Journal of Gerontology: MEDICAL SCIENCES
2000, Vol. 55A, No. 10, M585–M592

Worldwide Incidence of Hip Fracture in Elderly Women: Relation to Consumption of Animal and Vegetable Foods

Lynda A. Frassetto, Karen M. Todd, R. Curtis Morris, Jr., and Anthony Sebastian

Department of Medicine and General Clinical Research Center, University of California, San Francisco.

Background. Hip fracture, a major health problem in elderly persons, varies in incidence among the populations of different countries and is directly related to animal protein intake, a finding that suggests that bone integrity is compromised by endogenous acid production consequent to the metabolism of animal proteins. If that is so, vegetable foods might provide a countervailing effect, because they are a rich source of base (bicarbonate) in the form of metabolizable organic anions, which can neutralize protein-derived acid and supply substrate (carbonate) for bone formation.

Methods. We analyzed reported hip fracture incidence (HFI) data among countries ($N = 33$) in women aged 50 years and older, in relation to corresponding country-specific data on per capita consumption of vegetable and animal foods as reported by the United Nations Food and Agriculture Organization.

Results. HFI varied directly with total ($r = +.67$, $p < .001$) and animal ($r = +.82$, $p < .001$) protein intake and inversely with vegetable protein intake ($r = -.37$, $p < .04$). The countries in the lowest tertile of HFI ($n = 11$) had the lowest animal protein consumption, and invariably, vegetable protein (VP) consumption exceeded the country's corresponding intake of animal protein (AP): VP/AP > 1.0. By contrast, among the countries in the highest tertile of HFI, animal protein intake exceeded vegetable protein intake in nearly every case (10 of 11 countries). Among all countries, HFI correlated inversely and exponentially with the ratio of vegetable/animal protein intake ($r = -.84$, $p < .001$) and accounted for 70% of the total variation in HFI. Adjusted for total protein intake, vegetable food consumption was an independent negative predictor of HFI. All findings were similar for the subset of 23 countries whose populations are predominantly Caucasian.

Conclusion. The findings suggest that the critical determinant of hip fracture risk in relation to the acid-base effects of diet is the net load of acid in the diet, when the intake of both acid and base precursors is considered. Moderation of animal food consumption and an increased ratio of vegetable/animal food consumption may confer a protective effect.

IN 1992, Abelow and coworkers reported that the incidence of hip fractures in women aged 50 years and older correlates positively with a country's average annual per capita consumption of animal protein (1). Noting that animal protein is a rich source of sulfur-containing amino acids, which the body metabolizes to the fixed acid sulfuric acid, Abelow and coworkers interpreted the positive correlation of hip fracture rate and animal protein intake as consistent with the hypothesis that hip fractures result in part from deleterious effects of prolonged exposure to dietary acid (2,3).

If that interpretation is correct, however, the decisive risk factor for hip fracture would not be the rate of production of fixed acid (sulfuric acid) from animal protein but the net rate of endogenous acid production, when all sources of dietary acid and base are considered. Net endogenous acid production is determined by dietary factors in addition to animal protein intake, including factors that result in endogenous base production and that attenuate or counteract the acid-producing effect of animal protein (4). Vegetable foods in particular are rich in bicarbonate and in organic anions that can be metabolized to bicarbonate (5,6), which in turn reduces the net rate of endogenous acid production for a given rate of sulfuric acid production (7).

Accordingly, for any protein intake, the net rate of endogenous acid production may vary over a substantial range, depending on the relative intakes of animal and vegetable foods. Taking vegetable food consumption into consideration, therefore, is necessary to fully assess the net acid-base effect of diet and to determine whether the hip fracture rate correlates with net endogenous acid production. One cannot predict a priori whether the contribution of vegetable foods will weaken or strengthen the case for a positive association between hip fracture rate and net acid production based on consideration of animal foods consumption alone.

This study examines the cross-cultural relation between hip fracture incidence (HFI) and acid-base potential of the diet, taking into consideration the consumption of both vegetable and animal foods.

METHODS

Country-specific surveys of HFI were identified by Medline searches and pursuit of the generated leads. Reports were selected only if hip fracture rates were recorded for women over the age of 50 years and if per capita food consumption data were available for the country surveyed (see below). Eighty-seven surveys from 33 countries met these criteria (8–74).

For each survey, hip fracture rates for women over the age of 50 were expressed as fractures per 100,000 person-years for each age group tabulated in the report. Age grouping varied among reports, most often in 5- or 10-year intervals. To allow between-country comparison of fracture rates, the fracture rate for each age group in each survey was adjusted to a common population base for that age group, using the direct method of standardization (75). The reference population for that standardization was the age group distribution of women in the United States for 1987, as reported by the US Census Bureau (76). For each survey, the cumulative standardized fracture rate for all age groups over 50 years was then calculated. For each of the 33 countries surveyed, a single estimate of fracture incidence was generated as the mean of the standardized cumulative fracture rates from all surveys for that country, and that value was used to represent hip fracture incidence for between-country comparisons and relation to food consumption parameters.

Estimates of per capita consumption of foods of both animal and vegetable origin were obtained from *Food Balance Sheets* (77), published by the Food and Agriculture Organization (FAO) of the United Nations. Whenever possible, for each hip fracture survey, the food consumption data used was that for the 10-year interval prior to the date of the fracture survey, averaged over the interval. Otherwise, data for the closest available prior decade were used. For each country, a single estimate of each per capita food consumption variable (see below) was then generated as the mean of the values for all surveys. The food consumption variables evaluated were animal protein (AP), vegetable protein (VP), total protein (TP), in grams/day, their ratios, and the quantities of animal, vegetable, and total foods consumed, in kilocalories/day, and their ratios.

Age-adjusted hip fracture rates were analyzed in relation to food consumption variables by linear, multiple linear, and nonlinear regression, using SigmaStat (Jandel Corp., San Raphael, CA).

Results

Table 1 lists the averages by country ($N = 33$) of HFI arranged in increasing order and the corresponding values of per capita consumption (g/day) of animal, vegetable, and total protein. Hip fracture incidence varied greatly, from less than 1.0 (Nigeria) to nearly 200 (Germany) per 100,000 per-

Table 1. Hip Fracture Incidence (HFI) and Dietary Protein Intake by Country

Tertile of HFI	Country	HFI per 100,000 Person-Years	Animal Protein Intake (AP) (g/day)	Vegetable Protein Intake (VP) (g/day)	VP/AP	Total Protein (TP) (g/day)
Lowest	Nigeria	0.8	8.1	40.2	5.0	48.3
	China	2.9	10.7	51.2	4.8	61.9
	New Guinea	3.1	16.3	29.7	1.8	46.0
	Thailand	5.0	14.7	34.3	2.3	49.0
	South Africa	7.7	27.8	45.4	1.6	73.2
	Korea	11.5	16.9	68.6	4.0	85.5
	Singapore	21.6	24.5	30.2	1.2	54.7
	Malaysia	26.6	24.3	32.7	1.3	57.0
	Yugoslavia	33.5	26.1	67.8	2.6	93.9
	Saudi Arabia	47.3	35.0	49.1	1.4	84.0
	Chile	56.8	25.0	44.8	1.8	69.8
Middle	Italy	57.2	52.1	51.9	1.0	104.0
	Holland	60.7	53.3	33.6	0.6	86.9
	Spain	65.1	50.1	44.1	0.9	94.2
	Japan	67.3	44.3	42.5	1.0	86.8
	Hong Kong	69.2	44.0	36.7	0.9	80.7
	Israel	75.5	39.7	51.0	1.3	90.7
	Ireland	76.0	59.6	41.7	0.7	101.3
	France	77.0	74.2	36.7	0.5	110.9
	Finland	93.5	55.7	36.4	0.7	92.1
	Canada	110.3	60.4	34.7	0.6	95.1
	Crete	113.0	53.1	55.9	1.1	109.1
Highest	United Kingdom	116.5	54.4	36.3	0.7	90.7
	Portugal	119.8	40.7	48.9	1.2	89.5
	United States	120.3	70.1	32.9	0.5	103.1
	Australia	124.8	64.7	33.3	0.5	98.0
	Switzerland	129.4	62.6	35.2	0.6	97.8
	New Zealand	139.0	70.6	34.3	0.5	104.9
	Argentina	147.8	68.2	36.9	0.5	105.0
	Denmark	165.1	55.6	30.5	0.5	86.1
	Sweden	172.0	59.9	29.8	0.5	89.7
	Norway	186.7	58.6	34.0	0.6	92.5
	Germany	199.3	62.4	35.3	0.6	97.7
Lowest tertile	mean ± *SD*	19.7 ± 18.4	20.9 ± 7.7	44.9 ± 13.1	2.5 ± 1.3	65.8 ± 15.9
Middle tertile	mean ± *SD*	76.8 ± 18.1	53.3 ± 9.0	42.3 ± 7.3	0.8 ± 0.2	95.6 ± 9.2
Highest tertile	mean ± *SD*	147.3 ± 27.8	60.7 ± 8.2	35.2 ± 4.8	0.6 ± 0.2	95.9 ± 6.3

son-years. Among the countries in the lowest tertile of HFI ($n = 11$ countries), hip fracture rates were less than 60 per 100,000 person-years. These 11 countries also had the lowest animal protein consumption of the 33 countries surveyed. Notably, in all 11 countries in the lowest tertile of HFI, vegetable protein consumption exceeded the country's corresponding intake of animal protein (VP/AP > 1.0). By contrast, among the countries in the highest tertile of HFI (>116 per 100,000 person-years), animal protein intake exceeded vegetable protein intake in 10 of 11 countries.

Among the 33 countries, HFI varied directly with total protein intake (HFI = $-97.9 + 2.1 \cdot$ TP, $r = +.67$, $R^2 = .45$, $p < .001$), directly with animal protein intake (HFI = $-26.591 + 2.413 \cdot$ AP, $r = +.82$, $R^2 = .67$, $p < .001$) (Figure 1, left panel), and inversely with vegetable protein intake (HFI = $167.272 - 2.093 \cdot$ VP, $r = -.37$, $R^2 = .14$, $p < .04$) (Figure 1, right panel). Hip fracture incidence was strongly correlated inversely and exponentially with the ratio of vegetable/animal protein intake (HFI = $257.6 \cdot e^{(-1.24 \cdot \text{VP/AP})}$, $R^2 = -.84$, $p < .001$) (Figure 2). Thus, 70% ($= 0.84^2 \cdot 100$) of the variation in HFI among countries was accounted for by the variation in vegetable/animal protein ratio. Among countries, vegetable and animal protein intakes correlated inversely (AP = $-0.19 \cdot$ VP + 49.5, $r = -.37$, $R^2 = .14$, $p < .04$).

Adjusting for animal protein intake in multiple regression analysis, vegetable protein intake was not a significant predictor of HFI. Animal protein intake, however, correlated directly with total protein intake (AP = $-33.5 + 0.91 \cdot$ TP, $r = +.86$, $p < .001$), whereas vegetable protein intake did not correlate significantly with total protein intake. After adjusting for total protein intake in multiple regression analysis, vegetable protein intake was a significant negative predictor of HFI (HFI = $+2.3 \cdot$ TP $- 2.8 \cdot$ VP $- 5.9$, $R^2 = .68$, $p < .001$).

Reanalysis of the data expressing per capita consumption of animal and vegetable foods in kilocalories per day instead of in grams of protein per day yielded essentially identical results. For example, HFI varied inversely and exponentially with the ratio of vegetable/animal kilocalories per day (VK/AK) consumed (HFI = $212.5 \cdot e^{-0.32 \cdot (\text{VK/AK})}$, $R = .82$, $p < .001$).

Discussion

The findings in this study confirm those of Abelow and coworkers (1) that HFI in women over the age of 50 is directly correlated with animal protein consumption. By extending the findings from 16 to 33 countries, spanning six continents, the present findings greatly strengthen the generalization of a worldwide association of hip fractures in women with animal protein consumption. The findings further extend the observations of Abelow and coworkers by demonstrating that HFI also correlates with vegetable protein consumption, but in the opposite direction.

The association of hip fractures with animal protein consumption was interpreted by Abelow and coworkers (1) as supporting the hypothesis that eating animal foods increases hip fracture risk by increasing endogenous fixed acid production from metabolism of the accompanying protein, and thereby promotes the development of osteoporosis (2). We reasoned that if this interpretation is correct, the critical risk factor for hip fracture would not be the rate of production of fixed acid (e.g., sulfuric acid) from animal protein but the net rate of endogenous acid production, when sources of di-

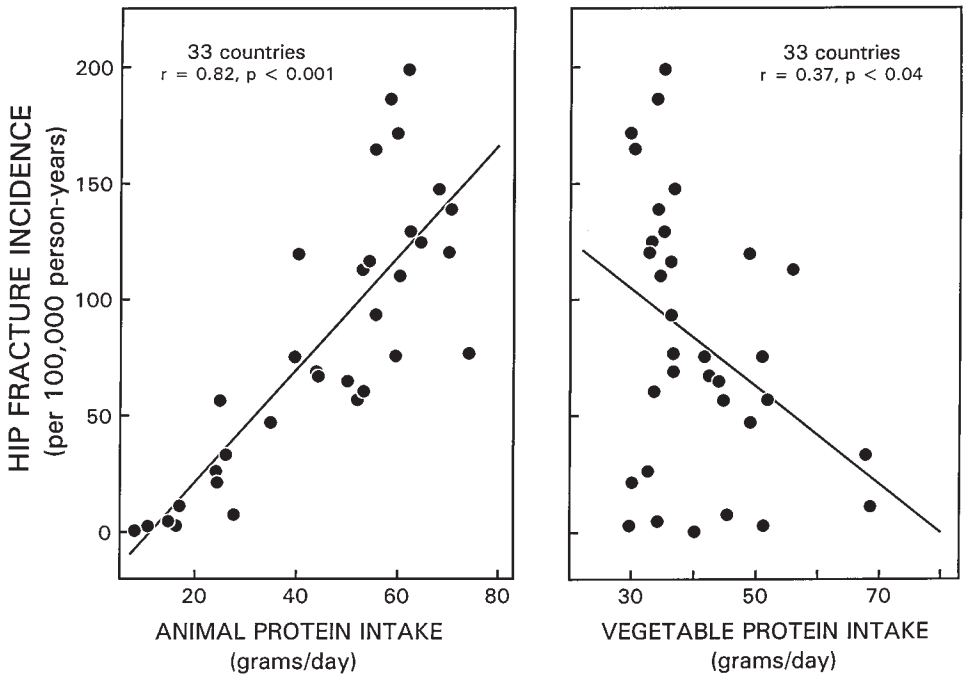

Figure 1. Cross-cultural relationship ($N = 33$ countries) between hip fracture incidence in women aged 50 years and older (per 100,000 person-years) and per capita animal protein (left panel) and vegetable protein consumption (right panel) (g/day).

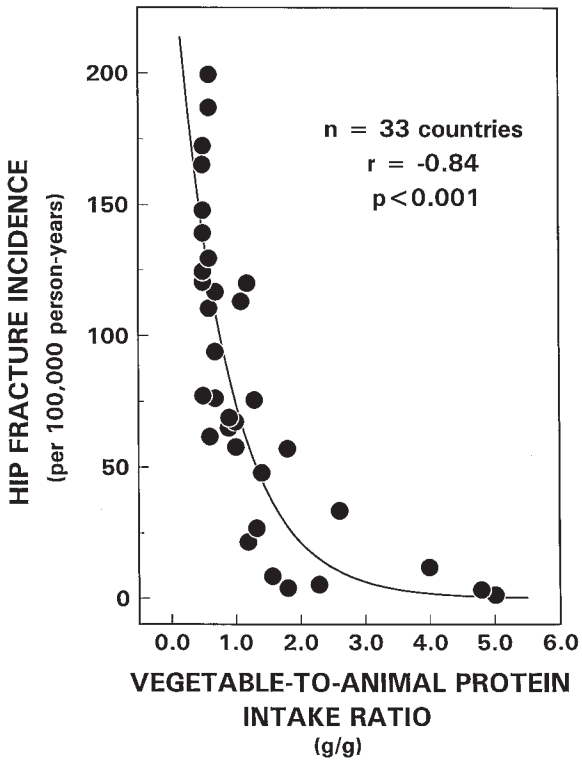

Figure 2. Cross-cultural relationship (N = 33 countries) between hip fracture incidence in women aged 50 years and older (per 100,000 person-years) and the ratio of vegetable-to-animal protein.

etary base as well as acid are considered. Vegetable foods are rich in organic anions (5) that can be metabolized to the base, bicarbonate, which in turn reduces the net rate of endogenous acid production for a given rate of acid production from animal foods (7,78,79). Vegetable protein intake may therefore be a marker of the total amount of vegetable foods ingested, which in turn indicates the amounts of base-producing organic anions ingested. (Because protein content varies among vegetable foods, per unit weight or kilocalorie of food, it is not a perfect index of the quantity of vegetable food consumed or of the quantity of whatever constituents are present in vegetable foods that may confer a skeletal protective effect.)

It seems unlikely that any beneficial effect of vegetable food consumption on hip fracture risk would be mediated by the proteins in the vegetable foods. Although vegetable proteins reportedly contain lesser amounts of sulfur-containing amino acids than do animal proteins (80), a corresponding lesser increase in the rate of metabolic acid production per unit increase in vegetable versus animal protein consumed would not be expected by itself to reverse a directional effect of protein intake on hip fracture risk.

[The general belief that the sulfur-containing amino acid content of animal proteins is greater than that of vegetable proteins is based on analyses of relatively few isolated proteins, whereas the more relevant issue is the relative contents of those amino acids in the entire complex of proteins making up individual foods of animal and vegetable origin. When the latter is examined from food composition data, the sulfur-containing amino acid content of common foods of animal origin, expressed in mEq of sulfur per 100 g of protein, is fairly uniform and generally higher than most common foods of vegetable origin (Table 2). But in a number of common vegetable foods, the sulfur-containing amino acid content is within the range and greater than that of common animal foods (Table 2). When we look at the potential sulfuric acid load from metabolism of vegetable proteins, we must take into consideration the specific foods ingested as well as their quantity.]

To further examine the influence of the relative amounts of vegetable and animal food intake on HFI, we examined the ratio of vegetable/animal protein intake across tertiles of HFI. Among the countries in the lowest tertile of HFI, vegetable protein intake invariably exceeded that of animal protein intake (VP/AP $>$ 1), and among those in the highest tertile, vegetable protein intake was nearly always lower than animal protein intake (VP/AP $<$ 1; 10/11 countries) (Table 1). On average, for every hip fracture occurring among women over the age of 50 in countries among the lowest tertile, 7 to 8 hip fractures occur among women in countries in the highest tertile. At the extremes, that is, comparing the countries with the highest (Germany) and lowest (Nigeria) hip fracture rates, the relative fracture incidences are 200 to 1 (Table 1). When all countries are considered together, the ratio of vegetable/animal protein intake correlated inversely and exponentially with HFI ($R = -.84$, $p < .001$) (Figure 2), and accounted for 70% of the total variation in HFI.

Because vegetable food consumption was significantly correlated with animal food consumption—inversely—it might be argued that vegetable food consumption is not an independent predictor of HFI. That is, the lower rates of hip fracture in countries in which people ate more vegetable foods might have occurred because they also were eating less animal foods. Yet, when total protein intake was held constant in multiple linear regression analysis, vegetable food consumption remained a significant negative predictor of hip fracture rate ($p < .001$). Thus, among countries with similar total protein intakes, vegetable food consumption varied independently and was an independent negative predictor of hip fracture rate.

Although HFI was more tightly correlated with animal protein intake ($r = +.82$) than with vegetable protein intake ($r = -.37$), the magnitude of effect on hip fracture rate per unit difference in intake was nearly the same, although in opposite directions (Figure 1). In both cases, a 10-g difference in protein intake was associated with a change of approximately 20 hip fractures per 100,000 person-years.

Consistent with the proposal of Abelow and coworkers (1) that the direct effect of animal food consumption on HFI is related to increased endogenous acid production, we propose that the inverse effect of vegetable food consumption on hip fracture is related to increased endogenous base production. The base precursors of natural foods are largely organic anions, such as citrate, succinate, and other conjugate bases of carboxylic acids, which the body metabolizes to bicarbonate. Foods contain both organic anions (e.g., citrate) and their corresponding undissociated organic acids (e.g.,

Table 2. Sulfur-Containing Amino Acid Content of Common Foods of Vegetable and Animal Origin Expressed as Potential Acid From Methionine and Cystine[†]

Food Item	Potential Acid From Methionine and Cystine (mEq/100 g protein)	Food Item	Potential Acid From Methionine Cystine (mEq/100 g protein)
Grapes	71.1	Oranges	46.2
Walnuts	66.5	Buckwheat	46.2
Rice	65.4	Soybeans	44.9
Chicken	58.4	Potatoes	42.5
Wheat bread	58.1	Bananas	41.8
Sweet corn	58.1	Apples	40.4
Salmon	57.5	Chickpeas	39.9
Cod	57.5	Yam	39.1
Ham	56.7	Cauliflower	38.3
Turkey	56.2	Black beans	38.3
Lamb	54.3	Zucchini	36.9
Beef	53.0	Kale	35.2
Brown rice	50.4	Tomatoes	32.6
Peaches	46.8	Cabbage	26.9
Pineapple	46.3	Broccoli	26.5

[†]Calculated as $2 \cdot$ (methionine $+ 2 \cdot$ cystine), where methionine and cystine contents are expressed in mmol/100 g protein.

citric acid). When an ingested organic acid, such as citric acid, is metabolized by the body, the end-products are carbon dioxide and water. When an ingested organic anion, such as citrate anion, is metabolized, the end-product is bicarbonate (78). Vegetarian diets yield significantly lower rates of net endogenous acid production than do mixed animal and vegetable diets, even when the diets are equal in protein content (81). Diets that consist predominantly of vegetable foods frequently yield negative rates of net endogenous acid production or net base production (79). Renal net acid excretion correlates positively with animal protein intake and negatively with vegetable protein intake (7).

Careful studies indicate that diet-dependent differences in net endogenous acid production are sufficiently large to perturb systemic acid–base equilibrium (82,83), which presumably is prerequisite to initiation of pathophysiological sequelae. Otherwise healthy subjects eating net acid-producing diets are in a chronic state of low-grade metabolic acidosis, which increases in severity because renal function normally declines with increasing age (82,83). These differences in systemic acid–base equilibrium induced by differences both in diet net acid load and age-related renal functional status thus provide a potential signal for adaptive responses of the body that have numerous maladaptive "trade-off" effects, including dissolution of bone (84,85).

Bone is a large reservoir of base, in the form of alkaline salts of calcium that are released into the systemic circulation in response to increased systemic acid loads (86–89). Experimentally induced chronic metabolic acidosis by acid loading induces loss of bone mass (86,90–94) because of participation of bone in this homeostatic response (86). Released bone base mitigates the severity of the metabolic acidosis. As acid loading continues, the bone minerals accompanying that base are wasted in the urine and bone mineral content, and bone mass progressively declines (91–93). The mechanism of bone loss includes acidosis stimulation of osteoclasts and inhibition of osteoblasts (95).

Evidently, even the low-level acid loading and metabolic acidosis that occur in humans eating ordinary diets is sufficient to impose a chronic demand for base of skeletal origin. In humans eating ordinary net acid-producing diets, the kidneys do not dispose of the entire daily acid load (82,96). As a result, normal subjects are in a state of chronic acid retention (82). Because the degree of acidosis in the systemic circulation does not increase measurably from day to day (82,86,88,96), there must be an internal reservoir supplying base to the systemic circulation. Bone is the only base reservoir with sufficient capacity for that mechanism to operate over a lifetime (97). Over decades, the magnitude of daily positive acid balance may be sufficient to induce osteoporosis (2,3). Reducing the diet net acid load to nearly zero by supplementing the diet with base improves calcium balance, reduces bone resorption, and stimulates bone formation (98).

Even if the findings in this study could be interpreted as indicating a causal relationship between diet net acid load and HFI, which they cannot because they are only associational, they could not be interpreted as implying that the diet net acid load is a major determinant of hip fracture rates in elderly women. These findings do, however, raise the possibility only that differences in net acid load might account for a major fraction of the differences in fracture rate in that segment of the population, whatever may be setting the underlying acid load–independent rate. Conceivably, the observed magnitude of the effect of net acid load differences is dependent in part on the presence or absence of other clinically more important determinants of the rate of bone turnover in elderly women, such as estrogen status, calcium intake, body weight, and levels of physical activity.

Furthermore, because differences in acid load–independent fracture risk factors perforce could not be controlled for in this study, the possibility that the dietary net acid load is a pathophysiologically benign covariate of one or more of those factors cannot be excluded. Such factors include physical activity, dietary variables other than protein intake, and other physiological factors influenced by cultural practices and state of economic development. Indeed, the issue whether "excess" dietary protein intake adversely affects bone in humans is a subject of current controversy in nutrition (3,99,100), with one group concluding that "excess protein will not harm the skeleton if the calcium intake is adequate" (100), and another group that "excessive dietary protein from foods with high potential renal acid load (e.g., animal foods) adversely affects bone, unless buffered by the consumption of alkali-rich foods (e.g., vegetable foods)" (3). Clearly, the present study cannot be interpreted as resolving this issue. Only the fact that the findings in this study are predictable a priori from our knowledge of acid–base effects on bone make them potentially clinically and epidemiologically relevant.

Nevertheless, the findings are only associational, and of the large numbers of potential confounders, the available data permitted adjusting only for age and for considering women only. Heaney, in particular, has been critical of interpreting cross-sectional associational studies, such as this

one, as suggesting causal relationship, and we share that view. In reviewing the smaller study ($n = 16$ countries) by Abelow and coworkers, Heaney noted, in particular, that many of the countries with lower hip fracture rates were predominantly inhabited by black and Asian populations, who may have lower risks for hip fracture, either because bone mass tends to be greater (blacks), or because the architecture of the hip differs (Asian) (100). The larger number of countries ($N = 33$) included in the present analysis gave us the opportunity to test whether the association of hip fracture rate and animal and vegetable food consumption continues to hold when those countries ($n = 10$) are excluded from the analysis. For the countries with predominantly Caucasian populations ($n = 23$), we found that the results were similar to those obtained in the primary analysis of all countries (Figure 3). That result does not, however, exonerate other confounders that might influence hip fracture risk among Caucasian women.

Another potential pitfall of this particular associational study stems from interpreting food consumption data (FAO *Food Balance Sheets*) for the combined population of a country as applicable to one segment of the population, in this case, women over the age of 50 (101). To the extent that animal and vegetable food consumption by such elderly women differs from the population average, the data would be skewed.

Based on our findings and the considerations and caveats offered in this discussion, we hypothesize that the relatively high incidence of hip fractures in women in industrialized countries is caused, at least in part, by the cumulative effects on bone of the body's chronic retention of a fraction of the high dietary net acid load characteristic of the inhabitants of those countries. This high dietary net acid load, in turn, is the result of disproportionate consumption of animal (acid precursors) relative to vegetable (base precursors) foods. The degree of acid retention is determined in part by the magnitude of the diet-determined net acid load and in part by the acid–base regulatory integrity of the kidney, which declines with increasing age, resulting in increasing degrees of chronic low-grade metabolic acidosis. The attendant increased blood acidity and hypobicarbonatemia provide the proximate signals for a cell-mediated increase in bone turnover that contributes to the development of osteoporosis and increases hip fracture risk in postmenopausal women. Moderation of animal food consumption and an increased ratio of vegetable/animal food consumption may confer a protective effect.

Acknowledgments

This research was supported in addition by the National Institutes of Health (Grants M01 RR00079, R01 AG/AR 05407, P01DK 39964, and R01HL47943); the University of California Research Evaluations and Allocation Committee (Grant MSC-22); UCSF Academic Senate Grant; and gifts from Church & Dwight Co., Inc., and the Emil Mosbacher, Jr., Foundation. The authors thank Vivian Weinberg for her invaluable biostatistical support and the UCSF General Clinical Research Center.

Address correspondence to Dr. Anthony Sebastian, Box 0126, 1202 Moffitt Hospital, University of California, San Francisco, CA 94143. E-mail: sebastia@gcrc.ucsf.edu

References

1. Abelow BJ, Holford TR, Insogna KL. Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. *Calcif Tissue Int*. 1992;50:14–18.
2. Wachman A, Bernstein DS. Diet and osteoporosis. *Lancet.* 1968;1: 9518–959.

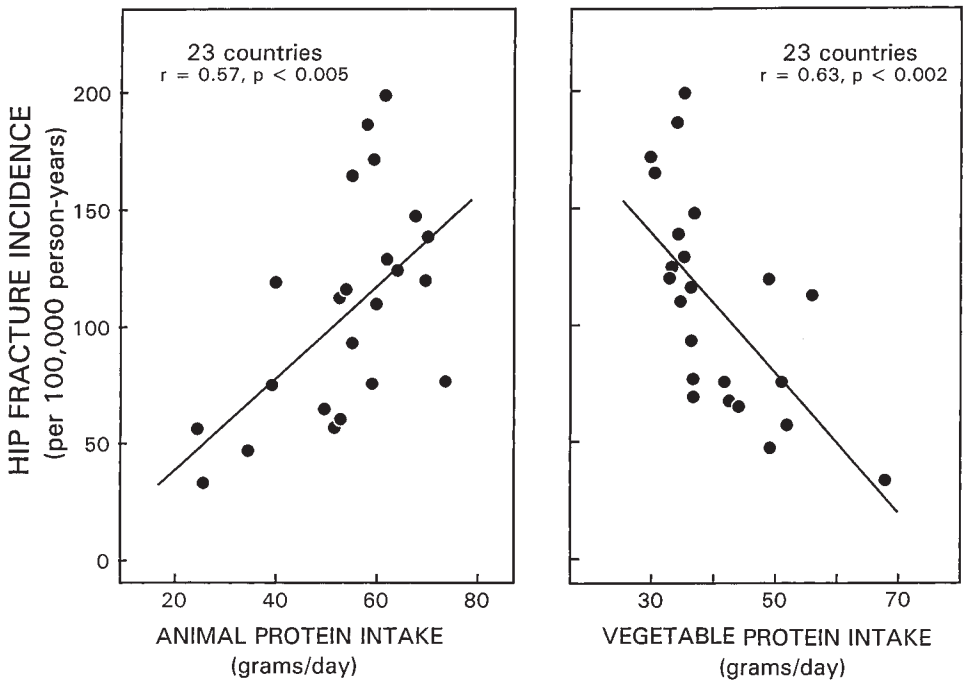

Figure 3. Cross-cultural relationship ($n = 23$ countries) between hip fracture incidence in Caucasian women aged 50 years and older (per 100,000 person-years) and per capita animal protein (left panel) and vegetable protein consumption (right panel) (g/day).

3. Barzel US, Massey LK. Excess dietary protein can adversely affect bone. *J Nutr*. 1998;128:1051–1053.
4. Kleinman JG, Lemann J, Jr. Acid production. In: Maxwell MH, Kleeman CR, Narins RG, eds. *Clinical Disorders of Fluid and Electrolyte Metabolism*. New York: McGraw Hill; 1987:159–173.
5. Souci SW, Fachmann W, Kraut H. *Food Composition and Nutrition Tables*. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH; 1986.
6. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc*. 1995;95:791–797.
7. Hu J-F, Zhao X-H, Parpia B, Campbell TC. Dietary intakes and urinary excretion of calcium and acids: a cross-sectional study of women in China. *Am J Clin Nutr*. 1993;58:398–406.
8. Barber J, Mills H, Horne G, Purdie G, Devane P. The incidence of hip fractures in Maori and non-Maori in New Zealand. *N Z Med J*. 1995; 108:367–368.
9. Coster A, Haberkamp M, Allolio B. Inzidenz von Schenkelhalsfrakturen in der Bundesrepublik Deutschland im internationalen Vergleich [Incidence of femoral neck fractures in the German Federal Republic in comparison to other countries]. *Soz Praventivmed*. 1994; 39:287–292.
10. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int*. 1994;4:277–282.
11. Baudoin C, Fardellone P, Potard V, Sebert JL. Fractures of the proximal femur in Picardy, France, in 1987. *Osteoporos Int*. 1993;3:43–49.
12. Fujiwara NK, Marti B, Gutzwiller F. Hip fracture mortality and morbidity in Switzerland and Japan: a cross-cultural comparison. *Soz Praventivmed*. 1993;38:8–14.
13. Nakamura T. Epidemiological study on hip fractures in Tottori Prefecture [in Japanese]. *Nippon Seikeigeka Gakkai Zasshi*. 1993;67: 189–200.
14. Prince RL, Knuiman MW, Gulland L. Fracture prevalence in an Australian population. *Aust J Public Health.* 1993;17:124–128.
15. Vaz AL. Epidemiology and costs of osteoporotic hip fractures in Portugal. *Bone.* 1993;14(suppl 1):S9.
16. Dretakis EK, Giaourakis G, Steriopoulos K. Increasing incidence of hip fracture in Crete. *Acta Orthop Scand.* 1992;63:150–151.
17. Ferrandez L, Hernandez J, Gonzalez-Orus A, Devesa F, Ceinos M. Hip fracture in the elderly in Spain. Incidence 1977–88 in the province of Salamanca. *Acta Orthop Scand.* 1992;63:386–388.
18. Olmos JM, Martinez J, Garcia J, Matorras P, Moreno JJ, Gonzalez-Macias J. Incidencia de fractura de cadera en Cantabria [Incidence of hip fractures in Cantabria]. *Med Clin (Barc).* 1992;99:729–731.
19. Adebajo AO, Cooper C, Evans JG. Fractures of the hip and distal forearm in West Africa and the United Kingdom. *Age Ageing.* 1991; 20:435–438.
20. Bagur A, Rubin Z, Garcia M, Mautalen CA. Epidemiologia de las fracturas del femur proximal en La Plata, Argentina [Epidemiology of proximal femoral fractures in La Plata, Argentina]. *Medicina (B Aires).* 1991;51:343–347.
21. Contreras L, Kirschbaum A, Pumarino H. Epidemiologia de las fracturas en Chile [Epidemiology of fractures in Chile]. *Rev Med Chil*. 1991;119:92–98.
22. Martin AD, Silverthorn KG, Houston CS, Bernhardson S, Wajda A, Roos LL. The incidence of fracture of the proximal femur in two million Canadians from 1972 to 1984. Projections for Canada in the year 2006. *Clin Orthop*. 1991;266:111–118.
23. Kellie SE, Brody JA. Sex-specific and race-specific hip fracture rates. *Am J Public Health.* 1990;80:326–328.
24. Lau EM, Cooper C, Wickham C, Donnan S, Barker DJ. Hip fracture in Hong Kong and Britain. *Int J Epidemiol.* 1990;19:1119–1121.
25. Ray WA, Griffin MR, West R, Strand L, Melton LJ. Incidence of hip fracture in Saskatchewan, Canada, 1976–1985. *Am J Epidemiol*. 1990;131:502–509.
26. Caniggia M, Morreale P. Epidemiology of hip fractures in Siena, Italy, 1975–1985. *Clin Orthop*. 1989;238:131–138.
27. Diez A, Puig J, Martinez MT, Diez JL, Aubia J, Vivancos J. Epidemiology of fractures of the proximal femur associated with osteoporosis in Barcelona, Spain. *Calcif Tissue Int.* 1989;44:382–386.
28. Hagino H, Yamamoto K, Teshima R, Kishimoto H, Kuranobu K, Nakamura T. The incidence of fractures of the proximal femur and the distal radius in Tottori prefecture, Japan. *Arch Orthop Trauma Surg*. 1989;109:43–44.
29. Rodriguez JG, Sattin RW, Waxweiler RJ. Incidence of hip fractures, United States, 1970–83. *Am J Prev Med.* 1989;5:175–181.
30. Silverman SL, Madison RE. Decreased incidence of hip fracture in Hispanics, Asians, and blacks: California Hospital discharge data. *Am J Public Health.* 1988;78:1482–1483.
31. Finsen V, Benum P. Changing incidence of hip fractures in rural and urban areas of central Norway. *Clin Orthop*. 1987;218:104–110.
32. Lizaur-Utrilla A, Puchades OA, Sanchez DC, Anta BJ, Gutierrez CP. Epidemiology of trochanteric fractures of the femur in Alicante, Spain, 1974–1982. *Clin Orthop*. 1987;218:24–31.
33. Makin M. Osteoporosis and proximal femoral fractures in the female elderly of Jerusalem. *Clin Orthop*. 1987;218:19–23.
34. Currie AL, Reid DM, Brown N. An epidemiological study of fracture of the neck of femur. *Health Bull*. 1986;44:143–148.
35. Hedlund R, Ahlbom A, Lindgren U. Hip fracture incidence in Stockholm, 1972–1981. *Acta Orthop Scand*. 1986;57:30–34.
36. Barss P. Fractured hips in rural Melanesians: a nonepidemic. *Trop Geogr Med.* 1985;37:156–159.
37. Boyce WJ, Vessey MP. Rising incidence of fracture of the proximal femur. *Lancet.* 1985;1:150–151.
38. Falch JA, Ilebekk A, Slungaard U. Epidemiology of hip fractures in Norway. *Acta Orthop Scand*. 1985;56:12–16.
39. Luthje P. Incidence of hip fracture in Finland. A forecast for 1990. *Acta Orthop Scand*. 1985;56:223–225.
40. Farmer ME, White LR, Brody JA, Bailey KR. Race and sex differences in hip fracture incidence. *Am J Public Health.* 1984;74:1374–1380.
41. Zain Elabdien BS, Olerud S, Karlstrom G, Smedby B. Rising incidence of hip fracture in Uppsala, 1965–1980. *Acta Orthop Scand*. 1984;55:284–289.
42. Zetterberg C, Elmerson S, Andersson GB. Epidemiology of hip fractures in Goteborg, Sweden, 1940–1983. *Clin Orthop*. 1984;191:43–52.
43. Frandsen PA, Kruse T. Hip fractures in the county of Funen, Denmark. Implications of demographic aging and changes in incidence rates. *Acta Orthop Scand*. 1983;54:681–686.
44. Luthje P. Fractures of the proximal femur in Finland in 1980. *Ann Chir Gynaecol*. 1983;72:282–286.
45. Swanson AJ, Murdoch G. Fractured neck of femur. Pattern of incidence and implications. *Acta Orthop Scand*. 1983;54:348–355.
46. Hoogendoorn D. Enkele gegevens over 64.453 fracturen van het proximale uiteinde van het femur (collum plus trochantergebied), 1967–1979 [Data on 64,453 fractures of the proximal end of the femur (neck and trochanter area), 1967–1979]. *Ned Tijdschr Geneeskd*. 1982;126:963–968.
47. Rees JL. Secular changes in the incidence of proximal femoral fracture in Oxfordshire: a preliminary report. *Community Med*. 1982;4: 100–103.
48. Baker MR. An investigation into secular trends in the incidence of femoral neck fracture using hospital activity analysis. *Public Health.* 1980;94:368–374.
49. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. *Clin Orthop*. 1980;150:163–171.
50. Jensen JS. Incidence of hip fractures. *Acta Orthop Scand.* 1980;51: 511–513.
51. Matkovic V, Ciganovic M, Tominac C, Kostial K. Osteoporosis and epidemiology of fractures in Croatia. An international comparison. *Henry Ford Hosp Med J*. 1980;28:116–126.
52. Stott S, Gray DH. The incidence of femoral neck fractures in New Zealand. *N Z Med J*. 1980;91:6–9.
53. Evans JG, Prudham D, Wandless I. A prospective study of fractured proximal femur: incidence and outcome. *Public Health.* 1979;93: 235–241.
54. Evans JG. Fractured proximal femur in Newcastle upon Tyne. *Age Ageing.* 1979;8:16–24.
55. Solomon L. Bone density in ageing Caucasian and African populations. *Lancet.* 1979;2:1326–1330.
56. Colbert DS, O'Muircheartaigh I, Chater EH, Wilson AL, Moore A. A study of fracture of the neck of the femur in the west of Ireland 1968–1973. *Ir Med J*. 1976;69:1–12.

57. Alhava EM, Puittinen J. Fractures of the upper end of the femur as an index of senile osteoporosis in Finland. *Ann Clin Res*. 1973;5:398–403.
58. Chalmers J, Ho KC. Geographical variations in senile osteoporosis. The association with physical activity. *J Bone Joint Surg Br*. 1970; 52:667–675.
59. Levine S, Makin M, Menczel J, Robin G, Naor E, Steinberg R. Incidence of fractures of the proximal end of the femur in Jerusalem. A study of ethnic factors. *J Bone Joint Surg Am*. 1970;52:1193–1202.
60. Solomon L. Osteoporosis and fracture of the femoral neck in the South African Bantu. *J Bone Joint Surg Br*. 1968;50:2–13.
61. Wong PC. Fracture epidemiology in a mixed southeastern Asian community (Singapore). *Clin Orthop*. 1966;45:55–61.
62. Alffram P-A. An epidemiologic study of cervical and trochanteric fractures of the femur in an urban population. Analysis of 1,664 cases with special reference to etiologic factors. *Acta Orthopaed Scand*. 1964(suppl 65):101–109.
63. Knowelden J, Buhr AJ, Dunbar O. Incidence of fracture in persons over 35 years of age. A report to the M.R.C. working party on fractures in the elderly. *Brit J Prev Soc Med*. 1964;18:130–141.
64. Buhr AJ, Cooke AM. Fracture patterns. *Lancet*. 1959;1:531–536.
65. Suriyawongpaisal P, Siriwongpairat P, Loahachareonsombat W, et al. A multicenter study on hip fractures in Thailand. *J Med Assoc Thai*. 1994;77:488–495.
66. Rowe SM, Yoon TR, Ryang DH. An epidemiological study of hip fracture in Honam, Korea. *Int Orthop*. 1993;17:139–143.
67. Pedrazzoni M, Alfano FS, Malvi C, Ostanello F, Passeri M. Seasonal variation in the incidence of hip fractures in Emilia-Romagna and Parma. *Bone*. 1993;14(suppl 1):S57–S63.
68. Lee CM, Sidhu JS, Pan KL. Hip fracture incidence in Malaysia 1981–1989. *Acta Orthop Scand*. 1993;64:178–180.
69. Lau EM, Cooper C. Epidemiology and prevention of osteoporosis in urbanized Asian populations. *Osteoporos Int*. 1993;3(suppl 1):23–26.
70. Ho SC, Bacon WE, Harris T, Looker A, Maggi S. Hip fracture rates in Hong Kong and the United States, 1988 through 1989. *Am J Public Health*. 1993;83:694–697.
71. Gullberg B, Duppe H, Nilsson B, et al. Incidence of hip fractures in Malmo, Sweden (1950–1991). *Bone*. 1993;14(suppl 1):S23–S29.
72. Agnusdei D, Camporeale A, Gerardi D, Rossi S, Bocchi L, Gennari C. Trends in the incidence of hip fracture in Siena, Italy, from 1980 to 1991. *Bone*. 1993;14(suppl 1):S31–S34.
73. Al-Nuaim AR, Kremli M, Al-Nuaim M, Sandkgi S. Incidence of proximal femur fracture in an urbanized community in Saudi Arabia. *Calcif Tissue Int*. 1995;56:536–538.
74. Matkovic V, Kostial K, Simonovic I, Buzina R, Brodarec A, Nordin BEC. Bone status and fracture rates in two regions of Yugoslavia. *Am J Clin Nutr*. 1979;32:540–549.
75. Armitage P. *Statistical Methods in Medical Research*. New York: Blackwell Scientific; 1971.
76. *United States Population Estimates, by Age, Sex and Race: 1980 to 1987*. Washington, DC: US Department of Commerce, Bureau of the Census; 1988:11–12. Series P-25 (No. 1022).
77. *Food Balance Sheets (1954–56; 1957–59; 1964–66; 1975–77; 1984–86)*. Statistics Division of the Economic and Social Policy Department. Rome, Italy: Food and Agriculture Organization of the United Nations; 1991.
78. Halperin ML. Metabolism and acid-base physiology. *Artif Organs*. 1982;6:357–362.
79. Blatherwick NR. The specific role of foods in relation to the composition of the urine. *Arch Int Med*. 1914;14:409–450.
80. Robertson WG, Peacock M, Heyburn PJ, et al. Should recurrent calcium oxalate stone formers become vegetarians? *Br J Urol*. 1979;51: 427–431.
81. Breslau NA, Brinkley L, Hill KD, Pak CYC. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab*. 1988;66:140–146.
82. Kurtz I, Maher T, Hulter HN, Schambelan M, Sebastian A. Effect of diet on plasma acid-base composition in normal humans. *Kidney Int*. 1983;24:670–680.
83. Frassetto L, Morris RC, Jr., Sebastian A. Effect of age on blood acid-base composition in adult humans: role of age-related renal functional decline. *Am J Physiol*. 1996;271:1114–1122.
84. Alpern RJ. Trade-offs in the adaptation to acidosis. *Kidney Int*. 1995; 47:1205–1215.
85. Alpern RJ, Sakhaee S. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. *Am J Kid Dis*. 1997;29:291–302.
86. Lemann J, Jr., Litzow JR, Lennon EJ. The effects of chronic acid loads in normal man: further evidence for participation of bone mineral in the defense against chronic metabolic acidosis. *J Clin Invest*. 1966;45:1608–1614.
87. Bushinsky DA. Internal exchanges of hydrogen ions: bone. In: Seldin DW, Giebisch G, eds. *The Regulation of Acid-Base Balance*. New York: Raven Press; 1989:69–88.
88. Lemann J, Jr., Lennon EJ, Goodman AD, Litzow JR, Relman AS. The net balance of acid in subjects given large loads of acid or alkali. *J Clin Invest*. 1965;44:507–517.
89. Lemann J, Jr., Litzow JR, Lennon EJ. Studies of the mechanism by which chronic metabolic acidosis augments urinary calcium excretion in man. *J Clin Invest*. 1967;46:1318–1328.
90. Barzel US. The role of bone in acid-base metabolism. In: Barzel US, ed. *Osteoporosis*. New York: Grune & Stratton; 1970:199–206.
91. Barzel US. The effect of excessive acid feeding on bone. *Calcif Tiss Res*. 1969;4:94–100.
92. Barzel US. Acid-induced osteoporosis: an experimental model of human osteoporosis. *Calcif Tiss Res*. 1976;21(suppl):417–422.
93. Barzel US, Jowsey J. The effects of chronic acid and alkali administration on bone turnover in adult rats. *Clin Sci*. 1969;36:517–524.
94. Jaffe HL, Bodansky A, Chandler JP. Ammonium chloride decalcification, as modified by calcium intake. The relation between generalized osteoporosis and osteitis fibrosa. *J Exp Med*. 1932;56: 823–834.
95. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. *Am J Physiol*. 1992; 262:F442–F448.
96. Lennon EJ, Lemann J, Jr., Litzow JR. The effect of diet and stool composition on the net external acid balance of normal subjects. *J Clin Invest*. 1966;45:1601–1607.
97. Green J, Kleeman CR. The role of bone in regulation of systemic acid-base balance. *Kidney Int*. 1991;39:9–26.
98. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC, Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate [see comments]. *N Engl J Med*. 1994;330:1776–1781.
99. Massey LK. Does excess dietary protein adversely affect bone? Symposium overview. *J Nutr*. 1998;128:1048–1050.
100. Heaney RP. Excess dietary protein may not adversely affect bone. *J Nutr*. 1998;128:1054–1057.
101. Willett W. *Nutritional Epidemiology*. New York: Oxford University Press; 1998.

Received July 13, 1999
Accepted December 23, 1999
Decision Editor: William B. Ershler, MD