler F, Galan M: Impact of acidosis on nutritional status in chronic peritoneal dialysis patients. *Adv Perit Dial* 12: 307–310, 1996
24. Mujais S: Acid-base profile in patients on PD. *Kidney Int Suppl* 88: S26–S36, 2003
25. Chauveau P, Fouque D, Combe C, Laville M, Canaud B, Azar R, Cano N, Aparicio M, Leverve X; French Study Group for Nutrition in Dialysis: Acidosis and nutritional status in hemodialyzed patients. *Semin Dial* 13: 241–246, 2000
26. Uribarri J, Levin NW, Delmez J, Depner TA, Ornt D, Owen W, Yan G: Association of acidosis and nutritional parameters in hemodialysis patients. *Am J Kidney Dis* 34: 493–499, 1999
27. Kirschbaum B: Spurious metabolic acidosis in hemodialysis patients. *Am J Kidney Dis* 35: 1068–1071, 2000
28. United States Renal Data System: *US Department of Public Health and Human Services, Public Health Service*, Bethesda, MD, National Institutes of Health, 2011
29. Torlén K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R: Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin J Am Soc Nephrol* 7: 1272–1284, 2012
30. Kovesdy CP, Regidor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K: Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2: 999–1007, 2007
31. Lim VS, Yarasheski KE, Flanigan MJ: The effect of uraemia, acidosis, and dialysis treatment on protein metabolism: A longitudinal leucine kinetic study. *Nephrol Dial Transplant* 13: 1723–1730, 1998.
32. Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship TH: Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 265: E230–E235, 1993
33. Graham KA, Reaich D, Channon SM, Downie S, Gilmour E, Passlick-Deetjen J, Goodship TH: Correction of acidosis in CAPD decreases whole body protein degradation. *Kidney Int* 49: 1396–1400, 1996
34. Graham KA, Reaich D, Channon SM, Downie S, Goodship TH: Correction of acidosis in hemodialysis decreases whole-body protein degradation. *J Am Soc Nephrol* 8: 632–637, 1997
35. Stenvinkel P, Chung SH, Heimbürger O, Lindholm B: Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. *Perit Dial Int* 21 [Suppl 3]: S157–S162, 2001
36. Bushinsky DA: Net calcium efflux from live bone during chronic metabolic, but not respiratory, acidosis. *Am J Physiol* 256: F836–F842, 1989
37. Taal MW, Roe S, Masud T, Green D, Porter C, Cassidy MJ: Total hip bone mass predicts survival in chronic hemodialysis patients. *Kidney Int* 63: 1116–1120, 2003
38. United States Renal Data System: *US Department of Public Health and Human Services, Public Health Service*, Bethesda, MD, National Institutes of Health, 2008
39. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ: Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: The CHOICE Study. *J Am Soc Nephrol* 13: 1918–1927, 2002

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See related editorial, "Basically, Dialysis Is Not Good Enough," on pages 177–178.