Cross-Cultural Association Between Dietary Animal Protein and Hip Fracture: A Hypothesis

Benjamin J. Abelow,[1] Theodore R. Holford,[2] and Karl L. Insogna[3]

[1]Yale University School of Medicine and Departments of [2]Epidemiology and Public Health, and [3]Medicine, Section of Endocrinology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA

Summary: Age-adjusted female hip fracture incidence has been noted to be higher in industrialized countries than in nonindustrialized countries. A possible explanation that has received little attention is that elevated metabolic acid production associated with a high animal protein diet might lead to chronic bone buffering and bone dissolution. In an attempt to examine this hypothesis, cross-cultural variations in animal protein consumption and hip fracture incidence were examined. When female fracture rates derived from 34 published studies in 16 countries were regressed against estimates of dietary animal protein, a strong, positive association was found. This association could not plausibly be explained by either dietary calcium or total caloric intake. Recent studies suggest that the animal protein-hip fracture association could have a biologically tenable basis. We conclude that further study of the metabolic acid-osteoporosis hypothesis is warranted.

Key words: Osteoporosis – Hip fracture – Acid-base equilibrium – Vegetarianism – Dietary proteins – Epidemiology.

Hip fracture, the most devastating of the osteoporosis-associated fractures, has been noted to be more common in industrialized countries than in nonindustrialized countries [1]. A variety of explanations have been offered to account for this distribution, including variations in both genetic and environmental factors [2]. One hypothesis that has received little attention is that fracture incidence may reflect osteopenia resulting from bone buffering of metabolically produced acid.

Protein catabolism is the source of most metabolically produced fixed acid [3], and raising dietary protein intake increases urinary net acid excretion [4–6]. This appears to be especially true for protein from animal sources [7]. It is well known that metabolic acidosis can lead to bone buffering with concomitant bone dissolution [8]. Wachman and Bernstein [9] hypothesized that diets rich in meat and protein might chronically increase endogenous acid production and cause osteoporotic bone loss by the same mechanism.

A variety of studies have produced results consistent with this hypothesis [10]. Most [11], but not all [12], epidemiologic studies suggest that aging-associated bone loss is accentuated in women eating diets high in meat and protein. With some exceptions [13], human metabolic studies suggest

that diets containing high levels of animal protein [7, 14, 15] or enriched with purified protein [4–6, 14] can elevate urinary calcium excretion and produce a negative calcium balance. Animal studies [10], too, have produced results consistent with the hypothesis.

The purpose of this study was to characterize the epidemiologic association between dietary animal protein and hip fracture in women over 50 in an attempt to assess whether the metabolic acid-osteoporosis hypothesis helps to explain the observed cross-cultural variation in fracture incidence.

Methods

Surveys of the incidence of hip fracture were identified by MEDLINE and several manual literature searches. All peer-reviewed, geographic reports containing numerical age-specific data on hip fracture incidence were analyzed. Of 37 surveys identified, 34 in 29 publications [16–44] from 16 countries met the inclusion criteria.

For each survey analyzed, hip fracture rates for women over age 50 were expressed as fractures/100,000 person-years and age-adjusted by the direct method [2, 45]. The distribution of women in the United States for 1987, as estimated by the U.S. Census Bureau [46], was taken as the reference population. The data were also analyzed using cumulative incidence rates [45] for ages 50–85. This was done to determine whether the results were sensitive to the choice of the reference population and to correct for incomplete data in the oldest age groups in some surveys.

Dietary estimates came from Food Balance Sheets [47, 48] and Per Caput Food Supplies [47] published by the Food and Agriculture Organization of the United Nations (FAO). These FAO publications are the only data source available for all countries studied here. Though these estimates do not account for food wastage, and there are differences in the quality of data among countries [47], the estimates are generated with a standard algorithm [47]. Thus, the estimates should provide a good relative measure of dietary intake in different countries.

Whenever possible, dietary data for time periods exactly coincident with that of the fracture surveys were included in the regression. When FAO dietary estimates were not available for exactly coincident years, dietary data for the closest available years were used.

Data on hip fracture incidence and dietary animal protein intake were analyzed in several ways. In each analysis, the regression line and R^2 value reflect the statistical association between dietary animal protein and fracture incidence. First, age-adjusted summary rates from all surveys meeting the inclusion criteria were regressed, unweighted, against dietary animal protein. Next, for those surveys that were sufficiently detailed to permit the calculation of an overall variance (26 of 34 surveys in 14 of 16 countries), a weighted regression was done for both age-adjusted and cumulative fracture rates, using 1/variance as the weighing factor.

Finally, to emphasize the cross-cultural association between diet

Table 1. Fracture incidence rates and dietary estimates, with source information

Country	Fracture survey reference	Figure symbol	Years of fracture survey	Years of dietary data	Fracture rate	Animal protein (g/day)	Calcium (mg/day)
Denmark	[16]	a	1971–76	1971–76	164.8	57.1	960[c]
	[17]	D	1973–79	1973–77	165.3	58.0	
Finland	[18]	F1	1968	1968	71.9	56.1	1332[c]
	[19]	F2	1970	1970	97.3	57.4	
	[20]	F3	1980	1979–81	111.2	60.5	
Holland	[21]	a	1967–79	1967–77	87.7	54.3	1006
Hong Kong	[22]	HK	1965–67	1967	45.6	34.6	356
Ireland	[23]	a	1968–73	1968–73	76.0	61.4	1110
Israel	[24]	IS	1957–66	1957–65, 67	93.2	42.5	794
New Zealand	[25]	NZ	1973–75	1973–75	119.0	77.8	1217
Norway	[26]	N1	1972–73	1972–73	148.8	56.4	1087[c]
	[27]	N2	1978–79	1979–81	220.9	66.6	
	[26]	N3	1983–84	1979–81	190.4	66.6	
Papua New Guinea	[28]	P	1978–82	1977	3.1	16.4	448
Singapore	[29]	SN	1955–62	1961–65	21.6	24.7	389
South African blacks	[30]	SA	1957–63	1961–65	6.8	10.4	196
Spain	[31]	SP	1974–82	1974–77, 77–79	42.4	47.6	766
Sweden	[32]	a	1950–60	1951–57	121.6	57.1	1104[c]
	[33]	S1	1965, 70, 75, 80[b]	1967–77, 79–81	191.8	58.2	
	[34]	S2	1972–81	1972–77, 1979–81	187.8	59.4	
	[35]	a	1981	1979–81	214.3	58.9	
United Kingdom	[36]	a	1954–58	1954–57	77.1	49.0	977[c]
	[37]	UK1	1975, 80[b]	1975–81	91.4	55.3	
	[38]	UK2	1977	1977	118.2	56.6	
	[39]	UK3	1978–79	1977	115.6	56.6	
	[40]	UK4	1983	1979–81	131.0	53.9	
United States	[41]	US1	1965–74	1967–74	144.9	72.0	973[c]
(Whites)	[42]	a	1974–79	1974–79	132.0	72.5	
(Non-White)	[42]	a	1974–79	1974–79	33.5	72.5	
(Whites)	[42]	USW	1980	1979–81	118.3	71.5	
(Blacks)	[42]	USB	1980	1979–81	60.4	71.5	
Yugoslavia	[43]	Y1	1968–73	1968–73	20.5	27.5	588[c]
	[43]	Y2	1968–73	1968–73	52.3	27.5	
	[44]	Y3	1969–72	1969–72	27.6	27.3	

Incidence rates are per 100,000 person-years for women over 50, age-adjusted to 1987 U.S. female population [46]

[a] Survey data were not detailed enough to calculate variance (see text)

[b] Fracture data for discreet years were pooled to calculate a single age-adjusted rate

[c] Average for all surveys in this country

and fracture incidence, a single estimate of fracture incidence was generated for each country. Each estimate was calculated as the weighted mean of age-adjusted fracture rates from all surveys within that country, using 1/variance as the weighing factor. Surveys not sufficiently detailed to calculate an overall variance were excluded, which meant that no estimates could be calculated for Holland and Ireland. When only a single survey was available for a given country, the age-adjusted rate from that survey was used. The estimates for each country were weighted by 1/(variance of the mean) and regressed against similarly weighted means of dietary animal protein for that country. This analysis was repeated using cumulative rates for ages 50–85 instead of age-adjusted rates. Similarly, dietary calcium and total caloric intake were considered as regression variables, both independently and in various combinations.

Results

For each fracture survey, Table 1 lists age-adjusted hip fracture incidence, the years during which fracture data were collected, the closest overlapping years for which FAO data on dietary animal protein are available, and estimated per capita dietary animal protein for those years. Country-specific FAO estimates of dietary calcium are also presented.

As expected, values for animal protein in the United States, and western and northern Europe, are higher than those for Asia and Africa. Countries of southern Europe tend to be intermediate. Some of the more industrialized countries have been the subject of several fracture surveys, but none of the lesser-industrialized countries has been surveyed more than once in sufficient detail to generate age-adjusted values. Of the countries studied more than once, it can be seen that in some (e.g., United Kingdom), there is considerable variation in the fracture rates derived from different surveys, whereas for others (e.g., Denmark), the values are quite close. Black women in the U.S. have a lower incidence of fractures than white women in the U.S. and Europe, but still experience a much higher rate than black women in South Africa. In general, the data show that women over 50 years of age tend to experience higher rates of hip fracture in industrialized countries than in lesser-industrialized countries.

When age-adjusted summary rates from all surveys meeting the inclusion criteria were regressed, unweighted, against dietary animal protein, a positive association was found. The best fitting regression equation is $y = -18.0 + 2.29x$, where y is hip fracture rate per 100,000 person-years, and x is animal protein in g/day. The fractional variation of the hip fracture rate that is explained by dietary animal protein, R^2, is 0.42 ($P < 0.001$).
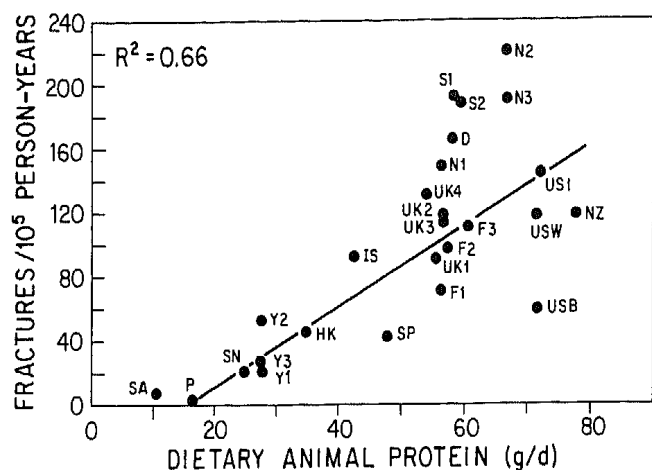
Fig. 1. Plot of age-adjusted hip fracture incidence in women over 50 against estimated per capita dietary animal protein, by fracture survey. See Table 1 for symbols and sources of data.
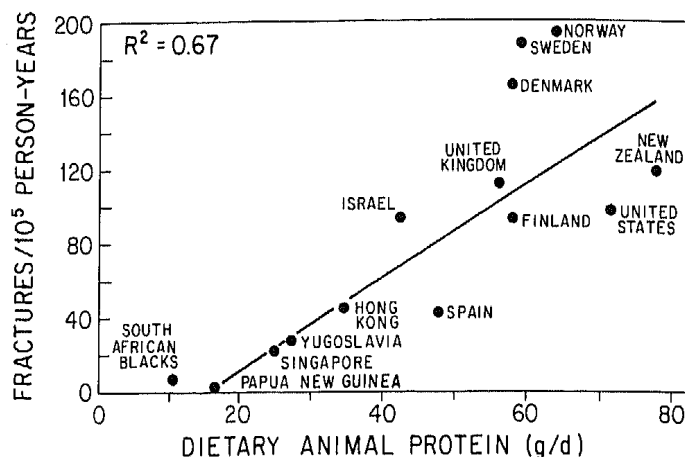

Fig. 2. Plot of age-adjusted hip fracture incidence in women over 50 against estimated per capita dietary animal protein, by country. See Table 1 for sources of data.

Given the limitations inherent in an unweighted regression analysis, weighing of the data sets was undertaken. When a weighted regression line was fitted to the age-adjusted summary rates from all surveys for which an overall variance could be calculated, a strong, positive association between fracture and animal protein remained. The best-fitting regression equation is y $= -38.7 + 2.51$x (R$^2 = 0.66$; $P < 0.001$). This association is shown graphically in Figure 1. Using the cumulative incidence of fractures for women between ages 50 and 85, the strength of the association was essentially the same: y $= -4350 + 314$x (R$^2 = 0.71$; $P < 0.001$).

When a weighted regression line was fitted to the 14 age-adjusted country estimates, a strong cross-cultural association was found between fracture incidence and animal protein. The best fitting regression equation for this cross-cultural association is y $= -38.4 + 2.50$x (R$^2 = 0.67$; $P < 0.001$). This association is shown graphically in Figure 2. Using estimates derived from cumulative rates, the results were as follows: y $= -4307 + 313$x (R$^2 = 0.72$; $P < 0.001$).

In summary, when age-adjusted and cumulative fracture rates were regressed against estimates of dietary animal protein on either a study-by-study or purely cross-cultural basis, a strong, positive association was found.

When FAO estimates of dietary calcium were regressed on country estimates of hip fracture incidence, a significant positive association was noted: y $= -41.0 + 0.14$z, where z equals mg/day calcium (R$^2 = 0.62$; $P < 0.001$). This finding is consistent with a previously reported association between hip fracture and dietary calcium [49]. It is interesting that the association is positive, whereas based on the likely protective role of dietary calcium on bone mass and fracture, a negative association might have been expected. To further clarify this relationship, dietary calcium and animal protein were simultaneously regressed against fracture incidence. The resulting equation is as follows: y $= -42.5 + 1.83$x $+ 0.041$z (R$^2 = 0.68$). Comparing the regression coefficients with their standard errors, the effect of calcium in the presence of animal protein is not significant ($P = 0.59$). Likewise, the effect of animal protein in the presence of calcium is not significant ($P = 0.19$), although this value falls closer to significance. Dietary calcium and animal protein are highly correlated (r $= 0.91$; $P < 0.001$); thus, the problem of multicolinearity makes it difficult to distinguish between the effects of these variables.

When estimated caloric intake was regressed against country estimates of hip fracture, a moderate association was found (R$^2 = 0.50$; $P = 0.005$). Caloric intake was then regressed with all combinations of dietary animal protein and calcium. When caloric intake and animal protein were simultaneously regressed, the association between animal protein and hip fracture remained significant ($P = 0.024$), whereas the calorie-fracture association did not ($P = 0.87$). When caloric intake and dietary calcium were simultaneously regressed, the association between fracture and calcium remained marginally significant ($P = 0.049$), whereas the calorie-fracture association did not ($P = 0.58$). As expected, when all three dietary variables were simultaneously regressed, none of the associations was significant.

Discussion

Epidemiologic Considerations

A variety of factors have previously been hypothesized to account for cross-cultural differences in fracture incidence. For instance, variables such as physical exercise and sunlight exposure have been shown to be plausibly correlated with female hip fracture [2]. A cross-cultural association between total dietary protein and hip fracture has been shown by Hegsted [49], a finding the author suggests might be due to protein-induced damage of renal calcitriol regulation. Low rates among blacks in South Africa [30] has raised the possibility that genetic factors may be responsible.

We considered the possibility that differences in animal protein intake, a relatively specific marker for metabolic acid production, might help explain the cross-cultural variability in hip fracture incidence. Our data demonstrate a striking cross-cultural association between estimated per capita dietary animal protein and fracture incidence in women over 50. These results do not imply a causal association, but they do suggest that the metabolic acid-osteoporosis hypothesis warrants serious study as a possible explanation of cross-cultural variations in hip fracture incidence.

Bone loss usually occurs from about age 40 until death, with accelerated losses in most women occurring for about 10 years after menopause [50]. Environmental modifiers of the rate of bone loss might thus be expected to act over many years. For this reason, fracture incidence might be expected

to correlate better with chronic dietary patterns than with dietary intake at the time when the fracture occurred. Over the past three decades, however, all industrialized countries studied here have had relatively high and stable levels of dietary animal protein [47, 48]. Of the lesser-industrialized countries, some have shown an increase in dietary animal protein [47, 48], but there is little reason to suspect that animal protein intake in any was higher than it is currently. Thus, the cross-cultural dietary differences reported in this study likely reflect stable long-term patterns. These chronic differences, therefore, may have affected bone mass and/or architecture and hence, fracture rates.

The aim of this study was to evaluate the explanatory power of dietary animal protein, and not to rigorously rule out other potential causal factors. Nonetheless, we did analyze data on dietary calcium and total caloric intake. As dietary calcium plays a protective role in osteoporosis, a negative cross-cultural association between dietary calcium and hip fracture incidence might have been expected; instead, we found a positive association. The biologic implausibility of this association suggests that calcium intake is likely an epidemiologic marker for another factor(s) that is causally related to fracture incidence. This interpretation is supported by a recent prospective study showing an inverse relationship between dietary calcium and hip fracture incidence, a finding that suggests a protective effect of increasing dietary calcium intake on fracture rate [51]. Given the high cross-cultural correlation between dietary animal protein and calcium, it seems plausible that calcium might be a marker for an animal protein-rich diet. However, because of the problem of multicolinearity, simultaneous analysis of calcium and animal protein could not assess this possibility.

When total caloric intake, a nonspecific marker of nutrient intake, was simultaneously regressed with animal protein, the fracture-animal protein association remained significant, whereas the fracture-calorie association did not. This indicates that the cross-cultural association between animal protein and fracture incidence cannot be explained by differences in caloric intake between the countries studied.

In the countries studied here, most hip fractures in women over 50 result from low or moderate trauma [17, 18, 21, 24, 25, 31, 33–35, 39–41, 44]. This appears to be true in the lesser-industrialized countries as well [28–30], although a higher proportion of fractures may due to severe trauma [30]. Thus, if bias was introduced by fractures caused by severe trauma, one would have expected it to make the analysis presented here more conservative.

The quality of data on fracture incidence analyzed in this study is determined by that of the surveys cited [16–44]. Inclusion criteria for fractures varied slightly among surveys, but the authors of almost all surveys present evidence that all or most fractures were identified [2]. In this study, fracture rates surveyed regionally were taken to reflect national rates, an assumption that might produce some distortions. Similarly, dietary estimates are per capita averages and do not reflect potential ethnic, regional, sex, age, or individual differences. Though these factors may have affected the quantitative accuracy of individual estimates, it is unlikely that the overall patterns observed in this study were artifactual.

Biologic Plausibility

In vitro and *in vivo* studies suggest that dietary animal protein is a marker for metabolic acid production. Relative dietary ash-acidity varies in the order omnivore > ovo-lacto-vegetarian > vegan [52]. Among individuals consuming diets matched for total protein, urinary net acid excretion increases with animal protein content [7]. Given the greater sulfur content of animal over vegetable protein [53, 15] and the metabolism of most amino acid sulfur to sulfuric acid [54], these findings are not surprising. It should be noted, additionally, that on a cross-cultural basis, dietary animal protein is strongly associated with total protein intake [47, 48], itself a source of metabolic acid [4–6].

Further, dietary protein supplementation leads to calciuresis [4–7, 14, 15], and there is evidence this is due to changes in acid-base status. For example, protein-induced negative calcium balance is accompanied by large increases in urinary net acid excretion [4–6] and is halted by the ingestion of sodium bicarbonate [6]. Omnivore diets can induce a more negative calcium balance than less-acidogenic vegetarian diets matched for total protein, and do so in association with relatively suppressed levels of urinary cyclic AMP, serum parathyroid hormone, and 1,25-dihydroxy-vitamin D [7]. These latter biochemical findings are consistent with acid-induced bone dissolution [7].

Finally, there is evidence that fixed acid loads currently considered physiologic may produce bone loss. When ammonium chloride is ingested at rates that elevate urinary acid excretion to levels just above those attained with high protein diets, fasting calcium excretion is increased [55]. Endogenous acid production in excess of 1 mEq/kg/day, well within the range considered physiologic, can lead to sustained mild metabolic acidosis and positive hydrogen ion balance [56]. This positive balance may result in the chronic titration of buffers in bone [8].

In conclusion, many epidemiologic, human metabolic, and animal studies have produced results consistent with the metabolic acid-osteoporosis hypothesis. Though our findings do not necessarily imply a causal relationship, the strength of the association does lend additional weight to the hypothesis. We conclude that further study of the endogenous acid-osteoporosis hypothesis is warranted. Given the epidemic of osteoporotic fractures in the West [1] and the possibility of dietary prevention or new adjunctive therapies [6], such study may be of considerable practical value.

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