Title

Low Serum Bicarbonate and Kidney Function Decline: The Multi-Ethnic Study of Atherosclerosis (MESA)

Journal

American Journal of Kidney Diseases, 64(4)

ISSN

0272-6386

Authors

Driver, Todd H
Shlipak, Michael G
Katz, Ronit
et al.

Publication Date

2014-10-01

DOI

10.1053/j.ajkd.2014.05.008

Peer reviewed

Published in final edited form as:
Am J Kidney Dis. 2014 October ; 64(4): 534–541. doi:10.1053/j.ajkd.2014.05.008.

Low Serum Bicarbonate and Kidney Function Decline: The Multi-Ethnic Study of Atherosclerosis (MESA)

Todd H. Driver, BA[1], **Michael G. Shlipak, MD, MPH**[2,3,4], **Ronit Katz, PhD**[5], **Leonard Goldenstein, MD**[6], **Mark J. Sarnak, MD, MS**[7], **Andrew N. Hoofnagle, MD, PhD**[8], **David S. Siscovick, MD, MPH**[8,9], **Bryan Kestenbaum, MD, MS**[8], **Ian H. de Boer, MD, MS**[8], and **Joachim H. Ix, MD, MAS.**[6,10,11]

[1]School of Medicine, University of California, San Francisco, CA

[2]Department of Medicine, University of California, San Francisco, CA

[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

[4]Department of General Internal Medicine, San Francisco VA Medical Center, San Francisco, CA

[5]Collaborative Health Studies Coordinating Center, University of Washington, Seattle, WA

[6]Division of Nephrology and Hypertension, Department of Medicine, University of California, San Diego, California

[7]Division of Nephrology, Tufts Medical Center, Boston, MA

[8]Kidney Research Institute and Division of Nephrology, University of Washington, Seattle, WA

[9]Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA

[10]Division of Preventive Medicine, Department of Family and Preventive Medicine, University of California, San Diego, California

[11]Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, California

Abstract

Corresponding Author: Joachim H. Ix, MD, MAS, Division of Nephrology and Hypertension, Department of Medicine, University of California San Diego, and Veterans Affairs San Diego Healthcare System, 3350 La Jolla Village Drive, Mail Code 111-H, San Diego, CA 92161, Phone: (858)552-8585, Fax : (858)552-7549, joeix@ucsd.edu.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: THD, MGS, JHI, LG, MJS, ANH, DSS, BK, IHD; data acquisition: DS, IHD, BK; data analysis and interpretation: RK, THD, MGS, JI, LG, MJS, ANH, DSS, BK, IHD; supervision or mentorship: JHI, MGS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JI takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Background—Among populations with established chronic kidney disease (CKD), metabolic acidosis is associated with more rapid progression of kidney disease. The association of serum bicarbonate concentrations with early declines in kidney function is less clear.

Study Design—Retrospective cohort study.

Setting & Participants—6380 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) with a baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2 using the CKD-EPI (CKD Epidemiology Collaboration) creatinine–cystatin C equation.

Predictors—Serum bicarbonate concentrations.

Outcomes—Rapid kidney function decline (eGFR decline >5% per year) and incident reduced eGFR (eGFR<60 mL/min/1.73 m^2 with minimum rate of eGFR loss of 1 mL/min/1.73 m^2 per year).

Results—The average bicarbonate concentration was 23.2 ± 1.8 mEq/L. 1730 (33%) participants had rapid kidney function decline, and 487 had incident reduced eGFR during follow-up. Each 1-SD lower baseline bicarbonate concentration was associated with 12% higher adjusted odds of rapid kidney function decline (95% CI, 6%–20%) and higher risk of incident reduced eGFR (adjusted incidence rate ratio, 1.11; 95% CI, 1.03–1.20) in models adjusting for demographics, baseline eGFR, albuminuria, and CKD risk factors. The OR for the associations of bicarbonate <21mEq/L relative to 23–24 mEq/L was 1.35 (95% CI, 1.05–1.73) for rapid kidney function decline, and the incidence rate ratio was 1.16 (95% CI, 0.83–1.62) for incident reduced eGFR.

Limitations—Etiology of metabolic acidosis cannot be determined in this study.

Conclusions—Lower serum bicarbonate concentrations are independently associated with rapid kidney function decline independent of eGFR or albuminuria in community-living persons with a baseline eGFR >60 mL/min/1.73 m^2. If confirmed, our findings suggest that metabolic acidosis may indicate either early kidney disease that is not captured by eGFR or albuminuria, or may have a causal role in the development of an eGFR <60 mL/min/1.73 m^2.

Index words

serum bicarbonate; metabolic acidosis; chronic kidney disease (CKD); kidney function; renal disease; disease progression; kidney disease trajectory

---

Patients with advanced chronic kidney disease (CKD) and earlier stages of CKD (ie, end-stage renal disease) often develop metabolic acidosis, which is reflected by a low serum bicarbonate level.[1,2] Acid-base regulation in the kidneys is maintained by renal tubular cells, thus the pathogenesis of metabolic acidosis in patients with CKD is thought to be due, in part, to tubular dysfunction, causing decreased bicarbonate production in the kidney tubules.[2] In addition to marking tubule disease, metabolic acidosis might also play a role in the pathogenesis of CKD by causing tubular damage via a compensatory increase in tubular ammonia production, resulting in complement activation and inflammation.[3] Metabolic acidosis is also associated with mortality risk.[4]

In the setting of established CKD, most have found that metabolic acidosis is associated with adverse kidney and mortality outcomes, including CKD progression, rapid kidney

function decline, faster progression to end-stage renal disease, and all-cause mortality.[4–9] Additionally, in one hospital-based study, lower serum bicarbonate concentrations were associated with increased risk of kidney disease progression in individuals with relatively preserved kidney function (estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2).[7]

The relationship between acid-base status and the incidence of CKD has not been fully characterized. Therefore, we evaluated associations of serum bicarbonate concentrations with longitudinal change in kidney function in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. For the kidney disease outcomes, we focused on individuals with eGFR > 60 mL/min/1.73m^2, to determine whether bicarbonate concentrations may predict incident reduced eGFR development and rapid declines in kidney function.

Methods

Study Overview

The MESA study was designed to understand subclinical CVD and its progression to clinical CVD in a multiethnic cohort selected for the absence of clinical CVD at baseline. Details for recruitment and design have been published previously.[10] Briefly, from July 2000 through July 2002 (examination 1), MESA recruited 6,814 men and women aged 45–84 years who were free of clinical CVD and who self-identified as White, Black, Hispanic, or Chinese. Participants were recruited from Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. After the baseline examination, participants returned for 3 additional visits: July 2002 to January 2004 (examination 2), January 2004 to July 2005 (examination 3), and July 2005 to July 2007 (examination 4). Repeated measurements of kidney function were obtained at examinations 3 and 4. The relevant institutional review boards at all participating centers approved the study.

Measurement of Serum Bicarbonate and Kidney Function

Total serum carbon dioxide (serum bicarbonate) was measured at MESA examination 1 in all participants at baseline using a pH rate-of-change method on a Beckman DxC automated clinical chemistry analyzer. The interassay imprecision across the study was determined to be 2.98%–3.19% (N=84). Kidney function was assessed by creatinine and cystatin C concentrations. All assays were performed in frozen serum specimens that were stored at −70°C. Serum creatinine was measured by rate reflectance spectrophotometry using thin-film adaptation of the creatinine amidinohydrolase method on the VITROS analyzer (Johnson & Johnson Clinical Diagnostics Inc, www.orthoclinical.com) at the Collaborative Studies Clinical Laboratory at Fairview–University of Minnesota Medical Center (Minneapolis, MN) and calibrated to the Cleveland Clinic. Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Siemens) with a nephelometer (BNII; Siemens, www.siemens.com) and corrected for assay drift. We used the CKD Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation to estimate GFR.[11]

Outcomes

The primary outcomes were incident reduced eGFR and rapid kidney function decline. Incident reduced eGFR was defined by reaching an eGFR < 60 mL/min/1.73m^2 with a minimum rate of eGFR loss of 1 mL/min/1.73m^2 per year. Rapid progression of kidney function decline was defined as a decline in eGFR of more than 5% per year, a rate of decline in eGFR that has been used in prior MESA papers.[12,13]

Candidate Covariates

Age, gender, race, income, education, past or current smoking, and alcohol use were ascertained by questionnaire at the baseline visit. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Fasting blood was collected and stored at −70°C until needed for the appropriate assays, including HDL cholesterol, triglycerides, glucose, and C-reactive protein. LDL cholesterol was calculated using the Friedewald equation.[14] Diabetes was defined as a self-report of diabetes, the use of insulin or oral hypoglycemic agents, or a fasting glucose of ≥126 mg/dl. At the baseline examination, usual dietary intake over the previous year was assessed with a modified block-style 120-item Block food frequency questionnaire (FFQ), which was patterned after the FFQ used in the Insulin Resistance Atherosclerosis Study.[15,16] Participants reported the size and frequency of consumption of specific beverages and foods and these data were converted to approximate daily intake of nutrients using the Nutrition Data Systems for Research database (Nutrition Coordinating Center, University of Minnesota).[17] Dietary acid load was defined by the ratio of daily protein to potassium intake.[18] In order to accommodate the MESA population, the FFQ was modified to include Chinese foods and culinary practices.[19] Smoking was dichotomized as ever versus never smoking. Hypertension was defined as the use of antihypertensive medications, a self-report of hypertension, or a blood pressure of >140/90 mmHg at the baseline visit. Three blood pressure measurements were obtained 5 minutes apart in the seated position. The mean of the second two measurements was used for analysis. Diuretic use was assessed during clinic visits.

Statistical Analysis

Baseline characteristics of participants were compared across pre-specified categories of bicarbonate concentration (<21, 21–22, 23–24, 25–26, >27 mEq/L), based on the observed distribution of serum bicarbonate concentrations in MESA, using ANOVA or Chi-squared tests as appropriate. We further evaluated these associations of characteristics with baseline bicarbonate concentrations by conducting multivariable linear regression with bicarbonate as the dependent variable. *A priori*, we planned analyses of bicarbonate categories with clinical outcomes, and additionally stratified analyses based on urine albumin-creatinine ratio (ACR), above or below 30 mg/g. For all outcomes, we also used spline functions to consider parametric nonlinear functions for serum bicarbonate concentration. Natural piecewise-cubic splines were used with the specified sequence of interior knots placed at the quartiles of the distributions of serum bicarbonate. Multivariable logistic models were used to determine the association of serum bicarbonate categories with rapid kidney function decline, while

Poisson regression was used to determine the association of serum bicarbonate categories with incident reduced eGFR. We initially adjusted for demographic covariates, then additionally adjusted for CVD risk factors, the ratio of daily protein to potassium intake, ACR, diuretic use, and baseline eGFR. Based on the MESA design, we repeated these analyses after stratification by race and with bicarbonate dichotomized at <23 mEq/L. Analyses were conducted using S-Plus (version 8.0, TIBCO Software Ine, Seattle, WA) and SPSS statistical software (version 15.0.1.1, SPSS Inc., Chicago, IL); p-values < 0.05 were considered statistically significant for all analyses including interaction terms.

Results

Among the 5810 participants with a baseline eGFR > 60 mL/min/1.73m^2, the mean age was 61 ± 10 (standard deviation [SD]) years; 53% were female; the race/ethnicity distribution was 38% white, 27% black, 22% Hispanic, and 12% Chinese; and the median follow-up time was 4.75 (interquartile range [IQR]. 4.52–4.97) years. The baseline eGFR was 84 ± 14 mL/min/1.73m^2, and the median urine ACR was 5.2 (IQR, 3.3–10.3) mg/g.

The distribution of baseline serum bicarbonate concentrations was normal with a mean level of 23 mEq/L (Figure 1). Participants with lower baseline serum bicarbonate concentrations were younger, more likely to be Hispanic and to have smoked, and had a higher eGFR and higher dietary sodium intake than those with normal or high serum bicarbonate concentrations. The lowest bicarbonate category also had the lowest prevalence of hypertension and diuretic use. Other risk factors appeared similar across bicarbonate categories (Table 1). In adjusted linear regression analyses, independent correlates of lower bicarbonate concentrations included younger age, white race, lower educational attainment, diabetes mellitus, higher BMI, higher eGFR, and a higher daily dietary acid load (as defined by a high dietary protein intake relative to potassium) and sodium intake (Table 2).[18]

Spline analyses showed higher odds of rapid kidney function decline at lower serum bicarbonate concentrations and lower odds of rapid kidney function decline at higher bicarbonate concentrations (Figure 2a). The association between serum bicarbonate and incident reduced eGFR was in the similar direction but weaker at serum bicarbonate concentrations between 21–26 mEq/L (Figure 2b).

In both unadjusted and adjusted analyses, each 1.8-unit (SD) lower baseline bicarbonate concentration was associated with an approximately 10% higher odds for rapid kidney function decline and incident reduced eGFR. When serum bicarbonate was analyzed as a categorical variable, concentrations <21 mEq/L were associated with approximately a 35% higher odds of rapid kidney function decline in adjusted models relative to 23–24 mEq/L; the bicarbonate concentrations greater than 25 mEq/L had similar associations with lower odds of rapid decline (Table 3). When we dichotomized the study population at an ACR cutpoint of 30 mg/g, a serum bicarbonate concentration <23 mEq/L was associated with a 20% higher adjusted odds of rapid kidney function decline (odds ratio [OR], 1.20; 95% CI, 1.06–1.37) in those with albuminuria, which persisted in those without albuminuria (OR, 1.24; 95% CI, 1.09–1.42). Dichotomizing by incident reduced eGFR, the mean rates of annual decline were −6.9 ± 4.5 and −1.1 ± 3.7 mL/min/1.73 m^2 per year for participants

with and without incident reduced eGFR, respectively. Additionally, the mean rates of annual decline were −5.9 ± 3.0 and 0.5 ± 2.9 mL/min/1.73 m^2 per year for those with and without rapid kidney function decline, respectively.

Although directionally similar, serum bicarbonate categories were not significantly associated with adjusted risk of incident reduced eGFR (Table 3). Similar findings were observed for the dichotomized analysis of bicarbonate (<23 mEq/L vs. higher: OR, 1.17; 95% CI, 0.99–1.39). Although there was no significant interaction detected across racial groups, the association was strongest and statistically significant for both outcomes among Black participants (Table 4).

Discussion

Low serum bicarbonate concentrations are associated with worsening CKD and its complications, including mortality, in populations with an eGFR <60 mL/min/1.73m^2,[4–7] but the relationship of serum bicarbonate concentrations with CKD progression in populations with an eGFR >60 mL/min/1.73m^2 is unknown. In this cohort of community-living individuals with a baseline eGFR > 60 mL/min/1.73m^2, lower serum bicarbonate concentrations were associated with rapid kidney function decline and incident reduced eGFR, independent of baseline eGFR and ACR. When stratifying these analyses by race, the association of low bicarbonate with both outcomes was strongest among Black participants.

Serum bicarbonate has been well studied as a predictor of progressive CKD in patients with established CKD. In a study of African Americans with a baseline eGFR of 20–65 mL/min/1.73m^2, each 1-mmol/L higher level of serum bicarbonate was associated with a significant reduction in a composite outcome of death, dialysis, or decline in kidney function.[5] In a cohort of patients in the Bronx, NY, low serum bicarbonate level was found to be associated with progression of kidney disease, irrespective of baseline eGFR.[7] However, another study in the MDRD (Modification of Diet in Renal Disease) Study cohort found that low serum bicarbonate concentrations were not significantly associated with elevated risk of kidney failure and all-cause mortality in non-diabetic patients with CKD stages 2–4.[9]

These findings are consistent with previous studies in individuals with relatively preserved kidney function (eGFR > 60 mL/min/1.73m^2). A study of patients in New York City found that lower serum bicarbonate concentrations are associated with increased risk of kidney disease progression, including those with relatively preserved eGFR (>60 mL/min/1.73m^2).[7] Additionally, a small randomized trial found that bicarbonate supplementation slowed eGFR decline in patients with baseline eGFR values between 60 and 90 mL/min/1.73m^2.[20]

The association between serum bicarbonate concentrations and kidney function decline in participants with an eGFR > 60 mL/min/1.73m^2 has at least two potential biological explanations. The first possibility is that acidosis, as indicated by low serum bicarbonate concentrations, plays a direct role in the pathogenesis of CKD. Rat models of kidney disease have shown that increased ammonia production in response to metabolic acidosis can result in direct kidney injury through increased complement activation and inflammation.[3] Support for this hypothesis comes from findings that supplementation of serum bicarbonate

concentrations slowed CKD progression in small randomized clinical trials in patients with and without CKD.[20,21] A second possibility is that lower serum bicarbonate is a marker of kidney tubule dysfunction, rather than directly injurious to the kidney. Under this possibility, our data suggest that early losses of the kidney's acid-base regulatory capacity could precede losses of glomerular filtration, or at least may occur early enough in the spectrum of CKD such that mild decrements in eGFR are not detectable using an eGFR equation combining both creatinine and cystatin C.

This study also produced novel observations regarding predictors of acid/base status in persons with preserved kidney function. What was especially surprising was the association of lower eGFR with higher bicarbonate concentrations. In contrast to our findings, other studies, including a companion study in the Health, Aging, and Body Composition (Health ABC) cohort[22] have found that lower eGFR is typically associated with metabolic acidosis in cross-section, even in those with relatively preserved kidney function (eGFR >60 mL/min/1.73m^2), which is thought to be the result of a reduced number of functioning nephrons.[2,23–25] Our finding that Hispanics in MESA had lower adjusted bicarbonate concentrations than Whites is similar to what has been shown in the Third National Health and Nutrition Examination Survey (NHANES III), although our finding that bicarbonate concentrations are higher in Blacks is different from that in the NHANES III cohort in which concentrations are similar between the two groups.[26] The other associations of education, diet, and diuretics with bicarbonate concentrations all suggest environmental factors can influence acid-base status. Future studies are needed to confirm these observations.

Our findings may ultimately have clinical implications. First, serum bicarbonate is an inexpensive laboratory test that is present on standard clinical chemistry panels; it may have the potential to identify persons at risk of developing CKD, perhaps in combination with other biomarkers, which could inform more aggressive management of kidney disease risk factors. Additionally, previous studies have shown the potential for correction of serum bicarbonate through oral bicarbonate supplementation to slow kidney function decline and progression to ESRD in a population of patients with and without CKD.[20,21] This could also inform dietary counseling, such as substituting alkali-poor meats and cheeses with more alkali-rich fruits and vegetables.[27] If these findings are confirmed, correction of serum bicarbonate concentrations may hold the potential to either slow or prevent the progression to clinical CKD. Future intervention studies may be warranted to test this important question.

Strengths of our study include the large study population with a baseline eGFR >60 mL/min/1.73m^2, the multiethnic composition of the cohort, and the 5-year follow-up with measures of creatinine and cystatin C. The study also has important limitations. These include the single measure of bicarbonate and the lack of COPD status reported in the cohort, although smoking and asthma status were recorded. Additionally, the results in the analyses by race should be interpreted with caution due to the small number of events in the lower bicarbonate categories.

Another important consideration is that the bicarbonate levels in this study were measured from frozen samples as opposed to at the point of collection. Freezing and storing serum samples has been associated with approximately 4-mEq/L lower bicarbonate concentrations compared to measurements taken at the point of care measurement in prior studies, which is likely the result of volatile loss of carbon dioxide.[28] This discrepancy likely did not affect the observed associations of bicarbonate with kidney outcomes since a companion study in Health ABC, which measured bicarbonate concentrations at the point-of-care, had higher mean bicarbonate concentrations, but found similar associations with change in kidney function over time.[22]

Given the high prevalence of CKD in the United States and its strong associations with CVD events and mortality, the early identification of CKD holds the potential to inform risk management to either slow or prevent the onset of CKD and associated morbid consequences in a large proportion of the population. This study presents serum bicarbonate as an early indicator of kidney function decline. Future studies in other cohorts are needed to confirm the association of metabolic acidosis with early declines in kidney function and to determine if bicarbonate is a modifiable risk factor for CKD in the general population or in targeted subgroups, such as the Black population.

Acknowledgments

Support: Drs Shlipak and Sarnak are supported by grant 5R01AG027002-07 from the National Institute on Aging; Drs Ix and Shlipak, by grant 1R01DK098234-01A1 from the National Institute of Diabetes and Digestive and Kidney Diseases; and Mr Driver, by grant TL1 TR000144 from UCSF-CTSI. MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung and Blood Institute in collaboration with MESA investigators; support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169 and Clinical and Translational Science Award UL1-RR-024156. None of the funding agencies had any role in the study design, collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

References

1. Moranne O, Froissart M, Rossert J, et al. Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol. Jan; 2009 20(1):164–171. [PubMed: 19005010]
2. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis. Jun; 2005 45(6):978–993. [PubMed: 15957126]
3. 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. Aug; 1985 76(2):667–675. [PubMed: 2993363]
4. Navaneethan SD, Schold JD, Arrigain S, et al. Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. Clin J Am Soc Nephrol. Oct; 2011 6(10):2395–2402. [PubMed: 21885787]
5. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int. Feb; 2011 79(3):356–362. [PubMed: 20962743]
6. Yaqoob MM. Acidosis and progression of chronic kidney disease. Curr Opin Nephrol Hypertens. Sep; 2010 19(5):489–492. [PubMed: 20539229]
7. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. Aug; 2009 54(2):270–277. [PubMed: 19394734]

8. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant. Apr; 2009 24(4): 1232–1237. [PubMed: 19015169]
9. Menon V, Tighiouart H, Vaughn NS, et al. Serum bicarbonate and long-term outcomes in CKD. Am J Kidney Dis. Nov; 2010 56(5):907–914. [PubMed: 20605301]
10. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. Nov 1; 2002 156(9):871–881. [PubMed: 12397006]
11. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. Jul 5; 2012 367(1):20–29. [PubMed: 22762315]
12. Shlipak MG, Katz R, Kestenbaum B, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol. Dec; 2009 20(12):2625–2630. [PubMed: 19892934]
13. Park M, Shlipak MG, Katz R, et al. Subclinical cardiac abnormalities and kidney function decline: the multi-ethnic study of atherosclerosis. Clin J Am Soc Nephrol. Jul; 2012 7(7):1137–1144. [PubMed: 22580783]
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry. Jun; 1972 18(6):499–502. [PubMed: 4337382]
15. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. Journal of clinical epidemiology. 1990; 43(12):1327–1335. [PubMed: 2254769]
16. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, et al. Validity and reproducibility of a food frequency interview in a Multi-Cultural Epidemiology Study. Annals of epidemiology. Jul; 1999 9(5):314–324. [PubMed: 10976858]
17. Gutierrez OM, Katz R, Peralta CA, et al. Associations of socioeconomic status and processed food intake with serum phosphorus concentration in community-living adults: the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. Sep; 2012 22(5):480–489.
18. Scialla JJ, Anderson CA. Dietary acid load: a novel nutritional target in chronic kidney disease? Adv Chronic Kidney Dis. Mar; 2013 20(2):141–149. [PubMed: 23439373]
19. Lutsey PL, Jacobs DR Jr, Kori S, et al. Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study. The British journal of nutrition. Aug; 2007 98(2):397–405. [PubMed: 17391554]
20. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int. Aug; 2010 78(3):303–309. [PubMed: 20445497]
21. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. Sep; 2009 20(9):2075–2084. [PubMed: 19608703]
22. Goldenstein L, Driver TH, Fried L, et al. Serum Bicarbonate Concentrations and Kidney Disease Progression in Community-Living Elders: The Health ABC Study. Am J Kidney Dis. 2014; 64 (●), ●●● ●●●.
23. Warnock DG. Uremic acidosis. Kidney Int. Aug; 1988 34(2):278–287. [PubMed: 3054224]
24. Frassetto LA, Morris RC Jr, Sebastian A. Effect of age on blood acid-base composition in adult humans: role of age-related renal functional decline. The American journal of physiology. Dec; 1996 271(6 Pt 2):F1114–1122. [PubMed: 8997384]
25. Abramowitz MK, Hostetter TH, Melamed ML. Association of serum bicarbonate levels with gait speed and quadriceps strength in older adults. Am J Kidney Dis. Jul; 2011 58(1):29–38. [PubMed: 21354683]
26. Foley RN, Wang C, Ishani A, Collins AJ. NHANES III: influence of race on GFR thresholds and detection of metabolic abnormalities. J Am Soc Nephrol. Sep; 2007 18(9):2575–2582. [PubMed: 17656476]
27. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc. Jul; 1995 95(7):791–797. [PubMed: 7797810]

28. Kirschbaum B. Spurious metabolic acidosis in hemodialysis patients. Am J Kidney Dis. Jun; 2000 35(6):1068–1071. [PubMed: 10845818]

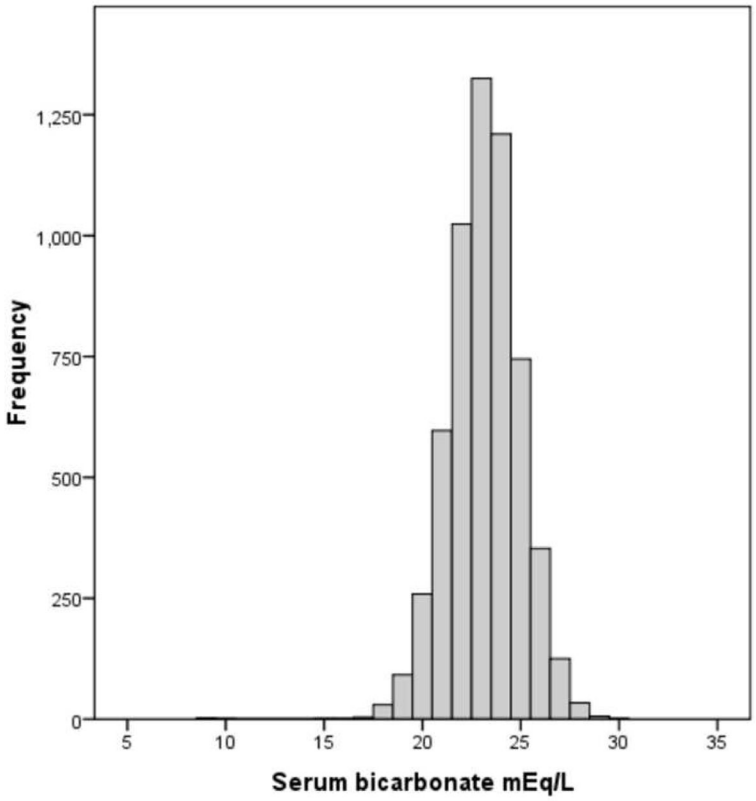

Figure 1.

Distribution of serum bicarbonate.

The distribution of baseline serum bicarbonate concentrations (n=5,810) was normal with a mean level of 23 +/− 1.8 (SD) mEq/L.

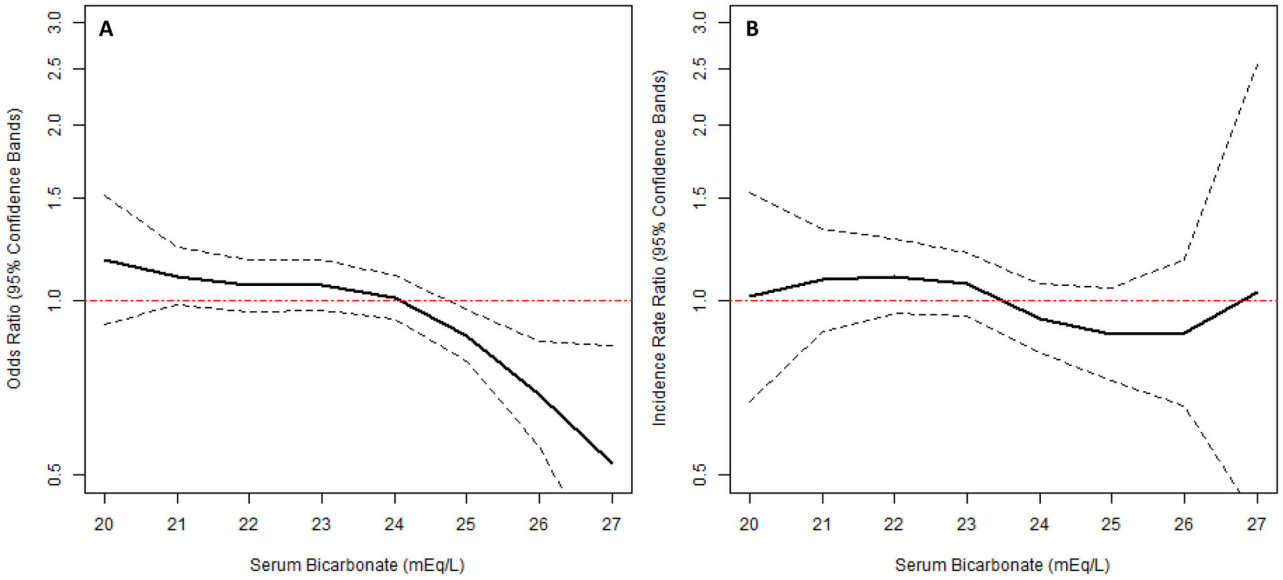

Figure 2.

Figure 2a: Adjusted association of serum bicarbonate with risk of rapid kidney function decline in MESA.

Spline analysis adjusted for age, race, gender, education, diabetes mellitus, hypertension, smoking, BMI, HDL, eGFR, diuretic use and albuminuria. Solid line represents the point estimate and dotted lines represent 95% CI.

Figure 2b: Adjusted association of serum bicarbonate with risk of incident reduced eGFR in MESA.

Spline analysis adjusted for age, race, gender, education, diabetes mellitus, hypertension, smoking, BMI, HDL, eGFR, diuretic use and albuminuria). Solid line represents the point estimate and dotted lines represent 95% CI.

Table 1

Characteristics of MESA participants by baseline serum bicarbonate categories

	<21 mEq/L	**21 – 22 mEq/L**	**23 – 24 mEq/L**	**25 – 26 mEq/L**	**≥ 27 mEq/L**	**p-value**
No. of participants	390	1621	2535	1098	166	
Age (y)	58 ±9	60 ±10	61 ±10	63 ±10	65 ±10	<0.001
Male sex	193 (50%)	778 (48%)	1192 (47%)	518 (47%)	64 (39%)	0.09
Race						<0.001
White	125 (32%)	618 (38%)	982 (39%)	433 (39%)	52 (31%)	
Asian	41 (11%)	210 (13%)	323 (13%)	125 (11%)	17 (10%)	
Black	90 (23%)	361 (22%)	693 (27%)	377 (34%)	75 (45%)	
Hispanic	134 (34%)	434 (27%)	537 (21%)	163 (15%)	22 (13%)	
Education						<0.001
< High School	73 (19%)	296 (18%)	459 (18%)	160 (15%)	35 (21%)	
High School + some college	194 (50%)	768 (48%)	1137 (45%)	483 (44%)	65 (39%)	
≥College	123 (32%)	550 (34%)	930 (37%)	453 (41%)	66 (40%)	
Diabetes mellitus	61 (16%)	217 (13%)	258 (10%)	125 (11%)	20 (12%)	0.007
Glucose (mg/dL)	103 ±40	99 ±32	96 ±27	95 ±28	94 ±18	<0.001
BMI (kg/m^2)	29.2 ±5.2	28.6 ±5.1	28.1 ±5.5	27.5 ±5.5	28.0 ±6.6	<0.001
Smoking						<0.001
Never	165 (42%)	779 (48%)	1310 (52%)	569 (52%)	89 (54%)	
Ever	225 (58%)	835 (52%)	1216 (48%)	528 (48%)	77 (46%)	
HDL-C(mg/dL)	48 ±14	50 ±15	51 ±15	54 ±15	56 ±16	<0.001
LDL-C (mg/dL)	117 ±33	117 ±32	117 ±31	117 ±31	113 ±31	0.5
Triglycerides (mg/dL)	129 [84–187]	118 [82–171]	108 [76–158]	98 [71–137]	96 [73–140]	<0.001
Hypertension	127 (33%)	607 (37%)	1042 (41%)	544 (50%)	109 (66%)	<0.001
ACR (mg/g)	5.6 [3.4–12.0]	5.3 [3.3–10.2]	4.9 [3.2–9.8]	5.5 [3.4–10.8]	5.8 [3.7–10.9]	0.002
eGFR (mL/min/1.73m^2)	90 ±14	88 ±15	87 ±14	86 ±14	83 ±13	<0.001
Protein:K ratio	0.025 ±0.006	0.024 ±0.007	0.023 ±0.006	0.023 ±0.006	0.022 ±0.006	<0.001
Dietary Na intake (mg)	2248 ±1221	2234 ±1312	2154 ±1253	2078 ±1198	1851 ±998	<0.001

	<21 mEq/L	21 – 22 mEq/L	23 – 24 mEq/L	25 – 26 mEq/L	≥ 27 mEq/L	p-value
Diuretic use	20 (5%)	110 (7%)	262 (10%)	205 (19%)	59 (36%)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; HDL-C and LDL-C in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

ACR, albumin-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; MESA, Multi-Ethnic Study of Atherosclerosis

Table 2

Associations of demographic and clinical characteristics with serum bicarbonate concentrations using multivariate linear regression

	β (95% CI)		p-value
Age, per-10 y older	0.21 (0.17 to 0.26)		<0.001
Male sex	−0.09	−0.19, 0.01	0.05
Race			
White	0.00 (reference)		
Chinese	−0.05	−0.20, 0.11	0.6
Black	0.29	0.18, 0.41	<0.001
Hispanic	−0.47	−0.59, −0.35	<0.001
Education			
< High School	−0.20	−0.34, −0.07	0.003
High School + some college	−0.21	−0.31, −0.10	<0.001
≥College	0.00 (reference)		
Diabetes	−0.23	−0.38, −0.09	0.002
BMI category			
<18.5 kg/m^2	0.67	0.16, 1.17	0.009
18.5 – 24.9 kg/m^2	0.00 (reference)		
25.0 – 29.9 kg/m^2	−0.38	−0.50, −0.27	<0.001
≥ 30 kg/m^2	−0.43	−0.55, −0.31	<0.001
Ever smoked	−0.19	−0.28, −0.09	<0.001
HDL-C, per 5-mg/dL lower	−0.07	−0.09, −0.06	<0.001
Hypertension	0.43	0.34, 0.52	<0.001
ACR >30 mg/g	−0.03	−0.20, 0.14	0.8
eGFR, per 14 mL/min/1.73 m^2 lower*	0.17	0.12, 0.21	<0.001
Asthma	0.01	−0.09, 0.11	0.3
Dietary protein:K ratio, per 0.006 higher*	−0.17	−0.22, −0.12	<0.001
Dietary Na, per 0.001 mg higher*	−0.11	−0.16, −0.06	<0.001
Diuretic use	0.97	0.82, 1.11	<0.001

Note: n=5810 participants with an eGFR > 60 mL/min/1.73m^2 in the Multi-Ethnic Study of Atherosclerosis.

*increment equivalent to 1 standard deviation.

ACR, albumin-creatinine ratio; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; K, potassium; NA, sodium; SD, standard deviation

Table 3

Associations of serum bicarbonate with rapid kidney function decline and incident reduced eGFR

Rapid Kidney Function Decline				
Serum Bicarbonate	**No.**	**No. with rapid decline**	**Demographics-adjusted* OR (95% CI)**	**Fully adjusted** OR (95% CI)**
Continuous, per 1.8 mEq/L decrease***	5165	1730 (33%)	1.15 (1.08, 1.22)	1.12 (1.06, 1.20)
Clinical Category				
<21 mEq/L	340	136 (40%)	1.46 (1.15, 1.85)	1.35 (1.05, 1.73)
21–22 mEq/L	1436	493 (34%)	1.10 (0.95, 1.26)	1.06 (0.91, 1.22)
23–24 mEq/L	2271	756 (33%)	1.00 (reference)	1.00 (reference)
25–26 mEq/L	974	297 (30%)	0.84 (0.71, 0.99)	0.82 (0.69, 0.97)
≥27 mEq/L	144	48 (33%)	0.86 (0.59, 1.23)	0.85 (0.58, 1.24)

Incident Reduced eGFR				
Serum Bicarbonate	**No.**	**No. with incident reduced eGFR**	**Demographics-adjusted* IRR (95% CI)**	**Fully adjusted** IRR (95% CI)**
Continuous, per 1.8 mEq/L decrease***	5165	487 (9%)	1.11 (1.02, 1.08)	1.12 (1.04, 1.22)
Clinical Category				
<21 mEq/L	340	30 (9%)	1.33 (0.93, 1.91)	1.18 (0.84, 1.67)
21–22 mEq/L	1436	142 (10%)	1.20 (0.99, 1.46)	1.15 (0.96, 1.38)
23–24 mEq/L	2271	205 (9%)	1.00 (reference)	1.00 (reference)
25–26 mEq/L	974	93 (10%)	0.97 (0.77, 1.21)	0.84 (0.67, 1.06)
≥27 mEq/L	144	17 (12%)	0.98 (0.63, 1.52)	0.83 (0.51, 1.36)

Note: Unless otherwise indicated, values are given as number or number (percentage).

CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; OR, odds ratio; SD, standard deviation.

* Adjusted for age, gender, race and education

** further adjusted for diabetes mellitus, hypertension, smoking, BMI, HDL, eGFR, diuretic use, daily protein:potassium intake, and albuminuria

*** increment equivalent to 1 standard deviation

Table 4

Associations of serum bicarbonate with rapid kidney function decline and incident reduced eGFR, stratified by race

Rapid Kidney Function Decline				
	No.	**No. with rapid decline**	**Demographics-adjusted* OR (95% CI)**	**Fully adjusted** OR (95% CI)**
White				
<23 mEq/L	674	209 (31%)	1.19 (0.96, 1.46)	1.11 (0.90, 1.38)
≥23 mEq/L	1356	397 (29%)	1.00 (reference)	1.00 (reference)
Chinese				
<23 mEq/L	215	63 (29%)	1.05 (0.73, 1.52)	1.03 (0.70, 1.52)
≥23 mEq/L	415	117 (28%)	1.00 (reference)	1.00 (reference)
Black				
<23 mEq/L	384	169 (44%)	1.42 (1.11, 1.82)	1.33 (1.02, 1.74)
≥23 mEq/L	992	363 (37%)	1.00 (reference)	1.00 (reference)
Hispanic				
<23 mEq/L	503	188 (37%)	1.18 (0.92, 1.52)	1.16 (0.89, 1.52)
≥23 mEq/L	626	224 (36%)	1.00 (reference)	1.00 (reference)

Incident Reduced eGFR				
	No.	**No. with incident reduced eGFR**	**Demographics-adjusted* IRR (95% CI)**	**Fully adjusted** IRR (95% CI)**
White				
<23 mEq/L	674	65 (10%)	1.11 (0.95, 1.29)	1.06 (0.91, 1.24)
≥23 mEq/L	1356	141 (10%)	1.00 (reference)	1.00 (reference)
Chinese				
<23 mEq/L	215	12 (6%)	0.93 (0.64, 1.35)	0.89 (0.62, 1.28)
≥23 mEq/L	415	26 (6%)	1.00 (reference)	1.00 (reference)
Black				
<23 mEq/L	384	50 (13%)	1.75 (1.45, 2.09)	1.69 (1.41, 2.03)
≥23 mEq/L	992	84 (9%)	1.00 (reference)	1.00 (reference)
Hispanic				
<23 mEq/L	503	45 (9%)	1.12 (0.92, 1.36)	1.17 (0.96, 1.43)
≥23 mEq/L	626	64 (10%)	1.00 (refence)	1.00 (reference)

* Adjusted for age, gender, race and education

** further adjusted for diabetes mellitus, hypertension, smoking, BMI, HDL, eGFR, diuretic use, and albuminuria

Note: Unless otherwise indicated, values are given as number or number (percentage). P-values for bicarbonate-race interaction = 0.4 for rapid kidney function decline and 0.1 for incident reduced eGFR.

CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; OR, odds ratio; SD, standard deviation;;