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Low Estimates of Dietary Acid Load Are Positively Associated with Bone Ultrasound in Women Older Than 75 Years of Age with a Lifetime Fracture[1,2]

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Abstract

Dietary acid load from Western diets may be a risk factor for osteoporosis. It can be estimated by net endogenous acid production (NEAP). No data currently exists for NEAP estimates and bone indices in the very elderly (i.e. ≥75 y). The aim of this study was to determine the association between NEAP estimates by using the potential renal acid load (PRAL) equation and quantitative bone ultrasound (QUS) measurements at the heel [broadband ultrasound attenuation (BUA)] in Caucasian women. We assessed NEAP and QUS in 401 very elderly Swiss ambulatory women. We evaluated dietary intake and NEAP estimates with a validated FFQ. QUS was measured using Achilles (Lunar). We identified 2 subgroups: 256 women (80.6 y ± 3; BUA, 96.8 dB/MHz) with a fracture history and the remaining 145 (79.9 y SD 2.9; BUA, 101.7 dB/MHz) without. Women who reported having suffered a fracture had lower BUA ($P < 0.001$) than nonfractured women but did not differ in nutrient intakes and NEAP. Lower NEAP ($P = 0.023$) and higher potassium intake ($P = 0.033$) were correlated with higher BUA, which remained significant even after adjustment for age, BMI, and osteoporosis treatment. BUA was positively correlated with calcium ($P = 0.016$) and BMI ($P < 0.001$). Women who reported no fractures had no significant correlations between nutrient intake, NEAP, and BUA. Low nutritional acid load was correlated with higher BUA in very elderly women with a fracture history. Although relatively weak compared with age and BMI, this association was significant and may be an important additional risk factor that might be particularly relevant in frail patients with an already high fracture risk. J. Nutr. 138: 1349–1354, 2008.

Introduction

To achieve optimum bone health, numerous factors are required, such as optimal genetics, good health, and adequate nutrition. There is growing evidence suggesting that the Western diet is a risk factor for osteoporosis through excess acid supply and that fruit and vegetable intake balances the excess acidity, mostly by providing potassium-rich, bicarbonate-rich foods (1–3). Indeed, Western diets consumed by adults generate 50–100 mEq acid/d (4). Therefore, healthy adults consuming such a diet are at risk of chronic low grade metabolic acidosis, which worsens with age due to a decline in kidney function (5).

Maintenance of acid-base homeostasis is tightly regulated in the extracellular fluid at pH 7.4 (± 0.05) (6). Almost every biological process in the human body is dependent on the acid-base balance, including bone metabolism. Bone contributes to the acid-base homeostasis as it delivers cations such as magnesium, potassium, calcium, and sodium, which can be associated with alkali salts such as citrate or carbonate. Over time, an overstimulation of this process will lead to the dissolution of the bone mineral content and, hence, to reduced bone mass (5,6). Therefore, long-term nutritional acid load may be harmful to bone health.

In vitro studies have shown that metabolic acidosis induces a calcium efflux from bone (7). In animal and human models, an acid environment is associated with a negative calcium balance and increased bone loss (8–10). Any reduction in extracellular pH enhances osteoclastic activity (11). Even a small change in pH, close (pH 7.1) but not exact to the physiological level (pH 7.4), stimulates osteoclasts (12). With a long-term nutritional acidic load, pH is kept constant at the expense of bone, which delivers the buffering substances through bone resorption (13). This statement is theoretical. The acidification of bone is not only linked to osteoclastic stimulation. Cultured osteoblasts show reduced collagen synthesis and mineralization in an acidic environment (14,15).

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Nutrition has long been known to strongly influence acid-base balance in humans (16). Intakes of potassium, magnesium, fruit, and vegetables have been associated with a more alkaline environment in the human body and a beneficial effect on bone health (17). In healthy male volunteers, an acid diet significantly increased urinary calcium excretion by 74% and urinary C-telopeptide excretion by 19% compared with an alkali diet (18).

In trans-sectional studies, the acid:base ratio has shown that there is a correlation between the nutritional acid load and bone health measured by bone ultrasound (19) or dual energy X-ray absorptiometry (20). However, data are still scarce. The primary objective of our study was to determine whether low dietary acid load and bone ultrasound measures [broadband ultrasound attenuation (BUA)[6]] were associated in a group of very elderly women aged ≥75 y who were representative of the Swiss population. To our knowledge, this very elderly population has not yet been assessed in terms of evaluation of dietary acid load and bone ultrasound measures.

Subjects and Methods

The cohort of 401 elderly ambulatory women (80.4 y; BMI, 25.2 kg/m^2) are a subgroup of women who participated in the Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study (21,22). The SEMOF study was a prospective and multicentered study that compared 3 bone quantitative ultrasounds (QUS) for the assessment of hip fracture risk in a population of 7609 Swiss women aged ≥70 y followed from 1997 to 2002. In 2004, the women of the local cohort were contacted by telephone and asked if they wanted to participate in the new Evaluation of Nutritional Intakes and Bone UltraSound study. A total of 401 women accepted. No significant effects of the acid load were observed in the whole group, which led us to examine women with a fracture history separately. Therefore, 2 subgroups were created: 256 women with a fracture history (of which 15.2% were treated for osteoporosis, including hormone replacement therapy) and 145 non-fractured women (of which 7.6% were treated). Indeed, previous fracture is an important risk factor that represents a component of many independent clinical risk factors such as body weight, comorbidities, genetic risks, physical weakness, and nutrition. During their only visit to the hospital, the participants were asked if they had ever had 1 or several fractures in their life. Because many women had difficulty recalling age, type, and cause of fracture, all women reporting any lifetime fracture were included in the fracture history subgroup. All patients were also weighed and measured.

The Mini Nutritional Assessment (MNA), a noninvasive and validated questionnaire to evaluate nutritional status in elderly people, was completed by each woman (23). The MNA contained 18 questions to evaluate the nutritional status of the subject. The score ranged from 0 to 30 (<17 indicates malnutrition, 17.5–23.5 risk of malnutrition, and ≥24 well nourished). Quantitative bone ultrasounds were conducted for each participant. The nondominant foot was measured. The Lunar-Achilles bone ultrasound machine was used and 1 result was obtained for BUA, speed of sound (SOS), and stiffness index (SI). The machine was calibrated on a weekly basis with a physical phantom.

Prior to their visit, all women received by post a FFQ specifically designed for this study that was validated against weighed records and tested for reproducibility (24). They completed the FFQ at home and brought it back to their appointment with a dietician who reviewed it with the respondent and completed and discussed any missing answers with the patient. The FFQ were coded to ensure anonymous data. The FFQ was designed to estimate the usual food intake during the previous year. All nutrients, as well as energy intakes, were computed using a specially designed computer program, which used a nutrient database containing German, Austrian, and French food composition tables (25), because at that time, the first Swiss food composition table was not available for use (26). The traditional potential renal acid load (PRAL) index was calculated for each individual with the following nutrients using the formula: PRAL (mEq/d) = [phosphorus (mg/d) × 0.037 + protein (g/d) × 0.49] − [potassium (mg/d) × 0.021+ magnesium (mg/d) × 0.0263 + calcium (mg/d) × 0.013] (27). In accordance with the standardization terminology agreement as proposed by Frassetto et al. (28), we refer to this as estimates of net endogenous acid production (NEAP). We chose to exclude sodium and chloride, as others did (19), because our FFQ could not quantify the salt added to food.

The study protocol was accepted by the University of Lausanne's Ethic Committee. Each subject gave written, informed consent.

Statistics. All analyses were performed by using the SPSS statistical software package (version 14). We determined descriptive statistics (means, medians, SD, and ranges) for all variables. Data were checked for normality with the Kolmogorov Smirnov test. We calculated significant differences between both subgroups with independent *t* tests. NEAP values, calculated on absolute nutrient intakes, were divided into tertiles and the corresponding mean values of BUA were calculated. Differences between BUA among the NEAP tertiles were assessed using the F test for linearity and 1-way ANOVA with post hoc test (Tukey test).

We used ANCOVA to assess differences after adjustment for important confounding factors (age, BMI, and osteoporosis treatment). BUA values were divided into quartiles and the mean values of MNA were calculated. Differences between MNA among the BUA quartiles were assessed by using the F test for linearity and 1-way ANOVA with post hoc test (Tukey test). We also used stepwise multiple regression analysis to determine whether the estimate of NEAP was an independent predictor of bone health.

Results

Descriptive data

The age, anthropometric data, and bone ultrasound measurements for all 401 subjects and for the subgroups of 256 fractured women and 145 nonfractured women are given (**Table 1**). Indeed, the acid load did not affect the whole group, which led us to examine women with a fracture history separately. The values of the ultrasound parameters, BUA and SI ($P < 0.01$), were lower in the subgroup of fractured women, although they were only 8 mo older ($P < 0.05$). The bone-ultrasound measurements and nutrition were not correlated in the nonfractured subgroup. Therefore, we did not present these results. All results presented hereafter are those of the subgroup of 256 fractured women.

Dietary intakes and estimates of NEAP are presented (**Table 2**). Daily intakes of energy were low compared with the recommended intake (29), as expected for this age group, and comparable to results from previous studies in the elderly (30,31). Protein intakes were within the reference nutrient intakes for

TABLE 1 Characteristics of the study population[1]

	All subjects	Subgroup with fracture history	Subgroup with no fracture history
n	401	256	145
Age, *y*	80.4 ± 3	80.6 ± 3	79.9 ± 2.94*
BMI, *kg/m^2*	25.2 ± 4.4	24.6 ± 4.4	25.5 ± 4.7
MNA, *score*	26.6 ± 2.4	26.5 ± 2.5	26.9 ± 2.3
BUA, *dB/MHz*	98.5 ± 9.7	96.8 ± 9	101.7 ± 10**

[1] Values are means ± SD. *Different from fractured subgroup, $P < 0.05$; **$P < 0.01$.

[6] Abbreviations used: BUA, broadband ultrasound attenuation; MNA, Mini Nutritional Assessment; NEAP, net endogenous acid production; PRAL, potential renal acid load; Q1, quartile 1; QUS, quantitative ultrasound; SEMOF, Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk; SI, stiffness index; SOS, speed of sound; T1, tertile 1.

elderly Swiss women; however, calcium, potassium, and magnesium intakes were below recommendations (32).

Correlations between estimates of NEAP, associate nutrients, and BUA

Lower estimates of NEAP were associated with higher BUA ($r = -0.142$; $P < 0.05$). Higher estimates of calcium ($r = 0.151$) and potassium ($r = 0.134$) were associated with higher BUA ($P < 0.05$). Differences remained significant after adjustment for age, BMI, and osteoporosis treatment.

Tertile analysis between estimation of NEAP and BUA. BUA decreased significantly between tertile 1 (T1) and T3 for the estimate of NEAP (**Table 3**; **Fig. 1**). The mean scores of BUA differed for the 3 groups, as determined by 1-way ANOVA ($P = 0.03$) with post hoc test (Tukey test), as well as for the F test for linearity ($P = 0.03$). Comparison of the means of BUA by tertiles of NEAP with post hoc test (Tukey test) showed trends (T1–T2, $P = 0.052$; T1–T3, $P = 0.070$).

The difference in BUA between T1 and T3 was 2.9 dB/MHz, which represents a 2.9% difference. Differences remained significant after adjusting for age, BMI, and osteoporosis treatment.

Estimation of NEAP as an independent predictor of bone health. The stepwise regression analysis included BUA, NEAP, BMI, osteoporosis treatment, MNA, and age. It explained 7.6% of the variation in BUA. BMI and osteoporosis treatment explained 6.3% and NEAP 1.3% ($P < 0.050$). Age and MNA were excluded from the equation, because they did not affect the stepwise regression analysis.

NEAP was an independent predictor of BUA after BMI, with the following equation:

$$\text{BUA} = 86.7 + (0.2 \times \text{BMI}) - (0.13 \times \text{NEAP}).$$

Age and MNA were excluded from this equation, because they were excluded from the stepwise regression. When BMI was held constant (using the mean values for the group), the difference in BUA between ± 1 SD of NEAP estimate was 4.1%. The lowest NEAP (most alkaline) was associated with the highest BUA. Absolute BUA values were 93.5 dB/MHz for the lowest and 89.7 dB/MHz for the highest NEAP estimate, a difference of 3.8 dB/MHz. Again, when BMI was held constant, the difference in BUA between the minimum and maximum intakes of NEAP estimate was 10.6%. Absolute BUA values were 102.04 dB/MHz for the lowest and 92.9 dB/MHz for the highest NEAP estimate, a difference of 9.14 dB/MHz.

Correlations between MNA and BUA

Although MNA was excluded from the stepwise regression analysis, a higher MNA score was associated with higher BUA ($r = 0.149$; $P < 0.05$).

Quartile analysis between MNA and BUA. BUA increased significantly between quartile 1 (Q1) and Q4 for MNA (Q1 = 23.5, Q2 = 26.5, Q3 = 28, Q4 = 30). The difference among the mean scores of BUA of the 4 groups was significant according to 1-way ANOVA ($P = 0.004$) with post hoc test (Tukey test), as well as the F test for linearity ($P = 0.015$). Comparison of the means of BUA by quartiles of MNA with post hoc test (Tukey test) differed between Q1 and Q2 ($P = 0.004$) and trends between Q1 and Q3 ($P = 0.074$) and Q1 and Q4 ($P = 0.076$).

Discussion

This study suggests that lower estimates of NEAP are significantly associated with greater bone ultrasound measures, an effect that is independent of confounding factors such as BMI, age, and osteoporosis treatment. Our findings also show that higher calcium and potassium intakes are associated with higher bone ultrasound measures, which are similar to previous studies and consistent with previous human and animal studies, which showed the positive effect of dietary interventions designed to alkalinize the blood and urine pH on bone turnover (19,20). However, we are cautious with the interpretation of our findings given the small size effect and the fact they were found in a subgroup of the studied population.

Traditionally, the NEAP estimate was based on the dietary protein:potassium ratio in normal diets (33). This method has limitations when estimating the acid:base ratio of whole diets, because it does not take into account other nutrients and the absorption rate of those included in the formula. Remer and Manz (27,34) developed a formula for calculating the acid or alkali load of each food item or of a diet, the PRAL. It can be accurately calculated when the nutrient data for protein, phosphorus, chlorine, potassium, magnesium, calcium, and sodium is known and hence we used the PRAL estimates in our study. We did not relate the calculations of Remer's formula to body surface area. In accordance with the recent Consensus Acid-Base Conference article, we have used the generalized terminology for NEAP estimates (29). Protein contributes positively to BMD (35); however, in excess, it also has an acidic effect on bone, which is thought to be undesirable and depends

TABLE 2 Dietary intakes and estimates of NEAP in elderly Swiss women[1]

Daily intake[2]	All subjects	Subgroup with fracture history	Subgroup with no fracture history	RDA[3]
n	401	256	145	
Energy intake, *kJ*	6462 (2222–13103)	6579 (2222–13103)	6248 (628–2698)	7115–8370
Protein, *g*	65.2 (21–134.3) (0.96g/kg)	66.2 (21–134.3) (1g/kg)	63.5 (31.9–125.1)	1g/kg
Sodium,[4] *mg*	1502 (436–3382)	1520 (436–3382)	1470.6 (545–3127.6)	4000
Calcium, *mg*	983.1 (147–2480)	1001.5 (147–2480)	950.7 (277–2306)	1200
Potassium, *mg*	2761 (820–6307.7)	2798 (820–6307.7)	2697 (1332–5763.9)	3000
Magnesium, *mg*	287.7 (84.1–627.1)	293.3 (84.1–627.1)	277 (126.6–618.2)	360
Phosphorus, *mg*	1163.7 (314.3–2570)	1189.1 (314.3–2570)	1119 (528–2537)	800
NEAP, *mEq*	−3.22 (−42.4–29.15)	−2.96 (−42.4–29.15)	−3.7 (−30.1–19.6)	—

[1] Values are means (range). Subgroups did not differ.
[2] Data were obtained with the FFQ.
[3] Reference (30).
[4] Sodium added to food has not been taken into account.

TABLE 3 Characteristics of the 256 women with fractures stratified by tertiles of NEAP[1]

	NEAP		
	T1	T2	T3
n	86	78	92
Age, *y*	80.06 ± 3.23	80.97 ± 2.7	80.9 ± 0.3
BMI, *kg/m²*	25.1 ± 0.5	24.4 ± 0.5	24.2 ± 0.5
NEAP, *mEq/d*	−15.35 ± 6.72	−2.59 ± 0.31	8.3 ± 0.7**
Protein, *g/d*	61.5 ± 19.6	64.7 ± 2.18	71.9 ± 2.2*
Calcium, *mg/d*	1051.9 ± 437.1	1028.6 ± 44.7	931.4 ± 37.9
Potassium, *mg/d*	3153.4 ± 971.6	2715.4 ± 88.8	2535.1 ± 85.9**
Magnesium, *mg/d*	306.4 ± 90.5	292.1 ± 10.9	282.2 ± 10.4
BUA, *dB/MHz*	98.8 ± 9.5	95.6 ± 1.1	95.9 ± 0.8*
MNA, *score*	26.6 ± 0.2	26.4 ± 0.3	26.4 ± 0.3

[1] Values are means ± SD. *Different from T1, $P < 0.05$; **$P < 0.01$.

on the amino acid composition (36). It is the metabolism of the sulfur amino acids methionine and cysteine that generates an acid load, resulting in a reduction in blood and urinary pH (5,37).

Cross-sectional results of a population-based study showed that lower estimates of NEAP were correlated with greater spine and hip BMD and greater forearm bone mass (measured by axial dual energy X-ray absorptiometry) (20). However, bone ultrasound also predicts fracture risk (SEMOF) and is easier and cheaper for large cohort studies (38). For this reason, we chose QUS for our study. Parameters assessed by QUS Achilles (Lunar), which uses water as a coupling agent, include BUA, SOS, and the combined SI.

The 2.9-dB/MHz difference in BUA between NEAP T1 and T3 represents ~30% of 1 SD (−1 SD doubles the fracture risk) and is clinically relevant, because it is higher than the short-term reproducibility, which is 2.2 dB/MHz (21). It is clinically meaningful, because BUA has been shown to be predictive of fracture and to be the preferential QUS parameter when assessing nutritional status (39). There is no difference in fracture prediction compared with SOS or SI, which justifies their exclusion from our data (40).

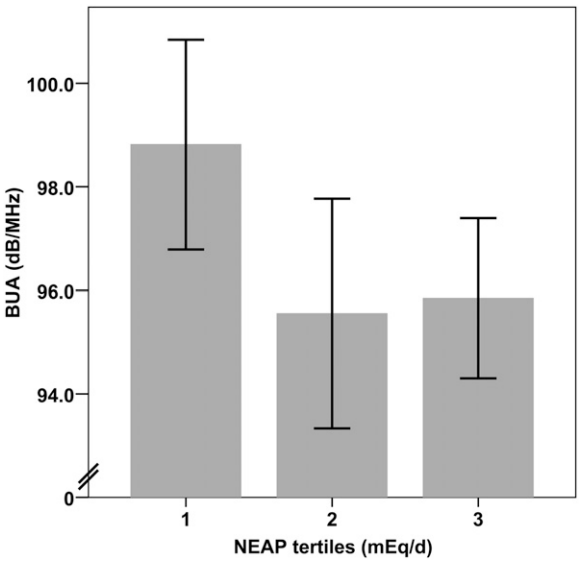

FIGURE 1 BUA in the 256 women with fractures stratified by tertiles of NEAP. Values are means ± SD, $n = 86$, 78, and 92 for T1, T2, and T3, respectively. For each tertile of NEAP, the mean NEAP values were −15.4, −2.6, and 8.3 mEq, respectively. The mean scores of BUA differed for the 3 groups, using 1-way ANOVA ($P = 0.03$) with post hoc test (Tukey test), as well as for the F test for linearity ($P = 0.03$). Comparison of the means of BUA by tertiles of NEAP by post hoc test (Tukey test) showed trends (T1–T2, $P = 0.052$; T1–T3, $P = 0.070$).

The large EPIC-Norfolk cross-sectional study investigated the relation between PRAL and calcaneal BUA in a younger population (mean age 62.9 y). It found ~2% difference in BUA between the highest and lowest quintiles of PRAL, close to the 2.9% we found. The study also concluded that PRAL was inversely associated with bone ultrasound measures in women (19). However, no relation was observed in men. The Framingham Heart study cohort showed that greater intakes of potassium, magnesium, fruit, and vegetables were associated with higher BMD in men (41). Our study adds to the present knowledge by examining a much older group, which in terms of osteoporosis risk is a very pertinent population to study. The risk of chronic low-grade metabolic acidosis worsens with age due to a decline in kidney function. This could be a confounding risk factor, but the study design did not include the assessment of glomerular filtration rate and there was no large age difference in the studied group (± 3 y) (5).

Although nutrition plays an important role in the maintenance of bone health, regardless of fracture status, no association was found in nonfractured women. This lack of association is intriguing. Possible reasons may be a greater susceptibility of fractured women to the detrimental effect of dietary acidity. This has already been suspected in a previous study of 7788 elderly women; low nutritional intake was associated with higher fracture incidence in the women with a high inactivity score and high fracture incidence (42). The effect of the association between NEAP and BUA was relatively small compared with the effect of age and BMI. However, nutritional acid load is an additional risk factor that might be relevant in patients with an already high fracture risk.

The MNA also appears to be a useful tool for the evaluation of osteoporotic patients. It assesses the subject's nutritional status and is positively correlated to BUA. In this study, BUA results were significantly lower when the MNA score was below 24 (risk of malnutrition). A trend for a correlation between the MNA and BUA was shown in a previous study (43). Another study showed that 50% of elderly free-living women who displayed an MNA score <27 had a tripled risk of having osteoporosis (44).

Our study was limited by the cross-sectional study design. Therefore, we state associations and not causal relations, which do not allow us to draw strong conclusions about the influence of nutrition on bone health. Several of the NEAP nutrients have additional effects apart from the acid-base balance on bone health and hence may confound the observed effect sizes. For example, potassium, which not only influence the acid-base balance but also has an effect on the processes that maintain calcium homeostasis, such as urinary calcium excretion, and acts as a surrogate measure of bicarbonate (45).

The subgroup analysis of patients with and without fracture history was not an a priori hypothesis but a finding of our explorations and this is a limitation. Although our FFQ was validated, errors are associated with FFQ, such as measurement errors and subjects' motivation and memory (46). However, our subjects were probably in better health than the general population, because they were able to travel alone to the hospital and were particularly motivated by their health status (47).

For future studies, a FFQ that evaluates sodium and chlorine added to food would be of interest, because they both have a substantial effect on bone health. It was also not possible to

measure NEAP estimates from 24-h urine collections, which would have been an additional parameter.

In conclusion, the findings of this study suggest that lower estimates of NEAP (i.e. more alkaline diets) are significantly associated with higher indices of BUA measured by bone ultrasound in the very elderly population (80.6 y) in a subgroup of fractured women. The interpretation of our findings must be cautious considering a small size effect and the subgroup analysis. These findings were independent of important confounding factors such as BMI and age. These data suggest that measures of NEAP may be an additional risk factor, particularly relevant in frail patients with a history of fracture and for this reason a high fracture risk.

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