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Serum Bicarbonate and Bone Mineral Density in US Adults

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Abstract

Background—Chronic metabolic acidosis leads to bone mineral loss and results in lower bone mineral density (BMD), which is a risk factor for osteoporosis-related fractures. The effect of low-level metabolic acidosis on bone density in the general population is unknown.

Study Design—Cross-sectional study.

Setting & Participants—9,724 nationally representative adults aged 20 years or older in the National Health and Nutrition Examination Survey 1999-2004.

Factor—Serum bicarbonate level.

Outcomes—Lumbar and total BMD as well as low lumbar and total bone mass defined as 1.0 SD below sex-specific mean of young adults.

Measurements—BMD was measured by dual-energy X-ray absorptiometry and serum bicarbonate levels were measured in all participants.

Results—Both men and women with lower serum bicarbonate levels were more likely to be current smokers and had higher body mass index and estimated net endogenous acid production. There was a significant linear trend across quartiles of serum bicarbonate with lumbar BMD among the total population as well as in sex-specific models (p=0.02 for all three models, p=0.1 for interaction). For total BMD, a significant association was seen with serum bicarbonate levels

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among women but not men (p=0.02 and p=0.1, respectively; p=0.8 for interaction); and a significant association was seen among post-menopausal women but not pre-menopausal women (p=0.02 and p=0.2, respectively; p=0.5 for interaction). Compared to women with serum bicarbonate level <24 mEq/L, those with serum bicarbonate ≥27 mEq/L had 0.018 g/cm^2 higher total BMD (95% CI, 0.004-0.032; p=0.01) and had 31% lower odds of having low total bone mass (OR, 0.68; 95% CI, 0.46-0.99; p=0.05).

Limitations—Cross-sectional study using a single measurement of serum bicarbonate level. The subgroup differences are not definitive.

Conclusions—Lower serum bicarbonate levels are associated with lower BMD in US adults. Further studies should examine whether serum bicarbonate levels should be incorporated into the diagnostic assessment and management of osteoporosis.

Keywords

serum bicarbonate; alkali therapy; metabolic acidosis; bone mineral density (BMD); lumbar BMD; osteoporosis; low bone mass; modifiable risk factor; National Health and Nutrition Examination Survey (NHANES); dual energy X-ray absorptiometry (DEXA)

Chronic metabolic acidosis as a result of chronic kidney disease (CKD) has been shown to have a negative effect on bone. It induces bone resorption and inhibits bone formation, resulting in lower total bone mineral density (BMD).(1-4) In otherwise healthy individuals, there is evidence of a clinically meaningful, low-level metabolic acidosis, largely mediated by the age-related decline in kidney function and the acidogenic Western diet.(5, 6) However, the effect of low-level metabolic acidosis on bone metabolism in the general population is unknown.

Osteoporosis is the most common bone disease in humans and is characterized by low bone mass. It is a silent disease until it is complicated by fractures.(7) Osteoporosis-related fractures result in high morbidity and mortality (8) and create a heavy economic burden, causing more than 432,000 hospital admissions, almost 2.5 million medical office visits and about 180,000 nursing home admissions annually in the United States.(9) As the population ages, the prevalence of bone disease and fractures increases markedly, representing a major public health problem.

Whether metabolic acidosis should be incorporated into diagnostic guidelines or management of osteoporosis remains unclear and warrants investigation. Therefore, we hypothesized that lower serum bicarbonate levels would be associated with lower BMD in the general population. In addition, because osteopenia and osteoporosis are more common among women than men, we hypothesized that the association between serum bicarbonate levels and BMD may differ between the sexes. We tested these hypotheses in adults aged 20 years or older who completed dual energy X-ray absorptiometry (DEXA) in the National Health and Nutrition Examination Survey (NHANES) 1999-2004.

METHODS

Study Population

The NHANES 1999-2004 was a nationally representative survey of the non-institutionalized civilian population in the United States.(10) A stratified, multistage, probability sampling design was used to select participants. Overall, 11,974 adults aged 20 years or older completed the interview and examination components, including DEXA scans and measurement of serum bicarbonate. We excluded participants who had an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 (n=34), a diagnosis of chronic obstructive pulmonary disease (n=893), were on a bisphosphonate (n=173) or were missing covariate data (n=1150). Thus, 9,724 participants were available for analysis. The NHANES protocol was approved by the National Center for Health Statistics (NCHS) ethics review board and written informed consent was obtained from all participants.

Data Collection

Information on household income, education, physical activity, smoking, comorbidities and medication use in the previous month was obtained by self-report. Race/ethnicity was self-identified. Poverty was defined as <100% of the poverty index based on self-reported household income.(11) Participants were asked about the frequency and duration of walking or bicycling, home or yard work, and moderate or vigorous leisure time physical activity performed within the past 30 days. These responses were used to calculate metabolic equivalents (MET-min/wk) based on intensity values recommended by the NCHS.(12) Activity level was classified as 0, <500, 500-2000, or >2000 MET-min/wk. Smoking was classified as never, former, or current smoker. Data on dietary intake were obtained from a 24-hour dietary recall questionnaire. The diet-dependent net acid load was estimated as estimated net endogenous acid production (mEq/d)=[54.5×protein(g/d)/potassium(mEq/d)]-10.2.(13) Hypertension was defined as a systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg, physician diagnosis and/or antihypertensive medication use.(14) A participant was considered to have diabetes mellitus if he or she reported a physician diagnosis while not pregnant or the current use of insulin or oral hypoglycemic mediations, or had a glycohemoglobin level ≥6.5%.(15) Cardiovascular disease was defined by self-report of a physician diagnosis of congestive heart failure, coronary heart disease, angina, myocardial infarction or stroke. Vitamin D supplementation was assessed by questionnaire and pill-bottle review. Participants were considered to use vitamin D supplementation when they used at least 400 IU per day of vitamin D, which was the recommended dose by the Institute of Medicine at the time. Menopausal status was determined by questionnaire. A participant was considered to be menopausal when she answered “going or gone through menopause” to the question “What is the reason that you have not had regular periods in the past 12 months?”

Serum chemistry values were measured using the Hitachi 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN) in 1999-2001 and the Synchron LX20 (Beckman Coulter Inc., Brea, CA) in 2002-2004. Serum bicarbonate was measured in 2 laboratories via the phosphoenolpyruvate carboxylase method in 1999-2001 and with a pH-sensitive electrode in 2002-2004. The coefficient of variation ranged between 2.3% and 5.6%. Serum bicarbonate

levels during these time periods were compared using weighted linear regression. Mean serum bicarbonate was 1.105±0.178 mEq/L (standard deviation [SD]) higher ($p<0.001$) among all NHANES participants in 2003-2004 compared with 1999-2002. Therefore, serum bicarbonate levels in 1999-2002 were adjusted by adding 1.105 mEq/L as has been done previously.(6, 16) As ingestion of food may affect serum bicarbonate levels, the period of fasting prior to phlebotomy was categorized as ≤2, >2-6, and >6 hours.(17) Serum albumin was measured by the bromocresol purple method. Serum creatinine was measured by a modified kinetic Jaffe reaction. Values from 1999-2000 were calibrated to the Cleveland Clinic laboratory standard by multiplying by 1.013 and then adding 0.147. Correction of values from 2001-2004 was not necessary. 25-Hydroxyvitamin D (25(OH)D) was measured using the 25(OH)D assay (DiaSorin, Stillwater, MN). eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.(18)

Outcome Variables

Bone mineral density (g/cm^2) was measured by DEXA scans. The DEXA scans were administered to eligible survey participants in NHANES mobile examination centers. Women younger than 60 years were permitted to take the DEXA examination only if a pregnancy test taken at the time of the examination was negative. Individuals were excluded from the DEXA examination who reported taking tests with radiographic contrast material or participated in nuclear medicine studies in the past 3 days, or had a self-reported weight (>300 lb) or height (>6 ft 5 in) over the DEXA table limit. The whole-body DEXA scans were acquired using a QDR 4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts) following the manufacturer's acquisition procedures. The scan for each survey participant was reviewed and analyzed by the University of California, San Francisco, Department of Radiology using standard radiologic techniques and study-specific protocols developed by the NCHS. Of the 21,230 eligible DEXA participants aged 8 years and older who participated in the examination, scans with 100% non-missing data were obtained from 16,973 or 80%. To resolve the problem of potential biases due to missing DEXA data, multiple imputation of the missing data was performed. Details of the DEXA protocol, quality control analysis, and the multiple imputation procedure are available.[18A] We specifically examined lumbar spine BMD and total BMD. We chose lumbar BMD because the lumbar spine is one of the most common sites of fractures.(7) We also categorized low lumbar bone mass and low total bone mass as 1 SD below the respective sex-specific mean of 30- year-old adults. This definition was chosen as it mirrors the clinical definition of osteopenia (19), and the majority of fractures occur in patients with osteopenia rather than osteoporosis because of the large number of individuals with osteopenia.(7)

Statistical Analysis

All analyses used NHANES-appropriate sampling weights and accounted for the complex multistage cluster design using the "survey" command in Stata 12.1 (StataCorp LP, College Station, TX, USA). The distributions of participant characteristics were examined by quartiles of serum bicarbonate levels. A multivariable linear regression model was created to further examine the association of participant characteristics with serum bicarbonate. Linear and logistic regression models were created to examine the association of serum bicarbonate levels with BMD (lumbar and total) and low bone mass (lumbar and total), respectively.

Serum bicarbonate levels were analyzed as continuous variables and within quartiles to examine non-linear associations with either outcome. A variable was included in the final model if it was associated with serum bicarbonate and the outcome ($p<0.2$) and based on *a priori* determination of confounders of the association of serum bicarbonate and bone mass. These included known determinants of bone mass and factors that may affect levels of serum bicarbonate. We determined *a priori* to examine models after stratification by sex, and also tested effect modification by sex by including multiplicative interaction terms in the multivariable linear regression models with serum bicarbonate levels as a continuous variable. Variables included in the final models were age, sex, race/ethnicity, body mass index (BMI), poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, eGFR, albuminuria, serum albumin, calcium, phosphate and C-reactive protein. Because the difference in the association between serum bicarbonate and BMD between the sexes could be due to different estrogen status, to examine the role of estrogen status, a subgroup analysis was performed among women with known menopausal status using multivariable linear regression models stratified by menopausal status. Effect modification by menopausal status was tested by including multiplicative interaction terms. A p-value <0.2 was considered suggestive of an interaction. A p-value <0.05 was considered statistically significant.

Sensitivity Analyses

Since high net endogenous acid production has been associated with lower serum bicarbonate levels in the general population (20), we repeated our analyses in multivariable linear regression models after including estimated net endogenous acid production. Given the different effects loop and thiazide diuretics have on urinary calcium excretion, we repeated the analyses adjusting for loop or thiazide diuretic use alone or with both of them in the models. In addition, we repeated multivariable linear regression models after restricting our population to participants with eGFR ≥60 mL/min/1.73 m^2, using serum bicarbonate levels without correction factors from 1999-2002, and after adjusting for 25(OH)D levels and vitamin D supplementation. Lastly, because low bone mass is more prevalent in the older population, we repeated the multivariable logistic regression models after restricting our population to participants older than 50 years.

RESULTS

Participant Characteristics

Among 9,724 participants in the analysis, 48.8% of them were women (Table S1, available as online supplementary material). The mean serum bicarbonate was 24.9 ± 2.2 mEq/L. Men had higher mean serum bicarbonate compared to women (25.2 ± 2.2 vs. 24.5 ± 2.2 mEq/L; $p<0.001$). This difference persisted in multivariable analysis including adjusting for net endogenous acid production (Table S2). Both men and women with lower serum bicarbonate levels were more likely to be current smokers, had higher BMI and estimated net endogenous acid production (Table 1). Men with lower serum bicarbonate received less education, and were also less likely to use diuretics, and more likely to have diabetes mellitus, hypertension, cardiovascular disease or albuminuria. Women with lower serum

bicarbonate levels were more likely to be younger, to have greater poverty and higher eGFR, less likely to be non-Hispanic white, to have fasted 2 hours or less prior to phlebotomy, or have used diuretics or calcium carbonate. In contrast to men, women with lower serum bicarbonate levels were less likely to have diabetes mellitus, hypertension or cardiovascular disease. In bivariate analysis, a statistically significant association of lumbar or total BMD across quartiles was only observed in women, but not men. There were 1,673 (36.1%) women and 1,290 (25.3%) men who had either low lumbar or low total bone mass. Participant characteristics in the full cohort and associations with serum bicarbonate after multivariable adjustment are shown in Tables S1 and S2, respectively.

Association of Serum Bicarbonate With BMD

Using multivariable linear regression models, there was a significant linear trend across quartiles of serum bicarbonate with lumbar BMD among the total population as well as in sex-specific models (p=0.02 for all three models) (Table 2). Among women, compared to the reference group (<24 mEq/L), those with bicarbonate between 24-25, 25.1-26.9 or ≥27 mEq/L all had higher lumbar BMDs (0.015 [95% confidence interval (CI), 0.002-0.028], 0.016 [95% CI, 0.003-0.030], and 0.019 [95% CI, 0.003-0.036], g/cm^2 respectively). For total BMD, there was no statistically significant association with serum bicarbonate in either the total population or among men (p=0.2 and p=0.1, respectively). For women, a significant association was seen between serum bicarbonate levels and total BMD (p=0.02). For every 2.2 mEq/L or 1 SD higher serum bicarbonate level, total BMD was greater by 0.005 (95% CI, 0.001-0.010) g/cm^2 (p=0.03). Compared to participants with serum bicarbonate level <24 mEq/L, those with serum bicarbonate ≥27 mEq/L had 0.018 (95% CI, 0.004-0.032) g/cm^2 higher total BMD (p=0.02). In the multivariable linear regression models, the p-value for interaction between sex and serum bicarbonate regarding their association was 0.1 with lumbar BMD and 0.8 with total BMD. Using multivariable logistic regression models, there was no statistically significant association of serum bicarbonate with low lumbar BMD in either sex. There was a significant association of serum bicarbonate level with low total bone mass only among women (Table 3). Specifically, compared to women with serum bicarbonate <24 mEq/L, those with bicarbonate ≥27 mEq/L had 32% lower odds of having low total bone mass (odds ratio, 0.68; 95% CI, 0.46-0.99; p=0.05).

Among 2,805 women with known menopausal status, there was a linear trend in association between serum bicarbonate and lumbar BMD among both pre-menopausal and post-menopausal women (p=0.04 and p=0.02, respectively) (Table 4). For total BMD, a statistically significant association was only observed among post-menopausal women (p=0.02), but not pre-menopausal women. Among post-menopausal women, compared to those with serum bicarbonate level <24 mEq/L, those with serum bicarbonate ≥27 mEq/L had 0.024 (95% CI, 0.006-0.042) g/cm^2 higher total BMD (p=0.01). The p-values for interaction between menopausal status and serum bicarbonate regarding their association with lumbar and total BMD were both 0.5.

Sensitivity Analysis

After including net endogenous acid production in the multivariable linear regression models, no substantial change was observed in terms of the association between serum

bicarbonate level and BMD (lumbar or total) (Table 5). Similarly, no substantial change was observed after we restricted our population to participants with eGFR ≥60 mL/min/1.73 m^2 (Table 6), or adjusting for loop or thiazide diuretic use alone or with both of them in the models, or adjusting for 25(OH)D levels or vitamin D supplementation, or using serum bicarbonate levels without correction factors from 1999-2002 (tables *a*-*f* of Item S1). For multivariable logistic regression models, there was no substantial change after restricting our population to participants older than 50 years (table *g* of Item S1).

DISCUSSION

Having low BMD is a risk factor for osteoporosis-related fractures.(21) It is important to identify modifiable risk factors since osteoporosis can be prevented and treated before fractures occur. Our results demonstrate that lower serum bicarbonate levels are associated with lower lumbar and total BMD among adults aged 20 years or older in the general US population. We have shown that this association was stronger among women, more specifically post-menopausal women than men. To our knowledge, this is the first study to examine these associations population-wide, and could be of potential public health importance given the scope of the problem and the morbidity and mortality associated with osteoporosis-related fractures. (22, 23)

Chronic acidosis could result in negative calcium balance from bone buffering.(1) *In vivo* experimental studies have shown that metabolic acidosis leads to bone disease. For example, Kraut et al.(2) demonstrated that metabolic acidosis enhanced bone resorption and impaired bone formation, and this might contribute to osteopenia. In addition, Gasser et al.(4) showed that chronic metabolic acidosis in rats decreased total BMD using quantitative computed tomography. The association we have found in this study is consistent with these experimental studies. In patients with CKD, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines suggest to supplement with alkali salts to maintain serum bicarbonate ≥22 mEq/L,(24) as bicarbonate supplements have been shown to improve skeletal metabolism in clinical studies. In children with renal tubular acidosis, alkali therapy helped to attain and maintain normal stature.(25) In postmenopausal women without kidney disease, administration of potassium bicarbonate improved calcium balance, reduced bone resorption and increased bone formation.(26, 27) In addition, in a randomized controlled study, Dawson-Hughes et al.(28) demonstrated that bicarbonate supplementation in men and women aged 50 years or older has a favorable effect on bone resorption and calcium excretion. Similarly, Jehle et al. randomized 161 postmenopausal women with low bone mass to receive potassium citrate or potassium chloride daily and found that women who received potassium citrate had increased bone mass.(29) In another randomized, double-blind, placebo-controlled trial, they randomized 201 healthy men and women older than 65 years without osteoporosis to potassium citrate or placebo and found that potassium citrate increased lumbar BMD after 24 months.(30)

Regardless of the existing evidence on the benefit of alkali therapy on bone health, alkali therapy is still not routinely given to persons without kidney disease in the clinical setting to maintain bone mass. Our study demonstrates that within a relatively normal range of serum bicarbonate levels, having higher serum bicarbonate is associated with higher BMD in the

general population without advanced CKD. These data give more support to providing alkali therapy in the general population for improvement of bone health.

Our study also suggests that the association between serum bicarbonate levels and BMD is stronger among women than men, and stronger among post-menopausal women than pre-menopausal women. We acknowledge that the p-values for interaction between sex and serum bicarbonate did not uniformly suggest the presence of an interaction (p=0.1 and p=0.8 for lumbar and total BMD, respectively). However, the decision to stratify the analyses by sex was *a priori.* In the stratified analysis for lumbar BMD, compared to participants with serum bicarbonate <24 mEq/L, women with bicarbonate ≥24 mEq/L had higher BMD, but men did not have higher BMD until bicarbonate was ≥27 mEq/L. For total BMD, an association was only observed among women, but not men (Table 2). This seems to suggest that the association between serum bicarbonate and BMD is stronger in women than men. Similarly, in the subgroup analysis by menopausal status, p for interaction did not suggest the presence of an interaction, but the decisions to stratify and to perform an exploratory analysis were also *a priori*. In addition, smaller sample size (n=2,805) could have limited the power to detect an interaction. Based on the stratified analysis by menopausal status, the association seems to be stronger among post-menopausal women than pre-menopausal women, particularly for total BMD (p=0.02 and p=0.2, respectively) (Table 4).

The differences in the association between sexes and by menopausal status could, in part, be due to the effect of estrogen. The role estrogen might play in the association of acidosis and bone metabolism was suggested by the study done by Gasser et al.(4) In their study, chronic metabolic acidosis decreased bone mass in both ovariectomized and sham-operated rats. Ovariectomized rats without acidosis had lower total BMD than both sham-operated rats with and without acidosis, and chronic metabolic acidosis further accelerated bone loss induced by ovariectomy. In other words, estrogen status might modify the association of acidosis with BMD. As postmenopausal women are at the highest risk of developing osteoporosis, the role of gender and hormonal status could be clinically relevant and warrants further investigation.

In our cross-sectional study, we found that serum bicarbonate levels were higher in men compared to women, and higher in older women compared to younger women. These associations persisted after multivariable adjustment. The lower serum bicarbonate in women could be, in part, explained by mild hypocapnia during the luteal phase of the menstrual cycle.(31) The positive association of serum bicarbonate with age seems unexpected given previous reports (5, 32), but it is consistent with our recent analysis of serum bicarbonate levels and aging in Americans using NHANES data.(20) Higher bicarbonate levels among older persons were partly, but not completely, explained by differences in dietary acid load related to age. However, adjustment for net endogenous acid production did not change our results here.

Our analysis has several important limitations. Because arterial pH and PCO_2 levels were not available, lower bicarbonate levels cannot be excluded as markers of alterations in respiratory status. However, participants with chronic obstructive pulmonary disease were not included in our analysis. Single measurements were used to ascertain serum bicarbonate

levels, and variability in handling of samples could affect bicarbonate levels.(33-35) This would presumably introduce non-differential misclassification and bias our results towards the null hypothesis. In addition, although our definition of low bone mass mirrored the clinical definition of osteopenia, they are not equivalent. Thus, this limits its clinical implication. Finally, because of the cross-sectional nature of our analysis, no causal association can be inferred; the possibility of reverse causality cannot be excluded.

In conclusion, we have shown that lower levels of serum bicarbonate were associated with lower lumbar and total BMD in US adults. Further studies are warranted to illuminate the determinants of serum bicarbonate in people without kidney disease and investigate whether serum bicarbonate levels should be incorporated into the diagnostic assessment guidelines or management of osteoporosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant Characteristics by Quartiles of Serum Bicarbonate Levels by Sex

	Men					Women				
Characteristic	**< 24**	**24-25**	**25.1-26.9**	**≥ 27**	**P**	**< 24**	**24-25**	**25.1-26.9**	**≥ 27**	**P**
No. of participants	1120	1175	1500	1298		1453	1180	1211	787	
Age (y)	44 (0.5)	45 (0.5)	44 (0.4)	45 (0.6)	0.06	41 (0.5)	45 (0.6)	48 (0.6)	54 (0.8)	<0.001
Race/Ethnicity					0.07					0.02
Non-Hispanic White	72% (2.6%)	73% (2.6%)	71% (2.3%)	72% (1.9%)		70% (2.2%)	71% (2.5%)	72% (2.3%)	73% (2.1%)	
Mexican American	10.4% (1.8%)	9.2% (1.2%)	8.7% (1.0%)	5.5% (0.7%)		9.2% (1.6%)	6.9% (1.0%)	5.9% (0.7%)	3.4% (0.5%)	
Non-Hispanic Black	8.0% (1.2%)	8.0% (1.1%)	10.1% (1.0%)	11.3% (1.1%)		10.2% (1.5%)	11.2% (1.3%)	12.2% (1.4%)	12.6% (1.6%)	
Body-mass index (kg/m^2)	29.4 (0.2)	28.2 (0.2)	27.8 (0.2)	26.7 (0.2)	<0.001	29.1 (0.3)	27.6 (0.3)	27.8 (0.2)	27.0 (0.3)	<0.001
Poverty*	11.7% (1.0%)	10.5% (1.0%)	11.0% (0.8%)	9.0% (1.1%)	0.1	17.5% (1.2%)	14.5% (1.5%)	13.8% (1.2%)	11.1% (1.2%)	<0.001
<High school diploma	21.4% (1.7%)	18.7% (1.2%)	19.5% (1.4%)	17.1% (1.3%)	0.05	18.9% (1.1%)	17.1% (1.2%)	19.2% (1.4%)	19.4% (1.6%)	0.6
Activity Level					0.5					0.09
0 MET-min/wk	12.9% (1.4%)	12.4% (1.0%)	13.8% (1.3%)	12.0% (1.2%)		18.1% (1.1%)	15.6% (1.2%)	18.8% (1.5%)	18.9% (1.5%)	
<500 MET-min/wk	21.2% (1.7%)	20.0% (1.7%)	17.9% (1.1%)	18.2% (1.3%)		22.7% (1.5%)	21.9% (1.2%)	19.1% (1.5%)	24.4% (1.6%)	
500-2000 MET-min/wk	36.1% (2.0%)	34.2% (1.2%)	36.9% (1.5%)	35.3% (1.5%)		34.4% (1.6%)	35.2% (1.6%)	38.7% (1.7%)	32.5% (1.9%)	
>2000 MET-min/wk	29.8% (2.0%)	33.4% (1.8%)	31.5% (2.1%)	34.5% (1.5%)		24.9% (1.3%)	27.3% (1.8%)	23.4% (1.4%)	24.2% (2.2%)	
Smoking					<0.001					<0.001
Never	40.3% (2.6%)	39.7% (2.0%)	44.6% (1.7%)	48.9% (1.9%)		54.8% (2.5%)	58.8% (1.6%)	62.5% (1.6%)	61.6% (1.6%)	
Former	26.8% (1.4%)	28.5% (1.5%)	28.7% (1.6%)	29.6% (1.4%)		18.7% (1.7%)	20.7% (1.4%)	20.0% (1.3%)	23.3% (2.0%)	
Current	32.8% (2.5%)	31.8% (1.5%)	26.6% (1.4%)	21.6% (1.6%)		26.6% (1.6%)	20.6% (1.6%)	17.5% (1.1%)	15.1% (1.6%)	
Estimated NEAP (mEq/d)	63.1 (0.9)	62.8 (1.0)	59.7 (0.9)	57.1 (0.7)	<0.001	59.3 (0.8)	57.6 (1.0)	51.5 (0.7)	48.5 (1.1)	<0.001
Fasting length ≤2 h	2.9 (0.5)	2.4 (0.5)	3.3 (0.5)	2.9 (0.6)	0.6	2.2 (0.5)	2.3 (0.5)	3.1 (0.5)	4.3 (0.9)	0.02
Diuretic use	7.1% (0.8%)	6.2% (0.8%)	6.4% (0.8%)	10.6% (1.2%)	0.02	5.5% (0.7%)	9.3% (1.2%)	13.2% (1.3%)	25.3% (1.9%)	<0.001
Calcium carbonate use	5.1% (0.9%)	3.2% (0.7%)	5.4% (0.7%)	4.3% (1.1%)	0.9	2.4% (0.5%)	3.3% (0.8%)	4.3% (0.7%)	5.3% (1.3%)	0.02
Hypertension	43.1% (1.8%)	36.5% (1.7%)	35.3% (1.7%)	36.5% (1.9%)	0.01	33.3% (1.3%)	35.7% (1.6%)	41.4% (2.0%)	53.5% (2.1%)	<0.001
Diabetes Mellitus	11.2% (1.1%)	8.9% (1.1%)	7.8% (0.8%)	6.4% (0.7%)	<0.001	7.6% (0.7%)	5.7% (0.6%)	7.9% (0.7%)	11.5% (1.2%)	0.01
Cardiovascular disease	9.8% (1.0%)	8.0% (1.1%)	8.6% (0.9%)	6.8% (0.7%)	0.03	5.2% (0.5%)	6.0% (0.8%)	6.9% (0.9%)	8.5% (0.9%)	0.001

	Men					Women				
Characteristic	**< 24**	**24-25**	**25.1-26.9**	**≥ 27**	**P**	**< 24**	**24-25**	**25.1-26.9**	**≥ 27**	**P**
eGFR (mL/min/1.73 m^2)	94.1 (0.8)	93.9 (0.7)	94.3 (0.7)	92.8 (0.6)	0.2	98.8 (0.7)	95.9 (0.8)	93.6 (0.8)	88.6 (1.1)	<0.001
Urine ACR > 30 mg/g	10.4% (0.8%)	8.6% (0.8%)	6.9% (0.7%)	6.7% (0.8%)	0.001	9.0% (0.7%)	8.9% (0.9%)	9.0% (1.0%)	10.1% (1.1%)	0.6
Serum albumin (g/dL)	4.41 (0.01)	4.43 (0.02)	4.45 (0.01)	4.50 (0.02)	<0.001	4.24 (0.01)	4.25 (0.01)	4.27 (0.01)	4.26 (0.02)	0.2
Serum calcium (mg/dL)	9.48 (0.02)	9.56 (0.02)	9.53 (0.02)	9.56 (0.02)	0.06	9.39 (0.02)	9.47 (0.02)	9.44 (0.02)	9.52 (0.03)	<0.001
Serum phosphate (mg/dL)	3.63 (0.03)	3.67 (0.02)	3.57 (0.02)	3.59 (0.02)	0.08	3.68 (0.02)	3.76 (0.02)	3.69 (0.02)	3.78 (0.02)	0.03
C-reactive protein ≥1.0 mg/dL	6.3% (1.0%)	5.1% (0.7%)	5.4% (0.6%)	4.8% (0.6%)	0.2	14.8% (1.2%) 8	10.4% (1.0%)	11.7% (1.5%)	12.4% (1.5%)	0.2
Lumbar BMD (g/cm^2)	1.05 (0.006)	1.04 (0.007)	1.05 (0.005)	1.06 (0.006)	0.1	1.05 (0.004)	1.05 (0.006)	1.05 (0.004)	1.03 (0.007)	0.03
Total BMD (g/cm^2)	1.19 (0.005)	1.19 (0.005)	1.19 (0.004)	1.19 (0.004)	0.9	1.10 (0.003)	1.10 (0.004)	1.09 (0.003)	1.08 (0.006)	<0.001

Note: Unless otherwise indicated, values for categorical variables are given as percentage (standard error); values for continuous variables, as mean ± standard error. Serum bicarbonate is expressed as mEq/L. Conversion factor for serum calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: MET, metabolic equivalent; NEAP, net endogenous acid production; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; BMD, bone mineral density.

Table 2

Association of Serum Bicarbonate with Lumbar and Total BMD

	Total Population	Men	Women
Lumbar BMD (g/cm^2)			
Continuous*	**0.005 (0.001,0.009)**	**0.008 (0.002,0.015)**	**0.007 (0.0004,0.013)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.004 (-0.007,0.014)	-0.005 (-0.023,0.013)	**0.015 (0.002,0.028)**
25.1-26.9 mEq/L	0.009 (-0.001,0.019)	0.011 (-0.005,0.027)	**0.016 (0.003,0.030)**
≥ 27 mEq/L	**0.014 (0.002,0.026)**	**0.019 (0.0004,0.038)**	**0.019 (0.003,0.036)**
P for trend	0.02	0.02	0.02
Total BMD (g/cm^2)			
Continuous*	0.003 (-0.001,0.007)	0.004 (-0.001,0.009)	**0.005 (0.001,0.010)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.006 (-0.003,0.016)	0.005 (-0.010,0.020)	0.009 (-0.0004,0.019)
25.1-26.9 mEq/L	0.003 (-0.006,0.012)	0.005 (-0.008,0.018)	0.006 (-0.002,0.014)
≥ 27 mEq/L	0.010 (-0.002,0.023)	0.012 (-0.003,0.027)	**0.018 (0.004,0.032)**
P for trend	0.2	0.1	0.02

Abbreviations: BMD, bone mineral density.

Note: Values are given as regression coefficient (95% confidence interval). **Bold** values indicate p<0.05. Models adjusted for age, sex, race/ethnicity, body mass index, poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, estimated glomerular filtration rate, albuminuria, serum albumin, calcium, phosphate and C-reactive protein.

* Per 1-standard deviation higher serum bicarbonate (standard deviation = 2.2 mEq/L).

Table 3

Odds Ratio of Low Lumbar and Total Bone Mass by Serum Bicarbonate Level

	Men	Women
Low Lumbar Bone Mass		
Continuous*	0.95 (0.85,1.06)	0.93 (0.83,1.05)
< 24 mEq/L	1.00 (reference)	1.00 (reference)
24-25 mEq/L	1.29 (0.87,1.91)	0.96 (0.75,1.24)
25.1-26.9 mEq/L	1.21 (0.87,1.70)	0.94 (0.74,1.21)
≥ 27 mEq/L	0.90 (0.62,1.31)	0.79 (0.56,1.12)
P for trend	0.5	0.2
Low Total Bone Mass		
Continuous*	0.96 (0.85,1.08)	0.91 (0.79,1.04)
< 24 mEq/L	1.00 (reference)	1.00 (reference)
24-25 mEq/L	0.91 (0.68,1.23)	1.05 (0.77,1.43)
25.1-26.9 mEq/L	1.03 (0.75,1.43)	0.92 (0.63,1.35)
≥ 27 mEq/L	0.85 (0.59,1.23)	**0.68 (0.46,0.99)**
P for trend	0.5	0.08

Note: Values are given as odds ratio (95% confidence interval). **Bold** values indicate $p<0.05$. Models adjusted for age, race/ethnicity, body mass index, poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, estimated glomerular filtration rate, albuminuria, serum albumin, calcium, phosphate and C-reactive protein.

* Per 1-standard deviation higher serum bicarbonate (standard deviation = 2.2 mEq/L).

Table 4

Subgroup Analysis Among Women based on Menopausal Status

	Total	Pre-menopause (n=1435)	Post-menopause (n=1370)
Lumbar BMD (g/cm^2)			
Continuous*	**0.011 (0.004,0.018)**	**0.012 (0.002,0.021)**	0.009 (-0.004,0.022)
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.009 (-0.008,0.027)	0.008 (-0.020,0.036)	0.008 (-0.021,0.037)
25.1-26.9 mEq/L	**0.017 (0.001,0.034)**	**0.021 (0.003,0.039)**	0.011 (-0.015,0.038)
≥ 27 mEq/L	**0.028 (0.009,0.048)**	0.021 (-0.012,0.054)	**0.033 (0.007,0.060)**
P for trend	0.01	0.04	0.02
Total BMD (g/cm^2)			
Continuous*	**0.006 (0.001,0.011)**	0.005 (-0.001,0.011)	0.007 (-0.0003,0.014)
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.004 (-0.007,0.015)	0.004 (-0.011,0.020)	0.002 (-0.016,0.020)
25.1-26.9 mEq/L	0.006 (-0.003,0.015)	0.009 (-0.003,0.021)	0.003 (-0.014,0.019)
≥ 27 mEq/L	0.017 (-0.0003,0.035)	0.009 (-0.018, 0.037)	**0.024 (0.006,0.042)**
P for trend	0.05	0.2	0.02

Abbreviation: BMD, bone mineral density.

Note: n=2,805. Table shows association of serum bicarbonate with lumbar and total BMD Values are given as regression coefficient (95% confidence interval). **Bold** values indicate p<0.05. Models adjusted for age, race/ethnicity, menopause status, body mass index, poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, estimated glomerular filtration rate, albuminuria, serum albumin, calcium, phosphate and C-reactive protein.

* Per 1-standard deviation higher serum bicarbonate (standard deviation = 2.2 mEq/L).

Table 5

Sensitivity Analysis After Adjustment for Net Endogenous Acid Production

	Total Population	Men	Women
Lumbar BMD (g/cm^2)			
Continuous*	**0.005 (0.001,0.009)**	**0.008 (0.002,0.014)**	**0.008 (0.001,0.014)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.005 (-0.006,0.016)	-0.006 (-0.024,0.013)	**0.018 (0.004,0.032)**
25.1-26.9 mEq/L	0.009 (-0.002,0.019)	0.009 (-0.007,0.025)	**0.017 (0.003,0.031)**
≥ 27 mEq/L	**0.014 (0.002,0.026)**	0.018 (-0.0003,0.037)	**0.020 (0.004,0.037)**
P for trend	0.02	0.02	0.01
Total BMD (g/cm^2)			
Continuous*	0.003 (-0.001,0.007)	0.004 (-0.001,0.008)	**0.005 (0.0004,0.010)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.007 (-0.002,0.017)	0.006 (-0.009,0.020)	**0.011 (0.002,0.021)**
25.1-26.9 mEq/L	0.003 (-0.006,0.012)	0.005 (-0.009,0.018)	0.005 (-0.003,0.014)
≥ 27 mEq/L	0.010 (-0.002,0.023)	0.011 (-0.004,0.026)	**0.018 (0.003,0.033)**
P for trend	0.2	0.2	0.03

Abbreviation: BMD, bone mineral density.

Note: Table shows association of serum bicarbonate with lumbar and total BMD Values are given as regression coefficient (95% confidence interval). **Bold** values indicate p<0.05. Models adjusted for age, sex, race/ethnicity, body mass index, poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, estimated glomerular filtration rate, albuminuria, serum albumin, calcium, phosphate, C-reactive protein and estimated net endogenous acid production.

* Per 1-standard deviation higher serum bicarbonate (standard deviation = 2.2 mEq/L).

Table 6

Sensitivity Analysis For Participants with eGFR ≥60 mL/min/1.73 m^2

	Total Population	Men	Women
Lumbar BMD (g/cm^2)			
Continuous*	**0.006 (0.001,0.011)**	**0.009 (0.001,0.016)**	**0.008 (0.002,0.014)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24-25 mEq/L	0.003 (-0.007,0.014)	-0.007 (-0.025,0.012)	**0.014 (0.001,0.027)**
25.1-26.9 mEq/L	**0.011 (0.001,0.021)**	0.012 (-0.005,0.029)	**0.017 (0.005,0.029)**
≥ 27 mEq/L	**0.016 (0.003,0.030)**	0.019 (-0.001,0.039)	**0.022 (0.005,0.039)**
P for trend	0.01	0.02	0.01
Total BMD (g/cm^2)			
Continuous*	0.003 (-0.001,0.007)	0.004 (-0.001,0.009)	**0.005 (0.001,0.009)**
< 24 mEq/L	(referent group)	(referent group)	(referent group)
24 -25 mEq/L	0.006 (-0.004,0.015)	0.005 (-0.010,0.019)	0.008 (-0.002,0.017)
25.1-26.9 mEq/L	0.003 (-0.006,0.012)	0.006 (-0.008,0.020)	0.003 (-0.004,0.011)
≥ 27 mEq/L	0.011 (-0.002,0.023)	0.012 (-0.004,0.028)	**0.017 (0.003,0.032)**
P for trend	0.1	0.1	0.03

Abbreviation: BMD, bone mineral density; eGFR, estimated glomerular filtration rate.

Note: n=8,877. Table shows association of serum bicarbonate with lumbar and total BMD. Values are given as regression coefficient (95% confidence interval). **Bold** values indicate $p<0.05$. Models adjusted for age, sex, race/ethnicity, body mass index, poverty, education, activity level, smoking status, fasting length, diuretic and calcium carbonate use, diagnosis of diabetes mellitus, hypertension and cardiovascular disease, estimated glomerular filtration rate, albuminuria, serum albumin, calcium, phosphate and C-reactive protein.

* Per 1-standard deviation higher serum bicarbonate (standard deviation = 2.2 mEq/L).