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Dietary protein is beneficial to bone health under conditions of adequate calcium intake: an update on clinical research

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Abstract

Purpose of review—To underscore recent clinical studies, which evaluate the association between dietary protein and bone health.

Recent findings—Epidemiologic studies show greater protein intake to be beneficial to bone health in adults. In addition, randomized controlled trials show that protein's positive effect on bone health is augmented by increased calcium intake. The relation between dietary protein and fracture risk is unclear. Dietary protein may positively impact bone health by increasing muscle mass, increasing calcium absorption, suppressing parathyroid hormone, and augmenting insulin-like growth factor 1 production; but the effects of other factors that contribute to this association, such as dietary protein dose and timing response, require further research.

Summary—The positive effects of protein intake on bone health may only be beneficial under conditions of adequate calcium intake. Dietary protein's relation with fracture risk requires further investigation.

Keywords

bone health; calcium intake; dietary protein

Introduction

Osteoporosis is characterized by low bone mass and can lead to increased risk of fracture at the hip, spine, and wrist. Hip fractures cause increased morbidity with mortality rates of up to 24% 1 year postfracture [1]. The economic burden of incident osteoporotic fractures in the USA was estimated at nearly $17 billion in 2005; cumulative cost over the next two decades is estimated to be $474 billion [2]. Therefore, it is imperative to identify risk factors associated with poor bone health to maximize the functional capacity of aging adults.

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Nutritional strategies to forestall osteoporosis are important because they are well tolerated, effective, and easily modifiable. Earlier short-term metabolic studies on this topic suggested that protein intake may be harmful for bone health because of its calciuric effect [3]. However, studies over the last decade suggest that dietary protein is beneficial to bone and this may be most apparent when calcium intake is optimal [4,5]. A higher protein diet increases insulin-like growth factor-1 (IGF-1, a key mediator of bone health), increases intestinal calcium absorption, suppresses parathyroid hormone, and improves muscle strength and mass, all of which may benefit the skeleton [6▪]. The purpose of this review is to highlight the most recent clinical evidence that addresses the impact of dietary protein on the calcium economy and bone health in adult men and women (summarized in Table 1).

Epidemiologic Studies

Cohort studies examining the direct relation between dietary protein and bone health in older adults support an overall positive relation, where higher protein intake has been linked with less bone loss over time [7]. Similarly, other epidemiologic studies do not support the hypothesis that greater dietary acid load (associated with chronic high protein intake) is detrimental to bone health [8,18]. One study found that in men alone, greater dietary acid load may be detrimental to bone only under conditions of very low calcium intake [9▪]. This would suggest that dietary calcium may act as a buffer under chronic conditions of high dietary acid load. However, this cross-sectional study was unable to distinguish whether this phenomenon was driven by high protein intake, low calcium intake, or a combination of dietary conditions. Taken together, the role of protein appears to be complex and is likely to be dependent on the presence of other nutrients available in a mixed diet.

Data from the Framingham Osteoporosis study show that greater protein intake is associated with decreased odds of falling [16], which is an important risk factor for fractures. Results from the same cohort reported that higher protein intake was protective against the risk of hip fracture [14]. Interestingly, when the association of dietary protein with fracture risk was further examined by calcium intake (high or low), greater dietary protein reduced fracture risk by 85% among individuals with calcium intake greater than 800 mg/day [4], whereas the effect may be reversed with low calcium intake. These results suggest that protein may be beneficial to bone only under conditions of adequate calcium intake.

Intervention Studies

Results from short-term feeding studies, which use sensitive calcium isotopic techniques to evaluate protein's impact on calcium homeostasis, have revealed that a high protein diet results in increased intestinal calcium absorption [19,20]. An augmentation in calcium absorption on a high protein diet may explain, in part, the calciuric effects of dietary protein. It is important to note that the positive effects of protein on calcium balance in these studies were limited to individuals on a low calcium diet (600–800 mg/day); at higher calcium intakes, the impact is less evident. An intervention trial evaluated whether supplemental calcium and vitamin D (500 mg+700 IU daily) influenced the associations between dietary protein and bone health in men and women at least 65 years. Overall, this study found that higher protein intake was associated with a favorable 3-year change in bone mineral density

(BMD) only under conditions of calcium plus vitamin D supplementation [5]. Taken together, these results suggest that the positive effect of high protein intakes on bone health may be enhanced by greater calcium intake, perhaps because of increased absorption of calcium.

A randomized controlled trial in women aged 50–70 years, evaluating the effect of a high protein diet (24% caloric intake; ≈86 g/day) on bone health during caloric restriction found that, in comparison to a normal protein diet (18%; ≈60 g/day), individuals on the high protein diet lost less bone over 12 months [10]. The high protein group also showed a significant increase in serum levels of IGF-1 during the intervention compared with the normal protein group. These results suggest that protein was not detrimental to bone, and may in fact be beneficial. However, in a 2-year whey protein supplementation trial in healthy women aged 70–80 years, there was no change in BMD in either the protein-supplemented (30 g/day whey protein; ≈96 g/day total protein) or placebo group (no whey; ≈73 g/day total protein) [11]. Again, serum levels of IGF-1 were significantly higher in the intervention group compared with control. The results from these two studies may differ for a few reasons. First, results from the 1-year trial examined younger women (average age 58 years) compared to the 2-year trial (average age 74 years). Further, bone may respond differently to supplemental protein intake during weight loss (as was observed during the 1-year trial) compared to weight maintenance. Lastly, the 1-year trial increased protein intake via dietary sources (fish, lean meat, legumes, and dairy) and by providing 1 scoop daily of whey protein powder (6 g/day). This is in comparison to the 2-year trial which strictly supplemented protein via a whey protein powder of approximately 30 g/day. The difference in source of protein may alter bone related outcomes. The results from both studies are from populations of healthy, protein-replete women. The effect of protein supplementation in frail populations with chronically low protein intake requires further attention.

Meta-Analysis

A comprehensive review and meta-analysis published in 2009 [21] found that the pooled correlation coefficients from 18 correlational studies (involving men, women, and both sexes combined) were significantly positive, where protein intake was related to greater BMD. Dietary protein explained 1–8% of BMD for lumbar spine, hip, and radius (clinically relevant sites). The same meta-analysis of nine intervention studies showed a positive influence of protein supplementation (total protein up to 20 g/day or milk basic protein up to 40 mg/day) on BMD, but not on bone turnover markers such as osteocalcin or deoxypyridinoline. Further, there was little evidence of a relation between dietary protein and fracture risk. This lack of association may be due to the limited number of studies examined (six included in the meta-analysis) and of the six studies examined, four were cohort studies carried out in younger populations (age range 35–74), where low-impact fractures are less common.

An additional review and meta-analysis published in 2011 by Fenton and colleagues [22] assessed 22 intervention trials, 2 meta-analyses, and 12 prospective cohort designs of bone outcomes (BMD, calcium balance, change in urinary calcium, and resorption markers) among healthy adults in which acid and/or alkaline intakes were manipulated. Overall, this

comprehensive qualitative analysis demonstrated that a causal association between dietary acid load and osteoporotic bone disease is not supported by research and an alkaline diet did not show to be protective of bone health. These two most recent meta-analyses demonstrate that dietary protein is not detrimental to bone health and may positively influence BMD.

Potential Mechanisms

There are many ways in which dietary protein may benefit bone structure and strength. Dietary protein has been shown to increase intestinal calcium absorption [19,20]; decrease bone resorption at the cellular level [19]; increase levels of IGF-1, a key mediator of bone health [19,23]; and improve lean muscle mass and strength [24,25], which may improve BMD via increased loading of bone [26]. It is likely that these pathways are not independent of one another, but are highly interrelated.

An Update from the Most Recent Literature

Updated literature from the last 18 months has broadened to include nonwhite populations, individuals with lower habitual protein intakes, and adults actively pursuing weight loss (a risk factor for low bone density). In a community-based cohort study conducted in Korea, 1182 men and 1393 postmenopausal women (mean age 60 years) provided measurements of bone stiffness index (assessed by quantitative ultrasound of the heel) and dietary protein intake assessed by a validated food frequency questionnaire [12▪]. Mean protein intake (52.3 g/day in men and 45.0 g/day among women) was lower than typical intakes observed in US populations. In multivariable adjusted models, meat protein intake was positively associated with bone stiffness index in men alone. No other measure of protein intake (total, animal, vegetable, or dairy) was significantly associated with bone stiffness index. This study is suggestive of a positive association between meat protein intake and bone health specifically in men. This is one of the few studies showing a sex difference in the association between dietary protein and bone health. The association observed only in men may be because of their greater range of meat protein intake compared with women. It is also unclear whether this association observed in men was due to chance as there was no correction for multiple testing in the statistical analysis.

In a study using a similar population from the Korean National Health and Nutrition Examination Survey, adults 19 years and older were assessed in a cross-sectional study, designed to evaluate the relation between dietary protein and prevalence of osteoporosis [13▪]. In both sexes, the group with the highest protein intake (>20% energy) had significantly lower odds of lumbar spine osteoporosis when compared to the lowest protein intake group (<10% energy). However, in men alone, the odds of osteoporosis at the femoral neck were greater with increasing protein intake. Due to the cross-sectional design of this study, it is possible that this result could be because of reverse causation, where a diagnosis of osteoporosis preceded an increase in dietary protein. Further, calcium intake in this cohort was low which can also contribute to low bone mass.

In a case–control study in Spain, the association of protein intake (total, animal, vegetable, and an animal : vegetable ratio) with osteoporotic fractures was examined in patients at least 65 years [15▪▪]. Cases were defined as patients with a low-impact fracture occurring in the

period 6–24 months before the study inclusion; age-matched and sex-matched controls from the same hospital had no history of fracture in the last 5 years. Overall, no significant associations were observed between any of the protein types and risk of fracture, which could be because the intake levels of protein in cases versus controls were similar. Furthermore, these participants were largely protein replete. However, participants with higher animal-to-plant protein ratio had 62% lower risk of fracture compared to those with lower animal-to-plant protein ratio. These results support the previously raised concerns regarding the importance of food sources of protein in relation to bone health.

Weight loss can cause bone loss. In a recent randomized controlled trial [17▪], 90 premenopausal women (age range 19–45 years) were randomized to one of three calorie restricted diets for 16 weeks: high protein (30% of total energy), high dairy (15% of energy from protein), high calcium (1600 mg/day); adequate protein (15%), medium dairy (7.5%), medium calcium (1000 mg/day); and adequate protein (15%), low dairy (<2%), low calcium (<500 mg/day) [17▪]. A diet high in dairy foods, dietary protein, and calcium significantly increased the bone formation markers (osteocalcin and procollagen 1 amino-terminal propeptide), increased 25-hydroxy vitamin D levels, decreased parathyroid hormone levels, and did not change levels of bone resorption markers. It is impossible to know whether changes in bone biomarkers were due to changes in protein intake or due to the adequate dietary calcium levels in the high protein high dairy group.

Conclusion

Although it was once thought that the acid generating components of a high protein diet were detrimental to bone, an updated review of the literature shows greater protein intake is not harmful to bone. The most recent research suggests the potential positive impact of dietary protein on bone health may be apparent under conditions of adequate calcium intake. The potential interaction between dietary protein and calcium intake in altering bone mass requires further attention. Studies examining specific food sources of protein and their potential differentiating associations with bone health also require more research. Additionally, further understanding of the mechanisms behind how protein modifies bone metabolism, and the interrelation with muscle function, will provide future therapeutic targets in forestalling bone loss with aging. It is of public health importance to create awareness of modifiable lifestyle factors which can improve the health and well-being of adults in an aging population.

Acknowledgments

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Key Points

- Recent research suggests higher protein intake may be beneficial to bone health under conditions of adequate calcium intake.
- The type of protein consumed may be differentially associated with bone health in adults.

Table 1

Associations of dietary protein with measures of bone health in humans

Author, year	Design	Population, *n*	Exposure or intervention	Outcome measure	Results	Interaction with calcium intake
Bone mineral density						
Hannan *et al*. 2000 [7]	Longitudinal, FOP Study	Men and women; mean age 75 years; *n*=615	Total protein, animal protein, FFQ	Femoral neck; lumbar spine; 4-year change	Less loss over 4 years with greater protein intake	Not tested
McLean *et al*. 2011 [8]	Cross-sectional, FOP Study	Women; mean age 60; *n*=1639	Dietary acid load, FFQ	Femoral neck; lumbar spine	No associations in women	No significant interactions observed for either sex
		Men; mean age 61; *n*=1280			No associations in men	
Mangano *et al*. 2013 [9▪]	Cross-sectional, NHANES	Women; mean age 69; *n*=907	Dietary acid load, average of two 24h recalls	Proximal femur; femoral neck; lumbar spine	Increase in proximal femur BMD with greater DAL	Significant inverse association at the proximal femur among men only, with intakes <800 mg/day
		Men; mean age 69; *n*=1218			No associations in men	
Sukumar *et al*. 2011 [10]	RCT, 1-year intervention	Women; mean age 58 years; *n*=47	Weight loss trial: high protein diet (24%); normal protein diet (18%)	Volumetric BMD:radius; lumbar spine; total hip	High protein diet attenuated loss of BMD	Not tested
Zhu *et al*. 2011 [11]	RCT, 2-year intervention	Women; mean age 74 years; *n*=219	Whey protein supplement 30 g/day	Total hip; femoral neck	No significant differences in BMD between intervention and placebo groups	Not tested
Oh *et al*. 2013 [12▪]	Cross-sectional, Korean National Cohort	Women; mean age 60; *n*=1393	Total, animal, vegetable, dairy protein, FFQ	Calcaneal bone density, stiffness index	No significant associations	Not tested
		Men; mean age 59; *n*=1182			Positive association with meat protein intake	

Author, year	Design	Population, *n*	Exposure or intervention	Outcome measure	Results	Interaction with calcium intake
Kim *et al*. 2013 [13▪]	Cross-sectional, KNHANES IV	Men and women; age >19 years; *n*=6952	Total protein, 24h recall	Prevalence of lumbar spine osteoporosis	High protein intake associated with lower odds of osteoporosis	Not tested
Risk of falls or fracture						
Sahni *et al*. 2010 [4]	Longitudinal; (12-year FU), FOP Study	Men and women; mean age 71 years; *n*=3656	Total, animal and plant protein; FFQ	Risk of hip fracture	Greater animal protein associated with reduced risk of hip fracture	High intake of animal protein associated with reduced risk among those with calcium ≥800 mg/day
Misra *et al*. 2011 [14]	Longitudinal (11-year FU), FOP Study	Men and women; mean age 75 years; *n*=946	Total protein; FFQ	Risk of hip fracture	Lower risk of fracture with greater dietary protein	Not tested
Martinez-Ramirez *et al.* 2012 [15▪▪]	Matched case–control study	Men and women; age ≥65 years; *n*=167	Total, animal, plant, animal: plant ratio; FFQ	Low impact fracture	No significant association of any type of protein with fracture	Lower animal protein intake among controls with calcium <800 mg/day
Zoltick *et al.* 2011 [16]	Longitudinal (1-year FU), FOP Study	Men and women; mean age 75 years; *n*=807	Total, animal, plant; FFQ	Risk of falls	Total and animal protein associated with reduced odds of falling among individuals with ≥5% weight loss	Not tested
Markers of bone turnover						
Josse *et al*. 2012 [17▪]	RCT, 16 weeks	Women; age 19–45 years; *n*=90	Three groups: high protein, high dairy; adequate protein, medium dairy; adequate protein, low dairy	OC, PTH, P1NP, 25(OH)D	High protein high dairy group significantly increased OC, P1NP, 25(OH) D and decreased PTH	High calcium intake (1600 mg/day) in the high protein high dairy group

25(OH)D, serum hydroxy vitamin D; BMD, bone mineral density; DAL, dietary acid load; FFQ, food frequency questionnaire; FOP, Framingham Osteoporosis Study; FU, follow-up; KNHANES, Korean National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey; OC, osteocalcin; P1NP, procollagen 1 amino-terminal propeptide; PTH, parathyroid hormone; RCT, randomized controlled trial.