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ORIGINAL CONTRIBUTION

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The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study

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Summary *Background* There continues to be considerable debate about the role of acid vs. basic components of the diet on the long-term status of bone mineral density.

Aim In a set of two analyses, we examined the effect of components in the diet thought to have basic effects (magnesium, potassium, fruit, vegetables) and acid effects (protein) on bone mineral density in an elderly cohort.

Methods Bone mineral density of participants in the Framingham Osteoporosis Study was measured at three hip sites and one forearm site at two points in time, four years apart. At the time of baseline measurement, participants ranged in age from 69–97 years. Dietary intake was assessed at baseline by food frequency questionnaire.

Results As hypothesized, magnesium, potassium, fruit and vegetable intakes were significantly associated with bone mineral density at baseline and among men, with lower bone loss over four years. In contrast to the hypothesis, higher rather than lower protein intakes were associated with lower bone loss.

Conclusion Together these results support the role of base forming foods and nutrients in bone maintenance. The role of protein appears to be complex and is probably dependent on the presence of other nutrients available in a mixed diet. A balanced diet with ample fruit and vegetables and adequate protein appears to be important to bone mineral density.

Key words Bone – Acid-base – Elderly – Minerals – Protein

Introduction

The theory that an acidic environment leads to progressive bone loss has long been proposed, and has been supported by numerous short-term human studies. Diets high in acid forming components, including several amino acids in protein foods, phosphorus and chlorine; and low in base forming components, including fruits and vegetables, potassium, calcium, magnesium, and vitamin C, are hypothesized to lead to lower bone mineral density (BMD) and higher fracture risk. Since this type of diet is common in modern societies, it is of great importance to understand whether and to what extent this theory translates to actual risk in free-living populations.

Nutritional factors are of particular importance because they are modifiable. Based largely on experimental studies, there is general agreement that calcium and vitamin D are important nutrients to bone health, and supplements containing calcium and vitamin D are widely prescribed to prevent osteoporosis and hip fracture [1–3]. The recent large increase in recommended calcium intake (from 800 mg recommended dietary allowance (RDA) to 1,200 mg defined as adequate intake (AI) for adults aged 51 years and older, for example) is

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primarily designed to protect bone status, based on studies of maximal calcium retention [4].

There is much less known about the effect of other nutrients on bone, although effects have been hypothesized for protein, phosphorus, magnesium, vitamin C, and vitamin K [5]. In 1968, Wachman and Bernstein [6] suggested that bone mineral functions as a buffer base, and that lifetime buffering of the acid load from the ingestion of mixed diets leads to gradual and accumulated bone loss. Based on this idea, they suggested that: "The therapy of osteoporosis may lie in its prevention… it might be worthwhile to consider decreasing the rate of bone attrition by the use of a diet favoring 'alkaline ash'. This type of diet would emphasize the ingestion of fruits, vegetables, vegetable protein, and moderate amounts of milk." Diets high in fruits and vegetables produce a more alkaline urine by contributing a variety of compounds which, during their metabolism, accept hydrogen ions [6, 7].

Over the past several years, we have been examining the association between dietary intake components and patterns in relation to bone mineral density and fracture risk in the Framingham Osteoporosis Study, including the effect of dietary patterns with high intakes of fruit and vegetables, potassium and magnesium, and of protein. In this paper, we will summarize our results from those investigations and discuss them in relation to the acid-base hypothesis.

Methods

The Framingham Heart Study is a longitudinal cohort study, initiated in 1948 to examine risk factors for heart disease. The original subjects were selected as a random sample of households in Framingham, MA and included 5,209 men and women, aged 28–62 [8]. Subjects are seen biennially for a physical examination and a series of questionnaires and tests. Since the inception of the cohort more than 50 years ago, nearly two-thirds of the original members have died. At biennial examination 20 (1988–89), 855 cohort members participated in the Framingham Osteoporosis Study and also completed dietary questionnaires. The study was approved by the Boston University Institutional Review Board, and written informed consent was obtained for all study subjects.

Bone mineral density

BMD was measured in the original cohort in 1988–89 and 1992–93, at the femur, spine and radius. Results from the baseline Framingham Osteoporosis Study have been previously reported [9]. Four years later (1992–1993), 615 subjects (72%) who had completed baseline BMD and Food Frequency Questionnaire assessments had repeat BMD measurements. Details on the longitudinal follow-up osteoporosis examination have also been reported [10]. BMD of the proximal right femur (femoral neck, greater trochanter and Ward's area), and lumbar spine (average L2 to L4) were measured in g/cm^2, with a Lunar dual photon absorptiometer (DP3) at baseline, and a dual x-ray absorptiometry (DPX-L) densitometer (Lunar Radiation Corporation, Madison, WI) at the 4-year follow-up exam. There were strong correlations between measures taken with dual photon and dual x-ray absorptiometry, but due to a small but consistent shift in BMD values between the two methods, femoral BMDs were adjusted for the change from DP3 to DPX-L technology, using published corrections [11]. Bone density at the proximal radial shaft was measured in g/cm^2 using a Lunar SP2 single photon absorptiometer (Lunar Radiation Corporation, Madison, WI) at both examinations.

Dietary intake

Usual dietary intake was assessed at the twentieth examination using a semi-quantitative 126 item food frequency questionnaire [12, 13]. Questionnaires were mailed to the subjects prior to the examination and they were asked to complete them, and to bring them to the exam where they were checked for completeness. This food frequency questionnaire has been validated for several nutrients against multiple diet records and blood measurements [12–15]. Dietary questionnaires resulting in energy intakes below 600 and above 4000 kilocalories (2.51–16.74 MJ) per day, or with more than 12 food items left blank were excluded from further analysis.

Measurement of confounders

Factors reported to affect BMD include body weight or body mass index (BMI), physical activity [16], alcohol use [17], smoking [18], estrogen use by women [19], dietary intake of calcium, vitamin D, and use of calcium and/or vitamin D supplements [1, 2]. In most of the analyses discussed here, we controlled for the influence of the following factors at baseline: total energy intake, age, sex, weight or BMI, smoking, caffeine, alcohol use, physical activity, calcium intake, use of calcium and/or vitamin D supplements, and for women, current estrogen use.

Physical activity was measured with the Framingham physical activity index, which asks about number of hours spent in heavy, moderate, light, or sedentary activity and number of hours spent sleeping during a typical day. Each component is then multiplied by an ap-

propriate weighting factor – based on estimated level of associated energy expenditure – and summed to arrive at a physical activity score [20].

Participants were also asked to quantify their weekly intake of liquor, wine and beer. Based on an assumed 13.2 grams per drink, a variable was created where subjects were then classified as non-drinkers, moderate drinkers (up to one drink per day for women and two drinks per day for men), or heavy drinkers (greater than these cutoffs). Smoking was defined as current smoker, former smoker or non-smoker. For women, estrogen use was defined as those currently using, with continuous use for at least two years, versus never or past users, based on evidence that past use does not sustain bone benefits [21]. Dietary calcium and vitamin D and caffeine intakes were assessed from the food frequency questionnaire. Use of calcium or vitamin D supplements were coded as yes/no variables.

We also created a categorical variable for time of BMD measurement, based on evidence that BMD is affected by seasonal variation in sunlight exposure [2, 22]. July, August and September were coded as summer; October, November and December as fall; January, February and March as winter; and April, May and June as spring.

Statistical analyses

In our first set of analyses, we examined the association between intake of magnesium, potassium, and fruit and vegetables with bone mineral density [23] both cross-sectionally and for longitudinal change over four-years of follow-up. Because potassium and magnesium intakes were highly correlated, it was not possible to assess the independent effects of potassium and magnesium on BMD in the same model. We therefore created a score by summing the standardized z-scores of these two variables and re-standardizing the score. We then examined the relationship between protein intake and change in BMD [24].

For each of these analyses we evaluated each BMD site separately, using linear regression to examine the relation of BMD with each intake measure, adjusting for potential confounding variables. Because most nutrients correlate with energy intake, we adjusted for this variable to account for differences in intake that may be due to body size or activity levels or measurement error inherent in the food frequency questionnaire [13]. Models also included age, weight or BMI, height, physical activity score, smoking status, alcohol use, calcium supplement use, vitamin D supplement use, dietary calcium intake, vitamin D intake, season of bone measurement and for women, current estrogen use.

Change in BMD was defined as BMD at examination 22 minus BMD at examination 20. These change measures were regressed on intake measures with all the potential confounders used in the cross-sectional analyses described above, plus the corresponding baseline measure of BMD at exam 20. This baseline BMD was included in these models because of the likelihood that change in BMD may be related to the initial BMD.

Men and women had similar distributions of overall protein intake and animal protein intake, as well as similar relations between protein intake and BMD change, and therefore, analyses for men and women were combined. Dietary protein intake was expressed as percent of energy from protein. Furthermore, components of protein were divided and expressed as percent of energy from animal protein and percent from non-animal protein. We evaluated percent protein as a continuous variable and as quartiles of intake, to evaluate the possibility of a non-linear relation.

Results

Cross-sectional associations between magnesium and potassium intake and bone measures

Average BMDs ranged from 0.69 g/cm^2 for Ward's area to 0.88 g/cm^2 for the femoral neck among men; and from 0.51 g/cm^2 for the radius to 0.72 g/cm^2 for the femoral neck among women. At 300±110 and 288±106 mg/day, mean magnesium intakes for men and women, respectively, fell below the recently released RDA of 420 and 320 mg/day for men and women in this age group [4]. Potassium intakes averaged 2988±1011 mg for men and 2930±995 mg for women. Average reported fruit and vegetable intakes were 4.7 servings of fruit or vegetables/day for men and 5.3/day for women. Simple correlations between potassium and magnesium were 0.85 and 0.88 for men and women, respectively, suggesting high collinearity. Because of this, models containing both potassium and magnesium tended not to show independent effects of either after control for the other, although they were each significant on their own.

Table 1 presents the results of the regression of BMD measures on 1) potassium, 2) magnesium, 3) the potassium+magnesium z-score variable and 4) fruit and vegetable intake, for men and women, respectively. As hypothesized, fruit, vegetable, magnesium and potassium intakes were significantly associated with greater BMD in both men and women at the first measurement [23].

For men, the associations between potassium and BMD were significant at all four bone sites, with slopes ranging from 0.022 to 0.04 g/cm^2, or up to 5.8 % of average BMD for every 1000 mg of potassium intake. For magnesium intake, results were significant at the radius ($p < 0.01$), and the trochanter ($p < 0.05$) and approached significance in the remaining two hip sites ($p < 0.1$). Differences in BMD associated with each 100 mg difference

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Table 1 Difference in bone mineral density (BMD) per unit difference in baseline magnesium, potassium or fruit and vegetable intake*

Dietary Variable	BMD (g/cm^2)			
	Femoral Neck	Trochanter	Ward's Area	Radius
Women, baseline difference				
Potassium (/1000 mg)	0.012	0.034[3)]	0.019[2)]	0.016[2)]
Magnesium (/100 mg)	0.012	0.020[2)]	0.016[1)]	0.006
Potassium + magnesium Z-score (/SD)	0.014[1)]	0.032[3)]	0.021[2)]	0.013[1)]
Fruits and vegetables (#/day)	0.0024	0.0056[2)]	0.0038[1)]	0.0049[3)]
Men, baseline difference				
Potassium (/1000 mg)	0.032[2)]	0.030[2)]	0.040[2)]	0.022[3)]
Magnesium (/100 mg)	0.023[1)]	0.027[2)]	0.026[1)]	0.023[3)]
Potassium + magnesium Z-score (/SD)	0.034[2)]	0.035[2)]	0.040[2)]	0.028[3)]
Fruits and vegetables (#/day)	0.0086[2)]	0.0068[1)]	0.011[2)]	0.0043[2)]
Men, relative 4 yr change[4)]				
Potassium (/1000 mg)	0.017[2)]	0.025[3)]	0.014[1)]	0.004
Magnesium (/100 mg)	0.017[3)]	0.020[3)]	0.013[1)]	0.004
Potassium + magnesium Z-score (/SD)	0.023[3)]	0.028[3)]	0.017[2)]	0.005
Fruits and vegetables (#/day)	0.0014	0.0047[1)]	0.0042[1)]	0.0011

* Adapted from Tucker et al. [23]. Adjusted for age, body mass index (BMI=weight in kg/height in m^2), energy intake, dietary calcium intake, dietary vitamin D intake, Ca supplement use, vitamin D supplement use, smoking status, alcohol use, season of measurement, physical activity scores, and estrogen use.
[1)] $p < 0.1$
[2)] $p < 0.05$
[3)] $p < 0.01$
[4)] None of the dietary variables significantly predicted change in BMD for women.

in magnesium intake ranged from 0.023–0.027 g/cm^2, or up to 3.8 % of average BMD. The combined z-score was significant at all four bone sites. Fruit and vegetable intake was significant at $p < 0.05$ for all sites except the trochanter, where it approached significance ($p < 0.1$). For the femoral neck, the slope of 0.0086 represents a 1 % greater BMD for every fruit or vegetable consumed per day.

For women, potassium was significantly associated with BMD at three sites, with a difference in bone per 1000 mg intake of 0.034 (5.4 % of average BMD) for the trochanter, 0.019 (3.4 %) for Ward's area and 0.16 (3.1 %) for the radius ($p < 0.05$). Magnesium intake was significantly associated with BMD at the trochanter, and approached significance at Ward's area. For each 100 mg difference in magnesium intake, there were 0.020 g/cm^2 (3.2 %) and 0.016 g/cm^2 (2.9 %) differences in average BMD for the trochanter and Ward's area, respectively. The combined z-score was significantly associated with the trochanter and Ward's area and approached significance for the other two sites ($P < 0.1$). Finally, fruit and vegetable intake was associated with BMD at the radius ($p < 0.01$), the trochanter ($p < 0.05$), and Ward's area ($p < 0.1$).

Effect of baseline magnesium, potassium and fruit and vegetable intake on subsequent four-year change in BMD

Mean 4-year BMD losses have been reported [10], and for women, ranged from –4.84 % (radial shaft) to –3.42 % (trochanter), while losses for men ranged from –3.59 % (radial shaft) to –0.17 % (trochanter). Results for the relationship between baseline dietary potassium, magnesium and fruit and vegetable intakes and subsequent four-year change in BMD are presented in Table 1 for men only, as none of the longitudinal results for women were significant.

Among men, greater baseline potassium intake was significantly associated with lower subsequent four-year loss in BMD at the femoral neck ($p < 0.05$) and trochanter ($p < 0.01$). Magnesium intake was significantly associated with subsequent change in BMD at the femoral neck and trochanter ($p < 0.01$), and approached significance at Ward's area ($p < 0.1$). The combined potassium+magnesium z-score was significant for the femoral neck and trochanter at $p < 0.01$, and Ward's area at $p < 0.05$. Fruit and vegetable intake approached significance at the trochanter and was significant at Ward's area.

Effect of baseline protein intake on subsequent four-year change in BMD

Mean protein intake for the participants was 68±23.6 g/day, ranging from 17 to 152 g/day. Protein comprised 16 % (range: 7–27 %) of total energy intake and the average percent of energy from animal protein was 10 %. Baseline BMD values at the femoral neck, trochanter, Ward's area, radial shaft and lumbar spine were not significantly associated with protein intake. Lower percent protein intake was significantly related to greater BMD loss over the 4 years of follow-up at the femoral neck, Wards area, and spine ($p < 0.05$).

When categories of percent protein intake were evaluated, the lowest quartile of intake showed the greatest bone loss (Fig. 1). Similar results were seen at the other femur sites and the lumbar spine, with a similar trend for the radial shaft. After adjusting for weight, weight change, height, age, sex, smoking and alcohol use, the lowest quartile of protein intake continued to have the greatest BMD loss. The highest quartile of protein intake (1.2–2.8 g/kg per day), showed the least BMD loss over four years.

Similar to the overall protein effect, lower percent of energy from animal protein was significantly related to bone loss at the femoral neck and lumbar spine ($p < 0.01$) but not the radial shaft. Percent of energy from non-animal protein did not contribute to these BMD models. Again, the lowest quartile of animal protein in-

take showed the greatest bone loss (Fig. 2) at all sites except the radial shaft.

Discussion

Taken together, our results appear to be internally contradictory with respect to the acid-base hypothesis. Fruit and vegetables, magnesium and potassium seem to protect bone, as hypothesized. In contrast to the hypothesis, we did not find that higher protein intakes lead to greater bone loss. Rather, we found that those with the greatest protein intakes in this study had the highest BMD.

When evaluating the protein results, it is important to note that these subjects were elderly and had, on average, relatively low protein intakes. The current RDA for protein is 0.8 mg/kg, and more than 30 % of the Framingham Cohort had protein intakes below this. The finding that higher protein intakes were associated with BMD in this population, therefore, does not suggest that much higher protein intakes than those seen here would not have negative effects.

Most studies that have examined the associations of magnesium and/or potassium with bone have seen protective effects [25–29]. Calcium balance studies have shown that potassium promotes renal calcium retention [30]. A study of 18 postmenopausal women showed improved calcium balance, increased serum osteocalcin concentrations and decreased urinary hydroxyproline excretion with the administration of potassium bicarbonate in sufficient quantity to neutralize endogenous acid loads from normal diets, and these authors concluded that this buffering protects the skeleton [31].

Adequate magnesium is also essential for appropriate calcium metabolism, with similar effects on calcium balance [32, 33]. Cancellous bone in osteoporotic women has been shown to have low magnesium content [34].

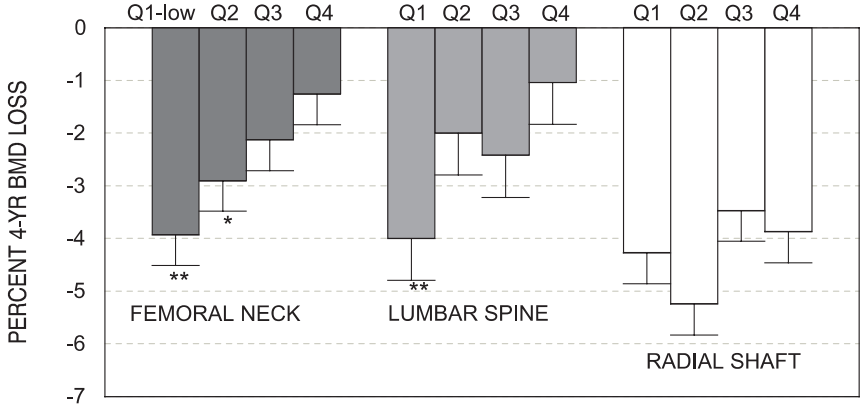

Fig. 1 Mean percent bone loss over 4 years (±SE) at hip, spine and radius by quartiles of protein intake, Framingham Osteoporosis Study. From Hannan et al. [24].

Least squares means adjusted for sex and total caloric intake
* 0.05 < P < 0.01, ** 0.01 < P < 0.001; All comparisons to highest quartile 4

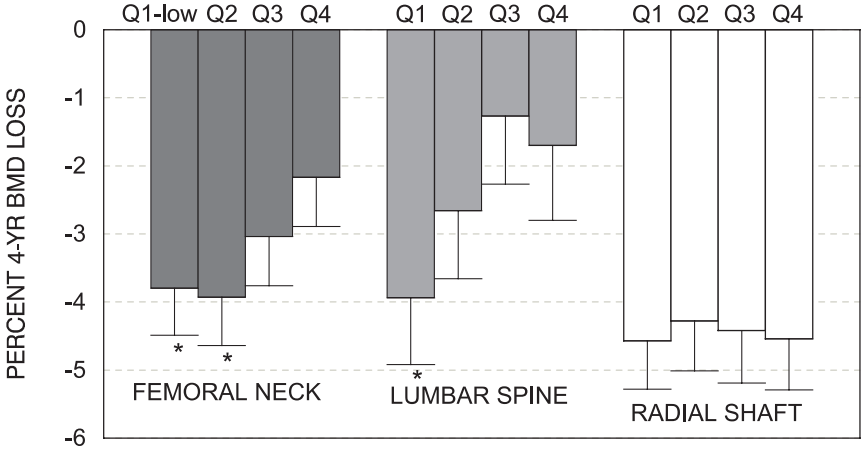

Fig. 2 Mean percent bone loss over 4 years (±SE) at hip, spine and radius by quartiles of animal protein intake, Framingham Osteoporosis Study. From Hannan et al. [24].

Least squares means adjusted for sex, age, weight, weight change, height, alcohol, smoking, non-animal protein and total caloric intake
* 0.05 < P < 0.01; All comparisons to highest quartile 4

When patients were given oral magnesium in one study, trabecular but not cortical bone improved [35]. The finding that fruit and vegetable intake is associated with BMD is also supported by New et al. [25], who found significant associations between past reported fruit intake and BMD among pre-menopausal women.

Together these findings provide a strong argument for the buffering effects of these base producing foods and nutrients. However, contrary to expectations, we found that elders with the highest intake of total protein and of animal protein had the least bone loss after controlling for known confounders. Rather than causing bone loss, as was hypothesized, animal protein intake appeared to be important in maintaining bone or minimizing bone loss in elderly persons. Consistent with these results, other studies have found that low protein intake was associated with low BMD in older women [29], in geriatric patients [36], and with hip fracture in elderly women [37]. Studies of protein supplementation in elderly women and others after hip fracture have been shown to have beneficial effects on bone mineral density and muscle strength [38, 39], implying that protein insufficiency, particularly in the oldest old, contributes to osteoporosis. On the other hand, a recent study reported greater bone loss and more hip fracture with higher animal/vegetable protein ratios [40].

Several short-term studies [41–43] have reported that a doubling of protein intake increases urinary calcium loss by 50% and that the acid load from dietary protein is partially buffered by skeletal bone loss, accounting for a portion of age-related bone loss [44]. Allen reported that urinary calcium loss correlated with protein intake, and suggested that high calcium diets may not prevent the negative calcium balance and bone loss induced by protein [45]. However, Hegsted reported that the negative effect of protein on calciuria was largely reversed with the addition of phosphorus to the diet [46].

Among elderly persons, the influence of dietary protein may differ metabolically from that in younger adults, since additional age-related changes in renal function and intestinal absorption may influence calcium balance [47]. The actual effect of protein intake on bone is complicated and is likely to be dependent on other components in the diet. Heaney [5] suggests, for example, that the calciuric effect of protein may be offset over time by increased intestinal calcium absorption. Low protein intake has also been shown to induce secondary hyperparathyroidism, which may lead to bone loss [48, 49]. Orwoll et al. [50] noted that although excess dietary protein has been shown to cause negative calcium balance, this occurs primarily with high protein intakes, not often seen in the elderly who are at the highest risk for osteoporosis. Chu et al. [51] doubled protein intake in elders and found that, rather than causing negative calcium balance, the increased protein improved the calcium balance in the majority of their subjects.

It seems clear that the relationship between protein intake and calcium balance is complex. It appears likely that the effect of protein in the diet is modified by other components in the protein foods themselves or in the mixed diet. This therefore does not argue against the acid-base hypothesis, but rather clarifies that it is not necessary, nor in fact, desirable, to avoid protein foods for the purpose of improving bone status. Rather, many older persons may not get enough protein in their diets. Campbell et al. [52] argue that the protein RDA for older persons in the United States, established from extrapolations from healthy young men, is too low. Based on several protein requirement studies of elderly subjects, they recommend a safe protein intake to range from 1.0–1.25 g/kg per day of protein. These values would correspond roughly to the third quartile in our analyses.

Together, these results suggest that a good quality diet with high intake of magnesium, potassium, fruit, and vegetables, with adequate protein, and limited in less nutrient dense foods may contribute to better accumulated and maintained BMD in older age. The associations between intake of magnesium, potassium, fruit and vegetables with BMD among older adults support the acid-base hypothesis. The effects of proteins appear to be more complex, with beneficial effects, perhaps, exceeding negative effects of the acid-forming amino acids, within normal intake ranges. Further studies on the subtleties of nutrient-nutrient interactions and on the interactions of other metabolic responses to dietary composition with acid-base maintenance are needed in order to fully understand their cumulative effects.

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