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Original Investigation

Serum Bicarbonate and Bone Mineral Density in US Adults

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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 20 years or older in NHANES (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 the sex-specific mean value of young adults.

Measurements: BMD was measured by dual-energy x-ray absorptiometry and serum bicarbonate was 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 in the total population, as well as in sex-specific models ($P = 0.02$ for all 3 models, $P = 0.1$ for interaction). For total BMD, a significant association was seen with serum bicarbonate level for women but not men ($P = 0.02$ and $P = 0.1$, respectively; $P = 0.8$ for interaction), and a significant association was seen for postmenopausal women but not premenopausal women ($P = 0.02$ and $P = 0.2$, respectively; $P = 0.5$ for interaction). Compared with women with serum bicarbonate levels < 24 mEq/L, those with serum bicarbonate levels ≥ 27 mEq/L had 0.018-g/cm^2 higher total BMD (95% CI, 0.004-0.032; $P = 0.01$) and 31% lower odds of having low total bone mass (OR, 0.68; 95% CI, 0.46-0.99; $P = 0.049$).

Limitations: Cross-sectional study using a single measurement of serum bicarbonate. 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.

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INDEX WORDS: 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

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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 20 years or older who underwent dual-energy x-ray absorptiometry (DEXA) in NHANES (National Health and Nutrition Examination Survey) 1999-2004.

METHODS

Study Population

NHANES 1999-2004 was a nationally representative survey of the noninstitutionalized civilian population in the United States.[10] A stratified, multistage, probability sampling design was used to select participants. Overall, 11,974 adults 20 years or older completed the interview and examination components, including DEXA scans and measurement of serum bicarbonate. We excluded participants who had estimated glomerular filtration rates (eGFRs) < 15 mL/min/1.73 m^2 (n = 34), had a diagnosis of chronic obstructive pulmonary disease (n = 893), were using a bisphosphonate (n = 173), or were missing covariate data (n = 1,150). 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 for household income, education, physical activity, smoking, comorbid conditions, 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 to 2,000, or > 2,000 MET-min/wk. Smoking was classified as never, former, or current smoker. Data for 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 systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, 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 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) in 1999 to 2001 and the Synchron LX20 (Beckman Coulter Inc) in 2002 to 2004. Serum bicarbonate was measured in 2 laboratories by the phosphoenolpyruvate carboxylase method in 1999 to 2001 and with a pH-sensitive electrode in 2002 to 2004. The coefficient of variation ranged between 2.3% and 5.6%. Serum bicarbonate levels during these periods were compared using weighted linear regression. Mean serum bicarbonate level was 1.105 ± 0.178 mEq/L (standard deviation [SD]) higher ($P < 0.001$) among all NHANES participants in 2003 to 2004 compared with 1999 to 2002. Therefore, serum bicarbonate levels in 1999 to 2002 were adjusted by adding 1.105 mEq/L, as has been done previously.[6,16] Because ingestion of food may affect serum bicarbonate levels, the period of fasting prior to phlebotomy was categorized as 2 or fewer, more than 2 to 6, and more than 6 hours.[17] Serum albumin was measured by the bromocresol purple method. Serum creatinine was measured by a modified kinetic Jaffé reaction. Values from 1999 to 2000 were calibrated to the Cleveland Clinic laboratory standard by multiplying by 1.013 and then adding 0.147. Correction of values from 2001 to 2004 was not necessary. 25-Hydroxyvitamin D (25[OH]D) was measured using the LIAISON 25 OH Vitamin D TOTAL Assay (DiaSorin). eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[18]

Outcome Variables

BMD (grams per centimeter squared) was measured by DEXA. DEXA was 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 having 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. Whole-body DEXA scans were acquired using a QDR 4500A fan-beam densitometer (Hologic Inc) 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 21,230 eligible DEXA-scanned participants in NHANES 1999-2004, scans with 100% nonmissing 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 multiple imputation procedure are available.[19] 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 because it mirrors the clinical definition of osteopenia,[20] and most 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). 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 level. 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 nonlinear associations with either outcome. A variable