A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women[1-3]

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ABSTRACT

Background: Different sources of dietary protein may have different effects on bone metabolism. Animal foods provide predominantly acid precursors, whereas protein in vegetable foods is accompanied by base precursors not found in animal foods. Imbalance between dietary acid and base precursors leads to a chronic net dietary acid load that may have adverse consequences on bone.

Objective: We wanted to test the hypothesis that a high dietary ratio of animal to vegetable foods, quantified by protein content, increases bone loss and the risk of fracture.

Design: This was a prospective cohort study with a mean (±SD) of 7.0 ± 1.5 y of follow-up of 1035 community-dwelling white women aged >65 y. Protein intake was measured by using a food-frequency questionnaire and bone mineral density was measured by dual-energy X-ray absorptiometry.

Results: Bone mineral density was not significantly associated with the ratio of animal to vegetable protein intake. Women with a high ratio had a higher rate of bone loss at the femoral neck than did those with a low ratio ($P = 0.02$) and a greater risk of hip fracture (relative risk = 3.7, $P = 0.04$). These associations were unaffected by adjustment for age, weight, estrogen use, tobacco use, exercise, total calcium intake, and total protein intake.

Conclusions: Elderly women with a high dietary ratio of animal to vegetable protein intake have more rapid femoral neck bone loss and a greater risk of hip fracture than do those with a low ratio. This suggests that an increase in vegetable protein intake and a decrease in animal protein intake may decrease bone loss and the risk of hip fracture. This possibility should be confirmed in other prospective studies and tested in a randomized trial. *Am J Clin Nutr* 2001;73:118–22.

KEY WORDS Diet, protein, bone mineral density, bone loss, fracture, osteoporosis, women, aging, acid-base balance

INTRODUCTION

Nutrition is an important component of bone health; the value of nutrients such as calcium is well documented (1). The value of other nutrients, such as protein, remains controversial. Inadequate protein intake can have adverse effects; however, abundant dietary protein may also be harmful in older persons (2–6). A high intake of dietary protein may adversely affect bone through effects on calcium excretion and acid-base metabolism (4, 7, 8).

Sulfur-containing amino acids in protein-containing foods are metabolized to sulfuric acid. Animal foods provide predominantly acid precursors; dietary animal protein intake is highly correlated with renal net acid excretion ($r = 0.84$, $P < 0.0005$) (9). In contrast, vegetables and fruit contain not only amino acids but also substantial amounts of base precursors; the metabolism of organic potassium salts (citrate, malate, and gluconate) in fruit and vegetables yields potassium bicarbonate (10).

Diets that are rich in animal foods and low in vegetable foods, typical of industrialized countries, lead to a dietary net acid load that has a negative effect on calcium balance (11, 12). The magnitude of this detrimental effect increases with age. With aging, the glomerular filtration rate falls and the kidney's ability to excrete this dietary acid load is impaired (13–16). Thus, otherwise healthy individuals develop progressively increasing blood acidity and decreasing plasma bicarbonate as they age (13, 17).

Because urinary excretion of acid is insufficient, other homeostatic systems, such as bone, buffer the excess dietary acid load (2, 18–21). Experimentally induced chronic metabolic acidosis leads to base being liberated from bone to restore acid-base balance, but accompanying minerals, including calcium, are wasted in the urine. This calcium wasting generates a progressive decline in bone mineral content and bone mass (2, 18, 22, 23). In addition, acidosis directly stimulates osteoclastic activity and inhibits osteoblastic activity (24). Even mild acidosis can have profound effects: if bone is mobilized to buffer only 1 mEq of acid each day, 15% of the total body calcium in an average person is lost in a decade (25).

To test the hypothesis that a diet with a high ratio of animal to vegetable foods increases the rate of bone loss and the risk of fracture, we analyzed data on dietary intake, bone mineral density (BMD), bone loss, and hip fracture from a prospective study of 1035 white women aged >65 y by using the protein content of ingested food to quantify the ratio of animal to vegetable foods.

SUBJECTS AND METHODS

Subjects

White women aged >65 y (n = 9704) were recruited between September 1986 and October 1987 from population-based listings into the Study of Osteoporotic Fractures at 4 clinical centers: the Kaiser-Permanente Center for Health Research, Portland, OR; the University of Minnesota, Minneapolis; the University of Maryland, Baltimore; and the University of Pittsburgh. The study protocol was approved by the appropriate institutional review boards and informed consent was obtained from all participants. The University of California, San Francisco, served as a data and administrative coordinating center.

Dietary data

Recent dietary history (for the preceding 12 mo) was assessed in a randomly selected subset of the cohort (n = 1061) at the year 2 visit (1989–1990) by using a 63-item food-frequency questionnaire derived from the second National Health and Nutrition Examination Survey (26). Food models were used to estimate portion sizes. Twenty-six food-frequency questionnaires contained almost no data; analyses were performed for the remaining 1035 women. Daily intakes of 31 nutrients were computed with use of DIETSYS software (Block Dietary, Berkeley, CA).

Bone data

BMD (in g/cm^2) of the total hip and subregions was measured by dual-energy X-ray absorptiometry (Hologic QDR-1000, version 6.10; Hologic, Inc, Waltham, MA) at the year 2 visit and at a follow-up visit an average of 3.6 y later by using quality-control methods described previously (27). The mean between-center CV for the femoral neck was 1.2% when performed in 2 research staff members who traveled to each site. The inter-scanner precision for an anthropomorphic femoral neck phantom showed a CV of 0.93%. The intrascanner CV for this phantom ranged from 0.62% to 1.86%.

The rate of bone loss was calculated as the percentage difference between 2 BMD measurements obtained in a subset of participants (n = 742) and annualized by time between measurements ($\bar{x} \pm$ SD: 3.6 ± 0.4 y).

Hip fractures were assessed prospectively for 7.0 ± 1.5 y with use of postcards every 4 mo, telephone calls to participants who did not return their postcards, and an annual questionnaire. Fracture follow-up data were available for all 1035 women for whom dietary data were collected. Fractures were confirmed with radiographs and review of radiologist reports.

Other measurements

Demographics and use of tobacco, alcohol, medications (eg, estrogen), calcium supplements, and multivitamins were assessed by questionnaire and interview at the clinical centers during the year 2 visit. A validated, modified Paffenbarger survey was used to assess physical activity, estimated as an average weekly energy

expenditure over the previous year (28). Weights of subjects without shoes were measured on a balance-beam scale; heights were measured with a wall-mounted Harpenden stadiometer (29).

Statistical analysis

Dietary intakes of animal, vegetable, and total protein were strongly correlated with energy intake, but the ratio of animal to vegetable protein intake did not correlate with total energy intake. Therefore, individual nutrients, but not the ratio, were energy-adjusted by using regression analysis. The energy-adjusted protein intake and the ratio of animal to vegetable protein were divided into 3 categories: low (lowest quintile), medium (middle 3 quintiles), and high (highest quintile). In all analyses, the low category was used as the reference group.

Linear regression was used to evaluate the relation between the dietary-protein variables (energy-adjusted animal, vegetable, and total protein intake and the ratio of animal to vegetable protein) and BMD with the stepwise addition of covariates significantly related to BMD in univariate models. All final multivariate models included age, energy intake (in kJ/d), total intake of calcium (dietary calcium plus supplements, in mg/d), energy-adjusted total protein intake, weight (in kg), current estrogen use (yes or no), physical activity (in kJ/wk), smoking status (yes or no), and alcohol intake (g/wk).

Results for all hip BMD regions (total hip, femoral neck, trochanter, and intertrochanter) were not significantly different; results for the femoral neck are reported. The relations between rate of bone loss and low, medium, and high ratios of animal to vegetable protein intake were examined by using linear regression, with annualized percentage change in femoral neck BMD as the outcome. The same covariates used in the BMD model were then added in a stepwise manner.

Proportional-hazards models were used to analyze the relation between hip fracture and animal and vegetable protein intake and the ratio of animal to vegetable protein. These models were analyzed with the energy-adjusted protein intakes alone and then after adjustment for the same potential confounders used in the BMD models. All analyses were performed with use of STATA software, version 5.0 (30).

RESULTS

Patient characteristics

Dietary data were collected for 1035 participants. The mean (±SD) length of follow-up was 7.0 ± 1.5 y. Descriptive data of the cohort are shown in **Table 1**. Most (72%) of the protein intake came from animal sources. Protein intake accounted for a median of 17% of daily energy intake; for 95% of the women, >12% of the daily energy intake came from protein. The mean intakes of animal and vegetable protein, as well as the ratios of animal to vegetable protein, for women with high, medium, and low ratios are shown in **Table 2**.

Bone mineral density

In models adjusted only for age, BMD tended to be positively related to a high ratio of animal to vegetable protein intake, although this relation was not significant ($P = 0.07$). The addition of energy intake, total calcium intake, current estrogen use, physical activity, smoking status, and alcohol intake did not change the relations between the ratio of animal to vegetable protein and BMD. However, women with high ratios of animal to vegetable

TABLE 1
Descriptive characteristics of the 1035 postmenopausal women, by ratio of animal to vegetable protein intake

Variable	Low ratio	Medium ratio	High ratio
Age (y)	74.3 ± 5.4[1]	73.2 ± 4.9	72.5 ± 4.5
Body mass index (kg/m²)	25.6 ± 4.6	26.5 ± 4.7	26.7 ± 4.9
Energy intake (kJ/d)	4858 ± 1754	4958 ± 1631	5012 ± 1732
Total protein intake (g)	42.0 ± 15.9	49.2 ± 16.9	58.3 ± 20.0
Total calcium intake (mg/d)	662 ± 356	826 ± 404	1124 ± 552
Ratio of animal to vegetable protein intake	0.46–1.58[2]	1.59–3.16	3.17–13.4

[1] $\bar{x}$ ± SD.
[2] Range.

protein were heavier and had higher intakes of total protein than did women with low ratios. When weight and total protein intake were included in the model, the ratio of animal to vegetable protein was not associated with BMD (**Figure 1**).

Bone loss

Repeat BMD measurements and complete data were obtained for 742 women. Women with a high ratio of animal to vegetable protein intake had a significantly higher rate of femoral neck bone loss than did women with a low ratio (0.78%/y and 0.21%/y, respectively) (**Figure 2**). Adjustment for age, energy intake, total intake of calcium, current estrogen use, physical activity, smoking status, weight, alcohol intake, and total protein intake did not change this relation.

Hip fracture

During the total 7291 person-years of follow-up, 48 hip fractures were validated. In age- and weight-adjusted analyses, the relative risk (RR) of hip fracture was significantly higher in women with a high intake of animal protein than in those with a low intake (RR = 2.7, P = 0.04). In contrast, women with a high intake of vegetable protein had an RR of hip fracture of 0.30 (P = 0.03).

In analyses adjusted for age and weight, a high ratio of animal to vegetable protein intake was associated with a substantially higher risk of hip fracture than was a low ratio (RR = 3.7, P = 0.04). The addition of energy intake, estrogen use, smoking status, physical activity, alcohol consumption, total calcium intake, and total protein intake did not appreciably change the relation. When the model was adjusted for BMD, the RR was slightly lower (RR = 3.3, P = 0.07). Fracture-free survival of women with low, medium, and high ratios of animal to vegetable protein intake is shown in **Figure 3**.

DISCUSSION

Previous studies showed an association between intake of animal protein and fracture risk. Worldwide, per capita consumption of animal protein is associated with a higher risk of hip

fracture in women aged >50 y (8) and consumption of vegetable foods is associated with a lower fracture risk (31). However, cross-cultural studies such as these are limited because many other factors differ between countries and could be responsible for the observed association. However, within-population studies also showed a high risk of fracture with high animal protein intake. For example, the Nurses Health Study found a 21% increase in forearm fracture over 12 y of follow-up in women aged 35–59 y in the highest quintile of both total and animal protein intake (32). Additionally, a prospective study in Norway showed that the risk of hip fracture in elderly men and women was nearly double in those in the highest quartile of dietary intake of nondairy animal protein in the presence of low (<623 mg/d) dietary calcium (7). Yet this area remains controversial. Recently, Munger et al (33) found an inverse relation between the risk of hip fracture and animal protein intake in women in Iowa. Although fracture results were mostly consistent, prior epidemiologic studies that examined the relation between dietary protein and BMD had mixed results (34–39).

Consistent with this previous work, the results of our study suggest a complex and important relation between the relative amounts of animal and vegetable foods consumed and bone health during aging. In the BMD analyses, there was no significant relation with the ratio of animal to vegetable protein, particularly after adjustment for body weight and total protein intake. This suggests that adequate nutrition as indicated by higher total protein intake and body weight may be important for achieving adequate bone density.

In this cohort of older women, the rate of bone loss was higher in women with high ratios of animal to vegetable protein intake. The detrimental effects on bone of an imbalance between dietary acid and base may become increasingly more important with age as renal function and the ability to excrete dietary acid loads decline. This may explain why women with higher ratios of animal to vegetable protein intake did not have significantly lower BMDs yet had higher rates of bone loss and hip fracture.

Women in the highest quintile of ratio of animal to vegetable protein intake (≥3.17) had nearly a 4-fold greater risk of hip

TABLE 2
Mean (±SD) ratios of animal to vegetable protein, animal protein, and vegetable protein intakes for the 1035 women with low (lowest quintile), medium (middle 3 quintiles), and high (highest quintile) ratios of animal to vegetable protein intake[1]

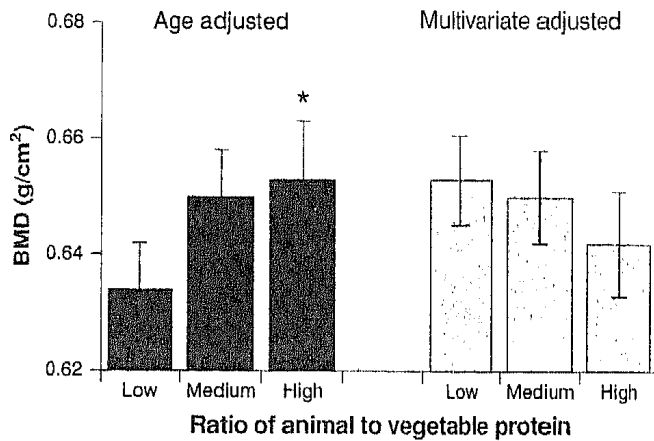|	Low ratio	Medium ratio	High ratio	P for trend
Ratio of animal to vegetable protein intake	1.2 ± 0.27	2.3 ± 0.44	4.2 ± 1.2	0.001
Animal protein intake (g)	23.6 ± 6.8	35.1 ± 6.5	48.2 ± 9.3	0.001
Vegetable protein intake (g)	19.6 ± 3.6	15.4 ± 2.7	11.6 ± 2.8	0.001

FIGURE 1. Mean (±SE) age and multivariate-adjusted bone mineral density (BMD) at the femoral neck in 1035 women with low, medium, and high ratios of animal to vegetable protein intake. The multivariate-adjusted model included age, energy intake, total calcium intake (dietary calcium plus supplements), total protein intake, weight, current estrogen use, physical activity, smoking status, and alcohol intake. *Nearly significantly different from low ratio, $P = 0.07$.

fracture compared with women with low ratios, independent of other potential risk factors, including age, calcium intake, weight, estrogen use, smoking status, alcohol use, and total protein intake (Figure 3). Addition of BMD to the model attenuated the relation. The relation between hip fracture and the ratio of animal to vegetable protein intake may be mediated in part through changes in BMD, given the increased rate of bone loss observed in women with a high ratio of animal to vegetable protein intake. However, other mechanisms besides effects on BMD may explain part of the relation between the ratio of dietary animal to vegetable protein and fracture.

Increased dietary acid might also be related to fracture through detrimental effects on muscle. Metabolic acidosis stimulates catabolism of skeletal muscle proteins but not their synthesis (40–43). Nitrogen end products increase and muscle mass
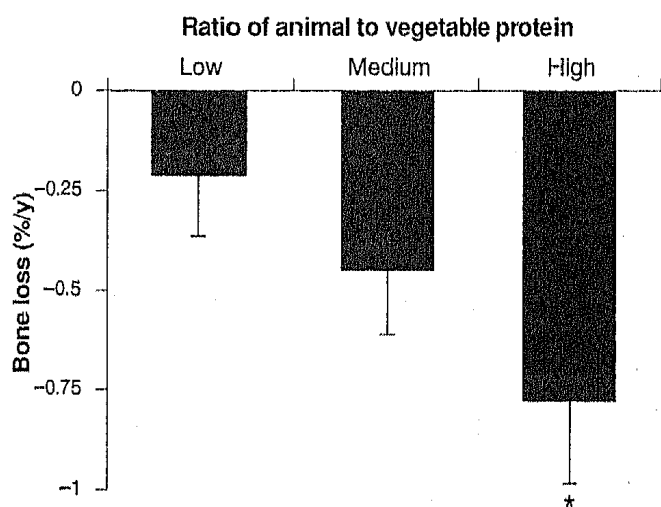

FIGURE 2. Mean (±SE) rate of femoral neck bone loss by ratio of animal to vegetable protein intake in 742 women, adjusted for age, energy intake, total calcium intake (dietary calcium plus supplements), total protein intake, weight, current estrogen use, physical activity, smoking status, and alcohol intake. *Significantly different from low ratio, $P = 0.02$.
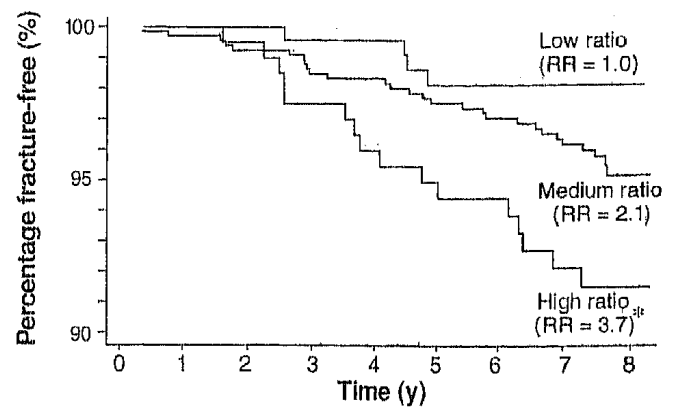

FIGURE 3. Hip fracture-free survival in 1035 women by ratio of animal to vegetable protein intake adjusted for age, energy intake, total calcium intake (dietary plus supplements), total protein intake, weight, current estrogen use, physical activity, smoking status, and alcohol intake. *$P = 0.04$. RR, relative risk.

decreases during experimentally induced metabolic acidosis (42, 44). This effect may be a homeostatic mechanism that maintains acid-base balance: catabolism of skeletal muscle provides glutamine, which the kidney extracts to produce the base ammonia, for the excretion of acid (as ammonium) (45). Reversal of diet-induced acidosis with oral potassium bicarbonate improves nitrogen balance (46, 47). Thus, skeletal muscle, like bone, may serve as a reservoir of base that is gradually depleted to maintain acid-base balance. Chronic depletion of skeletal muscle could lead to weakness and a greater number of falls, both factors in hip fracture.

Our study had limitations. We included only elderly, white, community-dwelling women who were physically able to attend clinic examinations. Because this was an observational study, it is possible that the association between a high ratio of dietary animal to vegetable protein intake and the higher rate of bone loss and hip fracture was due to a risk factor we did not measure. Bone loss and risk of hip fracture are multifactorial. We adjusted for as many factors related to BMD and fracture as possible, but there may be others we did not measure that could influence this relation. In particular, other nutrients associated with vegetable intake may be beneficial for bones. Additionally, the women in this cohort appeared to be fairly protein replete; half had dietary protein intakes in excess of the 50 g/d recommended for older women. Women with marginal total protein and energy intakes may not have had the same associations, particularly because the BMD relations appeared to be significantly influenced by total protein intake and body weight. Finally, we had insufficient power to assess the independent effects of dairy and nondairy sources of animal protein or to stratify our hip fracture analyses by calcium intake.

We conclude that elderly women who have relatively high dietary animal protein intakes and limited vegetable protein intakes have more rapid bone loss at the femoral neck and a greater risk of hip fracture than do those with lower dietary animal protein intakes and higher vegetable protein intakes. This suggests that increases in vegetable protein intake and decreases in animal protein intake may decrease bone loss and the risk of hip fracture. This possibility should be confirmed in other prospective studies and tested in a randomized trial.

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