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SHORT COMMUNICATION

Does dietary protein reduce hip fracture risk in elders? The Framingham osteoporosis study

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Abstract
Summary Association between dietary protein and fracture risk is unclear. We examined association between energy-adjusted protein intake and hip fracture risk in elders. The risk of hip fracture was reduced in upper quartiles of protein intake when compared with lowest quartile.
Introduction Studies of the association between dietary protein intake and hip fracture risk are conflicting. Therefore, we examined protein intake and hip fracture risk in a population-based group of elderly men and women.
Methods Five hundred seventy-six women and 370 men from the Framingham Osteoporosis Study with no previous history of hip fracture completed Food Frequency Questionnaires. Energy-adjusted protein intake was evaluated as a continuous variable and as quartiles. Incidence rates and hazard ratios were calculated, adjusting for age, BMI, sex, and energy intake.
Results Among 946 participants (mean age 75 years), mean protein intake was found to be 68 gm/d. Increased protein intake was associated with a decreased risk of hip fracture compared to those in the lowest quartile of protein intake

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(Q2 HR=0.70, Q3 HR=0.56, and Q4 HR=0.63; all p values≥0.044), p for trend was 0.07. When a threshold effect was considered (Q2–4 vs Q1), intakes in the higher quartiles combined were associated with a significantly lower risk for hip fracture (HR=0.63; p=0.04).
Conclusion Our results are consistent with reduced risk of hip fracture with higher dietary protein intake. Larger prospective studies are needed to confirm and extend this finding in elderly men and women.

Keywords Dietary protein · Elders · Hip fracture · Osteoporosis · Population study · Protein intake

Introduction

More than 25 million Americans over the age of 50 years have either osteoporosis or osteopenia [1]. Osteoporotic fractures result in higher morbidity and increased mortality compared with similar aged adults and also have significant costs associated with fracture aftercare. It has been hypothesized that increased dietary protein intake may produce sufficient organic acids as to have a deleterious effect on the skeleton[2]. In contrast to this hypothesis, greater dietary protein intake has been shown to be associated with higher bone mineral density [3]. Few large studies have shown an inverse relation between dietary protein intake and hip fracture risk in younger persons (<70 years) but in elders the association is not as clear [4–6]. Since dietary approaches to osteoporosis and related fractures may be modifiable, it is essential that the role of protein on fracture risk be more clearly understood. Therefore, we examined the relation between dietary protein intake and incident hip fracture risk in elderly men and women of the population-based Framingham Osteoporosis Study.

Methods

Participants

In 1948, The Framingham Study enrolled adults from two-thirds of households in Framingham, MA (n=5,206), aged 28–62 years, to study heart disease risk factors and followed this cohort for over 60 years with biennial examinations [7]. Our study subjects included attendees of the baseline 1988–1989 exam who completed 126-item Food Frequency Questionnaire (FFQ) with plausible total energy intake (>600 and <4,000 kcal per day) and less than 12 items missing (n=976). Participants with prior history of hip fracture (n=30) were excluded, yielding 946 study subjects.

Protein intake

FFQ assessed usual dietary intake by self-report over the past year and was completed at baseline. Although FFQ does not estimate actual intake of a particular nutrient, it is a valid and reproducible tool for assessing and ranking average nutrient intake [8]. Our prior work has shown that elderly men and women of the Framingham Original Cohort have similar distributions of dietary protein intake, such that the quartile cut-points were the same for men as for women and there was no difference in the mean protein intake between the sexes [3]. Total protein intake (g/day) was adjusted for total energy (from FFQ) to reduce error due to variation in total energy requirement, body size, and portion sizes, allowing interpretation of the effect of total protein intake.

Assessment of hip fracture

Framingham Fracture Registry ascertained fractures by interview at each biennial visit or telephone for participants unable to attend clinic visits. First-time (incident) fractures of proximal femur were confirmed by review of medical records (radiology reports, discharge summaries). Details of fracture ascertainment are described elsewhere [9].

Covariates

Baseline information was collected on age, sex, weight, height, smoking, physical activity, calcium intake, vitamin D intake, alcohol intake, caffeine intake, femoral neck BMD, and estrogen use (women only). Weight (to nearest pound, in light clothing) was measured using a standard balance beam scale; height (to nearest inch, without wearing shoes) was measured by stadiometer; Physical Activity Index score was calculated as weighted sum of hours spent during sleep, sedentary, slight, moderate, and heavy activities; and total intakes of calcium (mg/day), vitamin D (IU/day), alcohol (g/day), and caffeine (mg/day) were estimated from FFQ. Current smoking status (yes/no) and current estrogen use in women (yes/no) was obtained via questionnaire. Proximal femoral neck BMD (g/cm²) was obtained using Lunar dual photon absorptiometry, with standard positioning techniques.

Statistical analysis

Baseline characteristics of participants with and without fracture were compared using Student's t test for continuous variables and chi-square test for categorical variables. Energy-adjusted protein intake was analyzed as continuous variable and by quartiles. As protein intakes were similar in men and women, and the quartile cut-points for men and

women were identical, we analyzed men and women together. In order to compare our results with other studies, we also performed women-only analyses. Incidence rates for hip fracture (incident hip fractures divided by person-years of follow-up) were calculated for each protein quartile. Accrual of person-years at-risk began at exam 1988–1989 and continued until occurrence of hip fracture, death, dropout, or end of follow-up (December 31, 2005).

Hazard ratios were calculated for hip fracture using Cox proportional hazards regression, for 1 g difference in protein intake and for each quartile of protein intake (lowest quartile as referent). Cox regression was also used to test for linear trend across quartiles. Based on the observed quartile values, we considered a threshold effect of the upper three quartiles versus the lowest quartile of protein intake.

Our proportional hazard multivariable regression analyses included age, sex, weight, height, and total energy intake. We examined the possible contribution of femoral neck BMD to hip fracture as well. Other potential confounders (caffeine use, alcohol use, physical activity, smoking, vitamin D intake, total calcium intake, and estrogen use in women) were tested and as they did not contribute to the model, they were excluded from further analyses.

Results

Among 946 participants, 100 hip fractures (80 in women; 20 in men) occurred over a median follow-up of 11.6 person-years. Table 1 shows baseline characteristics of participants with and without hip fracture. Participants were mostly Caucasians (>98%). Although mean ages were similar, participants with hip fracture were more likely to be women, to be shorter ($p<0.01$), to weigh less ($p<0.01$), and consume less alcohol ($p=0.04$) than individuals without fracture. Total energy-adjusted protein intake in the two groups was similar ($p=0.79$). Increasing protein intake (per gram/day) showed a mild protective effect for hip fracture but result was not statistically significant ($p=0.26$).

Table 2 displays incidence rates per 1,000 person-years across quartiles of energy-adjusted protein intake. Although crude incidence rates of hip fracture declined across quartiles, no clear dose response pattern was seen. There was an apparent threshold effect at lowest quartile of dietary protein intake on the rate of hip fracture compared to incidence rates in the upper three quartiles. Table 2 also shows hazard ratios for hip fracture for each quartile of energy-adjusted protein intake. After adjusting for age, sex, weight, height, and total energy intake, the HRs for pairwise comparison of each upper three quartiles relative to lowest quartile were: 0.70 ($p=0.19$), 0.56 ($p=0.04$), and 0.63 ($p=0.10$). Trend across quartiles also was of borderline statistical significance ($p=0.07$). Based on observed threshold with incidence rates, we evaluated the upper three quartiles vs the lowest quartile, we found a significant protective effect of higher protein intake for hip fracture with HR of 0.63 ($p=0.04$, 95%CI 0.41–0.97). Adding femoral neck BMD did not change HR estimates. When analysis was restricted to women only, the risk of hip fracture was also found to be lower in quartiles 2–4 compared with quartile 1,with HR of 0.76 (95% CI 0.46–1.27), the result however was no longer statistically significant.

Discussion

Our findings suggest lower risk of hip fracture in elderly men and women with higher protein intake, after adjusting

Table 1 Characteristics of men and women in the Framingham osteoporosis study at baseline who had valid FFQ in 1988–1989, according to whether they had a hip fracture during follow-up (through December 2005)

Characteristic	No hip fracture ($n=846$)	Hip fracture ($n=100$)
Age (years)	75±5.0	76±5.2
Gender (% women)	58.6	80.0
Weight (pounds)	155±31.1	144±36.4
Height (inches)	64±3.7	63±3.9
Total energy intake (kcal/d)	1,741±585.9	1,724±628.4
Caffeine use (mg/d)	190±159.7	200±182.4
Alcohol use (g/d)	10±16.1	7±12.7
Calcium intake (mg/d)	802±423.5	805±468.6
Vitamin D (IU/d)	326±263.5	327±260.4
Current estrogen use in women only (%)	5.1	2.5
Physical activity score	33±5.5	34±5.5
Current smoking (%)	10.8	12.0
Energy-adjusted protein intake (g/d)	64.2	63.6

Mean±SD unless otherwise noted

FFQ Food Frequency Questionnaire

Table 2 Incidence rates (per 1,000 person-years) and multivariable-adjusted hazard ratios across quartiles of energy-adjusted protein intake for hip fracture for all participants and for women only in the Framingham osteoporosis study (1989–2005)

Energy-adjusted protein quartiles (mean protein intake in g/d ± SD)	No. of incident hip fractures/person-years	Incidence rate	Hazard ratios (95% CI) for all participants (n=100 fractures)	Hazard ratios (95% CI) for women only (n=80 fractures)
Q1 (46.45±7.29)	31/2,366.37	13.10	1 (ref)	1.0 (ref)
Q2 (59.61±2.24)	25/2,580.46	9.69	0.70 (0.41–1.19)	0.75 (0.40–1.40)
Q3 (67.70±2.43)	21/2,653.45	7.91	0.56 (0.32–1.0)	0.71 (0.37–1.35)
Q4 (82.74±10.27)	23/2,644.38	8.70	0.63 (0.37–1.09)	0.82 (0.44–1.51)

Adjusted for age, sex, weight, height, and total energy intake

for age, sex, weight, height, and total energy intake. This protective effect was estimated to be 37% lower and statistically significant for upper three quartiles versus lowest quartile of protein intake. Adjustment for femoral neck BMD did not change these results, implying that association between protein intake and fracture risk may not be mediated through effects on BMD in these elderly men and women. Alternative mechanisms for protective effects of protein on hip fracture risk include the possibility that greater protein intake results in greater lower extremity muscle mass and strength [10]. Most fractures occur after fall, which, among many possibilities and pathways, may be caused by lower muscle mass and strength.

Our results are consistent with previous studies that reported relation between greater protein intake and decreased risk of hip fracture. Iowa Women's Health Study, found a strong inverse relation between protein intake and risk of hip fracture among postmenopausal women ages 50–69 years [4]. The HRs across upper three quartiles vs lowest quartile were, 0.59, 0.63, and 0.31, p for trend= 0.037. Similar association was observed in a case–control study between high protein intake and reduced risk of hip fracture in men and women ages 50–69 years [5]. Odds ratio for higher quartiles were, 0.51, 0.53, and 0.35 ($p<$ 0.001); however, this study failed to show an association in those 70 and older. Authors speculated selection bias due to higher death and disability rates in older cases may have affected results. In contrast, the Nurses Health Study reported no relation between protein intake and risk of hip fracture over 12 years of follow-up among women ages 35–59 years although an increased risk of forearm fracture was observed with high dietary protein [6]. Interestingly, Dargent-Molina et al. [11] found increased risk of fracture with higher protein intake among postmenopausal women in lowest quartile of calcium intake but overall found no association between protein intake and fracture risk.

In previous calcium balance studies, consumption of high-protein diet resulted in high urinary calcium, leading some to speculate this may lead to bone resorption over time [2]. However, additional balance studies have shown that higher protein intake leads to increased intestinal absorption of calcium [12]. Thus, higher urinary calcium produced by high-protein diets may reflect this enhanced calcium absorption and not bone resorption. In fact previous studies have observed that subjects with greater protein intake had higher BMD and less bone loss, perhaps mediated through local production of IGF-I by amino acids arginine [13] and lysine[14, 15]. Yakar et al. showed low levels of IGF-1 in mice was associated with decreased bone strength [16] while another study found that lower IGF-1 levels were found to be associated with increased fracture risk in postmenopausal women, independent of BMD [17].

The present study was limited by relatively small number of fractures, affecting statistical power. Our study had 80% power to detect a 46% reduction in HR given our sample. Nonetheless, we found a statistically significant effect of low protein intake and risk of hip fracture. Also, we assessed protein intake by FFQ, a semi-quantitative estimate that does not necessarily accurately measure actual protein intake, although it is designed to rank individuals usual intake. Lastly, our study population was mostly Caucasians, thus limiting generalizability of these results.

The current study also has several strengths. The prospective design removes the potential problems of dietary recall bias (as well as for the other study covariables) that are frequently seen in case–control studies. Also, while most studies of osteoporotic fracture have focused on women, we included both men and women in our analysis, although we have too few fractures to evaluate men separately.

Despite limitations in statistical power, our study supports the likelihood of a protective effect of protein intake against hip fracture risk. In particular, the higher three quartiles of intake had a significantly lower incidence of fracture. Larger prospective studies with elderly men and women are needed to confirm the finding that, as our study and previous studies suggest, higher protein intake in elderly adults may protect against hip fracture.

Conflicts of interest None.

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