Serum bicarbonate and mortality in adults in NHANES III

Kalani L. Raphael1,2, Yingying Zhang2, Guo Wei2, Tom Greene2, Alfred K. Cheung1,2 and Srinivasan Beddhu1,2

1Salt Lake City VA Healthcare System, Salt Lake City, UT, USA and 2Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Correspondence and offprint requests to: Kalani L. Raphael. E-mail: kalani.raphael@hsc.utah.edu

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ABSTRACT

Background. Low serum bicarbonate concentration is a risk factor for death in people with chronic kidney disease (CKD). Whether low serum bicarbonate is a mortality risk factor for people without CKD is unknown.

Methods. National Health and Nutrition Examination Survey III (NHANES III) adult participants were categorized into one of four serum bicarbonate categories: <22, 22–25, 26–30 and ≥31 mM. Cox models were used to determine the hazards of death in each serum bicarbonate category, using 26–30 mM as the reference group, in the (i) entire population, (ii) non-CKD subgroup and (iii) CKD subgroup.

Results. After adjusting for age, gender, race, estimated glomerular filtration rate, albuminuria, diuretic use, smoking, C-reactive protein, cardiovascular disease, protein intake, diabetes, hypertension, body mass index, lung disease and serum albumin, the hazards of death in the <22 mM serum bicarbonate category were 1.75 (95% CI: 1.12–2.74), 1.56 (95% CI: 0.78–3.09) and 2.56 (95% CI: 1.49–4.38) in the entire population, non-CKD subgroup and CKD subgroup, respectively, compared with the reference group. Hazard ratios in the other serum bicarbonate categories in the entire population and non-CKD and CKD subgroups did not differ from the reference group.

Conclusions. Among the NHANES III participants, low serum bicarbonate was not observed to be a strong predictor of mortality in people without CKD. However, low serum bicarbonate was associated with a 2.6-fold increased hazard of death in people with CKD.

INTRODUCTION

In chronic kidney disease (CKD), low serum bicarbonate is commonly treated with alkali when the serum concentration falls to <22 mM because of adverse associations between metabolic acidosis and bone disease, muscle catabolism and malnutrition [1–7]. More recently, low serum bicarbonate levels have been observed to correlate with an increased risk of CKD progression and death [8–11]. Furthermore, the correction of low serum bicarbonate levels mitigates the effects of acidosis on the bone and nutritional status and is a promising strategy to slow CKD progression [12–17]. Thus, low serum bicarbonate concentration is a modifiable risk factor that is negatively associated with many important clinical factors in CKD.

Previous studies that included people without CKD have also observed that low serum bicarbonate concentration is associated with factors that correlate with adverse clinical outcomes, such as insulin resistance, inflammation, higher systolic blood pressure and poorer physical fitness [18–22]. Whether low serum bicarbonate levels are associated with worse long-term outcomes in people without CKD has not been extensively explored. Shah et al. [9] reported that low serum bicarbonate (<22 mM) was associated with an increased risk of glomerular filtration rate (GFR) deterioration in a longitudinal study of over 5000 adults, of which 91% had an estimated GFR (eGFR) of ≥60 mL/min/1.73 m² at baseline. While low serum bicarbonate levels appear to correlate with an increased risk of GFR reduction in people without CKD, the relationship between low serum bicarbonate and mortality in people without CKD has not been reported. We, therefore, tested the
hypothesis that low serum bicarbonate is a risk factor for death in adults without CKD using data from the National Health and Nutrition Examination Survey III (NHANES III). Secondary analyses explored whether low serum bicarbonate concentration is associated with an increased risk of death in people with CKD and whether the CKD status modifies the relationship between low serum bicarbonate concentration and mortality.

**MATERIALS AND METHODS**

**Brief description of NHANES III**

NHANES III was conducted from 1988 to 1994 to assess the health and nutritional status of adults and children in the USA as of the early 1990s. A complex sampling design was employed so that results could be extrapolated to represent the general, non-institutionalized, civilian US population [23]. Trained personnel gathered data on age, gender, race and medical and nutritional history during the home interview. The interview was followed by an examination at a mobile examination center. The examination included vital signs, anthropometric and physiological measurements and laboratory testing.

Although NHANES III was a cross-sectional study, the National Center for Health Statistics created an NHANES III Linked Mortality File that contains mortality follow-up data from the time of NHANES III participation. This information was based on the results from a probabilistic match between NHANES III participants and National Death Index death certificate records, the details of which are provided elsewhere [24]. Mortality data up until 31 December 2000 were used in this analysis.

**Study population, definitions and ascertainment of laboratory data**

Participants were included in this analysis if they were older than 20 years and had serum bicarbonate measured. Participants were categorized into one of four serum bicarbonate categories: <22, 22–25, 26–30 and ≥31 mM. The rationale to select <22 mM as the low threshold cut-off was because values <22 mM are commonly used to diagnose metabolic acidosis [1]. The rationale to select 26–30 mM was based on previous work in which serum bicarbonate values in this range were associated with the lowest risk of CKD progression and death in people with CKD [8, 10]. The other categories were created from the boundaries of these two categories.

Diabetes was defined as a self-reported history of diabetes, the use of oral hypoglycemic agents or insulin, or fasting plasma glucose ≥126 mg/dL. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, current treatment for hypertension, or if the participant was ever told to take medication for high blood pressure or had hypertension. Cardiovascular disease was defined as a history of myocardial infarction, stroke or congestive heart failure. History of smoking included previous and current smokers. Lung disease included diseases such as asthma or chronic obstructive pulmonary disease. Protein intake was estimated from the participant’s self-reported dietary history.

Serum for the biochemistry profile was frozen at ≤−20°C, transported on dry ice to the central laboratory and stored at −20°C until analysis. Serum bicarbonate and albumin were measured using a Hitachi 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Serum bicarbonate was measured using the phosphonoenolpyruvate method; the normal range of serum bicarbonate using this assay was 23.0–29.0 mM. Serum C-reactive protein (CRP) was measured by latex-enhanced nephelometry using a Behring Nephelometer Analyzer System using reagents from Behring Diagnostics, Inc., (Somerville, NJ, USA). Serum creatinine was measured using a kinetic rate Jaffé method and recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH, USA) as standardized creatinine = −0.184 + 0.960 × NHANES III measured serum creatinine [25]. The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration formula [26]. CKD was defined as an eGFR of <60 mL/min/1.73 m². Individuals with an eGFR of 60–150 mL/min/1.73 m² were classified as not having CKD. The serum anion gap was calculated as the difference between the sodium concentration and the sum of the chloride and bicarbonate concentrations in serum.

**Statistical analyses**

We used the *svy* suite of commands in Stata 12 (StataCorp LP, College Station, TX, USA) and followed the analytical guidelines for NHANES data proposed by the Centers for Disease Control and Prevention [27]. The *svy* suite of commands in Stata use the survey design elements of NHANES to calculate the expected means and proportions of the entire US population from data obtained from NHANES participants. Continuous variables are presented as means with standard deviations, unless otherwise specified. Categorical variables are presented as percent with 95% confidence intervals. Tests of significance were performed using ANOVA for continuous variables and Chi-squared tests for dichotomous variables.

**Survival analyses**

Cox survival analyses were performed separately in the (i) entire population (CKD and non-CKD), (ii) non-CKD subgroup and (iii) CKD subgroup. The 26–30 mM serum bicarbonate category served as the reference group in each analysis. Cox analyses were first adjusted for demographic factors (age, gender and race). Model 2 added other potential confounders of the relationship between serum bicarbonate and mortality, including eGFR, log-transformed urinary albumin-to-creatinine ratio, cardiovascular disease, lung disease, diabetes, hypertension, history of smoking, CRP and estimated protein intake normalized to body weight. Assumptions of proportional hazards were examined by comparing the logarithm of the hazard ratio for each predictor variable in the first 2 years of the follow-up to the logarithm of the hazard ratio of the predictor variables after 2 years using *z*-tests. If the P-value was <0.05, then proportional hazard assumptions were regarded as violated and the variable was included as a
After adjusting for demographic factors, those with serum bicarbonate concentrations <22 mM (22–30 mM) and 15.9% (≥31 mM). In the CKD subgroup, the hazard of death in the low serum bicarbonate category was 2.96 (95% CI: 1.48–5.95) when compared with the reference category after adjusting for demographic factors. After adjusting for other potential confounders in Model 2, the hazard of death was 2.56 (95% CI: 1.49–4.38). The hazards of death for the other serum bicarbonate categories were not different from the reference category in either Cox model (Figure 3). The CKD status did not modify the relationship between serum bicarbonate concentration and mortality (P-values >0.2 using z-tests and multiplicative interaction terms).

DISCUSSION

The primary objective of this study was to investigate whether low serum bicarbonate concentration is a risk factor for death in people without CKD. A non-statistically significant 56% increased hazard of death was observed in people without CKD with serum bicarbonate concentrations <22 mM when compared with those with serum bicarbonate concentrations of 26–30 mM. Despite the absence of statistical significance in the non-CKD subgroup, there was a trend toward an increased risk of death in participants with low serum bicarbonate. It is plausible that statistical significance was not achieved because there were few deaths in the non-CKD category, which limited statistical power. Alternatively, these results could be accurate; that is, low serum bicarbonate concentrations do not correlate with an increased hazard of death in people without CKD.

A secondary analysis observed that serum bicarbonate <22 mM is associated with a 2.6-fold increased hazard of death in people with CKD. The strong relationship between low serum bicarbonate concentration and subsequent mortality in participants with CKD contributes to the mounting evidence suggesting that low serum bicarbonate levels are a risk factor for poor outcomes in CKD. These results are consistent with previous survival analyses in CKD that described an increased hazard of death with lower serum bicarbonate levels [10, 11]. Lower serum bicarbonate concentrations have also been reported to be a risk factor for CKD progression in some [8, 9], albeit not all [28], observational studies. More importantly, results from single-center studies suggest that correcting low serum bicarbonate with alkali reduces the progression of CKD.

RESULTS

Among NHANES III participants, 15,836 were at least 20 years of age and had serum bicarbonate measured. Table 1 presents characteristics of these participants by serum bicarbonate category. The prevalence of serum bicarbonate <22 mM was 1.6%. Individuals in this category were more likely to be younger, female, have CKD and cardiovascular disease and have higher BMI and lower protein intake.

The prevalence of CKD was 8%. The mean (SD) age for those in the non-CKD and CKD subgroups was 43.4 (16.1) and 72.9 (11.4) years (P < 0.001), respectively. The mean (SD) eGFR in the CKD and non-CKD subgroups was 48.3 (10.2) and 101.4 (18.1) mL/min/1.73 m² (P < 0.001), respectively. In the CKD subgroup, 93.6% had Stage 3, 5.1% had Stage 4 and 1.3% had Stage 5 CKD. The percent of individuals in each serum bicarbonate category according to the CKD status is presented in Figure 1. The prevalence of serum bicarbonate <22 mM in the non-CKD and CKD subgroups was 1.5 and 3.4% (P = 0.03), respectively.

Survival analyses

In the entire population, 16% of participants died over a mean follow-up period of 8.6 years. The unadjusted probability of survival was highest in the 22–25 mM serum bicarbonate category and lowest in the <22 mM category (Figure 2). After adjusting for variables in Model 2, those in the <22 mM serum bicarbonate category had 75% increased hazard of death (95% CI: 1.12–2.74) compared with the reference category. The other serum bicarbonate categories did not have a statistically significant difference in the hazard of death compared with the reference group (Figure 3).

In the non-CKD subgroup, 12% died over a mean follow-up period of 8.7 years. Cardiovascular disease accounted for 41.2% of deaths in the non-CKD subgroup. The percent mortality by serum bicarbonate category was 11.3% (<22 mM), 9.2% (22–25 mM), 12.0% (26–30 mM) and 15.9% (≥31 mM). After adjusting for demographic factors, those with serum bicarbonate <22 mM had a 54% increased hazard of death compared with the reference category, although this did not reach statistical significance (95% CI: 0.81–2.90). After adjusting for variables in Model 2, the hazard of death for the low serum bicarbonate category was 1.56 (95% CI: 0.78–3.09). The hazards of death in the other serum bicarbonate categories were not different from the reference group in either Cox model (Figure 3).

Effect modification of the relationship between serum bicarbonate and CKD status on mortality was tested using two strategies. The first compared the log of the hazard ratios from the non-CKD and CKD subgroups in the non-reference group serum bicarbonate categories using z-tests. In the second, multiplicative interaction terms of the CKD status and serum bicarbonate were included in the Cox analyses of the entire population.
It is unknown whether normalizing the low serum bicarbonate level improves survival in CKD patients and provides a potential therapeutic strategy for improving poor survival outcomes for CKD patients. Future studies of alkaline treatment in populations with CKD should include survival as an outcome measure.

The major strength of this analysis is that it was conducted using data from a large, well-characterized cohort of individuals selected to represent the US population as of the early 1990s. The long-term mortality data from NHANES III is also a significant strength. Potential confounders of the association between serum bicarbonate level and mortality were carefully considered. There are several limitations in this study. The prevalence of serum bicarbonate <22 mM in the non-CKD subgroup was low, limiting statistical power. Similar to all observational studies, residual confounding may be present; therefore, only inferences about the relationship between low serum bicarbonate concentrations and mortality can be made. Also, it is uncertain whether the low serum bicarbonate levels reflect a primary metabolic acidosis or compensation for respiratory alkalosis since arterial blood gas analyses were not performed in NHANES III. The association between low serum bicarbonate and changes in renal function over time could not be analyzed because of the cross-sectional design of NHANES III. Finally, delays in performing the bicarbonate assay could have resulted in the loss of bicarbonate as CO₂ from the sample, resulting in falsely low values [29]. However, if the loss of bicarbonate from the sample were a significant issue, the prevalence of low serum bicarbonate would be expected to be >1.6%. This would also have led to the inclusion of low serum bicarbonate levels in the non-CKD subgroup, which was not observed.

Table 1. Characteristics of adult NHANES III participants by serum bicarbonate category

<table>
<thead>
<tr>
<th>Serum bicarbonate (mM)</th>
<th>&lt;22</th>
<th>22–25</th>
<th>26–30</th>
<th>≥31</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US prevalence (%)</td>
<td>1.6</td>
<td>22.7</td>
<td>52.2</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>Number in NHANES IIIb</td>
<td>374</td>
<td>3884</td>
<td>7877</td>
<td>3701</td>
<td></td>
</tr>
</tbody>
</table>

Demographics

| Age (years) | 42.0 (20.0) | 42.0 (16.6) | 45.2 (16.8) | 46.6 (17.7) | <0.001 |
| Men (%)     | 29.9 (23.6–7.2) | 37.2 (34.9–39.6) | 49.6 (47.9–51.3) | 55.4 (53.2–57.6) | <0.001 |
| African-American race (%) | 16.8 (11.8–23.4) | 12.1 (10.2–14.3) | 10.6 (9.3–12.0) | 9.4 (7.7–11.5) | 0.32 |

Clinical characteristics

| Chronic kidney disease (%) | 10.2 (6.2–16.6) | 4.6 (3.7–5.8) | 4.8 (4.0–5.6) | 5.2 (4.4–6.1) | 0.03 |
| Cardiovascular Disease (%) | 7.5 (4.7–11.8) | 4.6 (3.5–6.0) | 5.9 (5.1–6.8) | 6.4 (5.5–7.4) | 0.05 |
| Diabetes (%) | 8.8 (5.9–13.1) | 6.8 (5.7–8.2) | 6.7 (5.9–7.7) | 8.3 (7.1–9.6) | 0.09 |
| Hypertension (%) | 30.3 (23.1–38.6) | 29.9 (27.0–33.0) | 31.2 (28.8–33.8) | 33.0 (30.6–35.4) | 0.36 |
| Lung disease (%) | 3.6 (1.7–7.3) | 8.2 (6.6–10.2) | 7.5 (6.7–8.4) | 7.4 (6.2–8.8) | 0.30 |
| History of smoking (%) | 45.3 (36.2–54.7) | 42.6 (40.0–45.3) | 46.8 (44.6–49.1) | 46.5 (43.4–49.6) | 0.10 |
| Diuretic use (%) | 6.5 (3.8–10.6) | 4.2 (3.2–5.5) | 7.2 (6.4–8.1) | 10.5 (9.0–12.2) | <0.001 |
| BMI (kg/m²) | 28.8 (7.8) | 27.1 (6.4) | 26.5 (5.3) | 26.0 (5.3) | <0.001 |
| Protein intake (gm/kg/day) | 1.0 (0.7) | 1.1 (0.6) | 1.1 (0.6) | 1.1 (0.6) | 0.02 |

Laboratory characteristics

| Serum bicarbonate (mM) | 20.2 (1.9) | 24.0 (1.0) | 27.8 (1.3) | 33.3 (2.3) |
| eGFR (mL/min/1.73m²) | 100.9 (35.4) | 101.7 (22.7) | 98.5 (20.3) | 97.5 (21.4) | <0.001 |
| Urinary albumin:creatinine (mg/gm)b | 6.6 (3.5–11.3) | 5.8 (3.5–10.3) | 5.5 (3.4–10.0) | 6.2 (4.1–11.3) | 0.01 |
| Serum albumin (gm/dL) | 4.0 (0.5) | 4.1 (0.4) | 4.2 (0.3) | 4.2 (0.4) | <0.001 |
| Serum CRP >3 mg/L | 32.2 (23.9–41.8) | 28.5 (25.8–31.4) | 25.1 (22.8–27.6) | 25.1 (22.6–27.7) | 0.02 |
| Serum anion gap (meq/L) | 14.5 (4.0) | 11.8 (2.9) | 9.2 (3.0) | 4.0 (3.8) | <0.001 |

Percentages shown as percent (95% CI); continuous measures shown as mean (standard deviation).
aN values in NHANES III sample are not proportional due to the complex survey sampling design and statistical weighting.
bPresented as median and inter-quartile range.
of healthier people in the low serum bicarbonate category and bias the study toward the null hypothesis.

In summary, serum bicarbonate <22 mM is associated with a trend toward an increased hazard of death in people without CKD. Whether low serum bicarbonate concentrations are a mortality risk factor in people without CKD should be further investigated in other non-CKD cohorts with high-mortality risk. In NHANES III participants with CKD, low serum bicarbonate was a strong predictor of subsequent mortality, consistent with previous reports. Correcting low serum bicarbonate concentrations, such as with chronic oral alkali, could improve survival outcomes in people with CKD.

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CONFLICT OF INTEREST STATEMENT

All authors had access to the data and had a role in writing the manuscript.

REFERENCES


BLOG COMMENTARY

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The authors 15,836 individuals enrolled in the NHANES III study between 1988–1994 to examine whether differences in serum bicarbonate levels (< 22 mM, 22 – 25 mM, 26 – 30 mM, and ≥ 31 mM) were associated with increased mortality in the whole population, patients with CKD (eGFR < 60ml/min) and those with non-CKD (eGFR > 60ml/min). Previous studies suggested that low serum bicarbonate levels are associated with a higher risk of mortality. Also, some studies have suggested that low serum bicarbonate levels may be associated with a faster rate of eGFR decline and higher death rate in CKD. However, a recent systematic analysis of the impact of alkali therapy on the progression of CKD remains inconclusive (1). The current study shows a non-significant trend towards a higher mortality rate in the non-CKD population with the lowest serum bicarbonate level (<22mM), whilst confirming a 2.6 fold increased mortality in those with CKD and low serum bicarbonate. Mortality The authors adjusted their analysis for a large number of confounders. 1.6% of the studied population more from the authors of this very interesting article about:

1. Could the metabolic acidosis observed in 1.6% of the population studied be related to diet?

Although we should have evolved in such a way as to adapt to changes in our diet over human evolution, there remains a significant mismatch between our genetically determined
nutritional requirements and our modern diet. This is particularly true of our current low potassium intake as a consequence of our diet deficient in potassium-based rich fruit and vegetable diet. Such a deficiency of potassium alkali and their substitution by sodium chloride may underlie the increased prevalence of hypertension and the associated CVD; the main causes of mortality of the modern man (2). A diet deficient in potassium increases the net systemic acid load imposed by the diet. This, in turn, has been associated with essential hypertension (3).

It is therefore plausible that a lifetime of eating diets that deliver evolutionarily superphysiologic loads of acid to the body contribute to diet-induced low-grade systemic metabolic acidosis with its nutritional, metabolic but also cardiovascular consequences.

2. Could the observed metabolic acidosis be associated with undiagnosed hypertension or diabetes?

A number of observations have linked net increased dietary acid load and the consequent low grade metabolic acidosis with increased risk of both diabetes and hypertension as well as cardiovascular risk (4). Dietary-induced low grade acidosis has also been linked to insulin resistance; a known risk factor for essential hypertension and diabetes mellitus.

Now, the data provided by Kalani and his colleagues shows the risk of increased mortality linked to low serum bicarbonate levels to be independent of hypertension or diabetes. However, the prevalence of undiagnosed hypertension in the USA is high. This is particularly true of the foreign born americans where the prevalence of undiagnosed and untreated hypertension is highest as shown in the National Health and Nutrition Examination Survey (1998-2008) (5). Also, unawareness of hypertension, diabetes and dyslipidemia is highest in uninsured americans (6).

Unawareness of hypertension, and inaccurate and occasional casual BP measurements, may grossly underestimate the true prevalence of hypertension worldwide. Hypertension induced by low grade, diet-associated, metabolic acidosis in the US population may explain the observed trend between low serum bicarbonate levels and increased population mortality.

Professor Meguid El Nahas

REFERENCES


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