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Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans

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Recent studies suggest that correcting low serum bicarbonate levels may reduce the progression of kidney disease; however, few patients with chronic kidney disease have low serum bicarbonate. Therefore, we examined whether higher levels of serum bicarbonate within the normal range (20–30 mmol/l) were associated with better kidney outcomes in the African American Study of Kidney Disease and Hypertension (AASK) trial. At baseline and during follow-up of 1094 patients, the glomerular filtration rates (GFR) were measured by iothalamate clearances and events were adjudicated by the outcomes committee. Mean baseline serum bicarbonate, measured GFR, and proteinuria were 25.1 mmol/l, 46 ml/min per 1.73 m^2, and 326 mg/g of creatinine, respectively. Each 1 mmol/l increase in serum bicarbonate within the normal range was associated with reduced risk of death, dialysis, or GFR event and with dialysis or GFR event (hazard ratios of 0.942 and 0.932, respectively) in separate multivariable Cox regression models that included errors-in-variables calibration. Cubic spline regression showed that the lowest risk of GFR event or dialysis was found at serum bicarbonate levels near 28–30 mmol/l. Thus, our study suggests that serum bicarbonate is an independent predictor of CKD progression. Whether increasing serum bicarbonate into the high-normal range will improve kidney outcomes during interventional studies will need to be considered.

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Long-term follow-up of participants in the African American Study of Kidney Disease and Hypertension (AASK) showed that >50% died or developed a doubling of serum creatinine or end-stage renal disease at 10 years of follow-up.[1,2] This is particularly concerning as >80% of participants in the cohort phase of AASK were on renin–angiotensin blockers and blood pressure was maintained near recommended target values.[1] Given that most patients with chronic kidney disease (CKD) progress over the long term, it is clear that other strategies are necessary to slow advancing CKD.

In addition to renin–angiotensin blockade, correcting metabolic acidosis might be a useful additional maneuver to prevent CKD progression. Metabolic acidosis resulting from impaired urinary acid excretion is a complication of CKD. There are some data suggesting a detrimental effect of low serum bicarbonate with outcomes in CKD. In a recent study, individuals with hypertensive nephropathy and serum bicarbonate <22 mmol/l treated with sodium citrate had improved surrogate markers of kidney disease, such as reduced urinary excretion of endothelin-1, transforming growth factor-β1, and albumin, compared with those who were not treated with alkali.[3] In a randomized study of 134 CKD patients with serum bicarbonate levels in the range of 16–20 mmol/l, correcting low serum bicarbonate reduced the rate of kidney function decline when compared with placebo.[4] Thus, those CKD patients with overt reduction in serum bicarbonate levels might benefit from correction of low serum bicarbonate levels. However, >85% of people with estimated glomerular filtration rate (eGFR) in the range of 30–49 ml/min per 1.73 m^2 and >75% of those with eGFR in the range of 20–29 ml/min per 1.73 m^2 do not have low serum bicarbonate (<22 mmol/l).[5] Thus, it is important to examine whether serum bicarbonate in the upper limit of normal range is associated with better outcomes.

In a retrospective chart review of 5422 adults visiting a general medical clinic, compared with those with serum bicarbonate levels of 25–26 mmol/l, the low serum bicarbonate (<22 mmol/l) group had a higher hazard of kidney disease progression after adjusting for eGFR.[6] In a study of 1106 veterans with mean eGFR of 37 ± 17 ml/min per 1.73 m^2, the lowest hazard of death was in those with

baseline serum bicarbonate levels of 24–29 mmol/l, but the associations of serum bicarbonate with kidney outcomes were not specifically reported.[7] These studies used GFR estimated from serum creatinine by the modification of diet in renal disease (MDRD) equation to adjust for confounding among the level of renal impairment, serum bicarbonate, and the outcomes. Even though these analyses controlled for eGFR, it is possible that lower serum bicarbonate levels might still reflect low true GFR,[8] and therefore, these observational results could still be confounded by the level of kidney function. This report of the AASK cohort investigates the hypothesis that higher serum bicarbonate levels within the normal range are associated with improved renal outcomes, while rigorously controlling for GFR using iothalamate clearance, rather than eGFR, and other potential confounders.

RESULTS

Baseline characteristics

Characteristics of AASK study participants according to baseline serum bicarbonate (<20 mmol/l, 20–24.9 mmol/l, 25–29.9 mmol/l, and $\geqslant 30$ mmol/l) are presented in Table 1. Only 4.3% of the AASK cohort (mean GFR 34 ± 13 ml/min per 1.73 m^2) had serum bicarbonate levels <20 mmol/l, whereas 35.5% had serum bicarbonate in the low-normal range (20–24.9 mmol/l). The lowest serum bicarbonate group had lower mean GFR and higher median baseline proteinuria. Body mass index was lower in the lowest bicarbonate group. Only 39% of the participants in the lowest bicarbonate group, but 83% of the participants in the highest bicarbonate group, were on diuretics at baseline.

Death, dialysis, or GFR event composite in entire cohort

There were a total of 359 death, dialysis, or GFR composite events occurring over 4475 patient-years of follow-up (0.08 events per patient-year). The unadjusted cumulative incidence of this outcome by serum bicarbonate groups is shown in Figure 1. The event rates for those with baseline serum bicarbonate <20, 20–24.9, 25–29.9, and $\geqslant 30$ mmol/l were 0.17, 0.10, 0.06, and 0.06 events per patient-year, respectively.

To account for confounding between serum bicarbonate and other baseline factors, the association of serum bicarbonate with the composite outcome was next examined in Cox models (Table 2). After adjusting for age, gender, and randomization groups, each 1 mmol/l increase in serum bicarbonate was associated with an 11.1% reduction in the hazard of the clinical composite outcome of death, dialysis, or GFR events (hazard ratio (HR) 0.889, 95% confidence interval (CI) 0.859–0.921). Further adjustment for baseline-measured iothalamate GFR and proteinuria attenuated, but did not eliminate this association (HR 0.950, 95% CI 0.916–0.985). Even though GFR was measured directly based on iothalamate clearance in this cohort, recognizing that there could be errors in measurements of both proteinuria and GFR, we next built an errors-in-measurement Cox regression model adjusting for these covariables. The associations of serum bicarbonate with the above composite outcome remained significant in that model (Table 2). In sensitivity analyses, when further adjusted for baseline atherosclerotic conditions, congestive heart failure, mean arterial blood pressure, body mass index, smoking, serum albumin, and use of diuretics, each 1 mmol/l increase in

Table 1 | Characteristics of AASK participants by baseline serum bicarbonate

	Serum HCO_3^- (<20 mmol/l)	Serum HCO_3^- (20–24.9 mmol/l)	Serum HCO_3^- (25–29.9 mmol/l)	Serum HCO_3^- ($\geqslant 30$ mmol/l)	*P*-value
Number	47	388	599	60	
Age (years)	54 ± 11	54 ± 11	55 ± 10	55 ± 10	0.167
Male (%)	51.1	62.4	61.3	60.0	0.514
Randomized drug group (%)					
Ramipril	34.0	42.3	39.2	35.0	0.514
Metoprolol	38.3	40.5	41.1	33.3	0.696
Amlodipine	27.7	17.3	19.7	31.7	0.034
Randomized BP group (%)					
Strict control	46.8	51.0	48.4	50.0	0.854
Usual control	53.2	49.0	51.6	50.0	0.854
Atherosclerotic conditions (%)	12.8	12.1	16.1	10.0	0.259
Congestive heart failure (%)	4.3	2.6	2.3	3.3	0.849
Current or past smoking (%)	63.8	62.4	54.9	53.3	0.088
Body mass index (kg/m^2)	26.8 ± 6.5	30.5 ± 6.5	30.8 ± 6.5	31.8 ± 7.1	<0.001
Mean arterial pressure (mm Hg)	116 ± 16	113 ± 15	114 ± 16	117 ± 19	0.286
GFR (ml/min per 1.73 m^2)	34 ± 13	43 ± 14	49 ± 13	49 ± 12	<0.001
Urine protein/creatinine ratio (mg/g)[a]	410 (50, 1110)	130 (40, 580)	60 (20, 230)	70 (30, 260)	<0.001
Serum albumin (g/dl)	4.2 ± 0.3	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.019
Diuretic use (%)	39.1	61.6	65.1	83.1	<0.001

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ANOVA, analysis of variance; BP, blood pressure; GFR, glomerular filtration rate.
[a]Median (interquartile range) presented.
P-values are calculated by ANOVA for continuous variables and χ^2-values for dichotomous variables. Continuous measures are shown as mean ± standard error.

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