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Review Article

Dietary protein intake and bone health

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Abstract

Considerable attention has recently focused on dietary protein's role in the mature skeleton. The aim was to conduct a systematic review evaluating the effects of dietary protein intake alone on bone health measures in adults (Bone Mineral Density (BMD) and bone biomarkers. Searches across 3 databases were conducted through February 2019 including randomized controlled trials (RCT's) and prospective cohort studies examining the effects of ''high versus low'' protein intake. Studies in various populations are currently limited, varying doses and dietary compositions were used or prescribed, respectively, and there was medium risk of bias among the RCTs and the cohort studies examined. Moderate evidence suggested that higher protein intake may have protective effect on lumbar spine (LS) bone mineral density (BMD) compared with lower protein intake but no effect on total hip (TH), femoral neck (FN), or total body BMD or bone biomarkers. Current evidence shows no adv erse effects of higher protein intakes. Although there were positive trends on BMD at most bone cites, only the LS showed moderate evidence to support benefits of higher protein intake. Studies were heterogeneous. High-quality, long-term studies are needed to clarify dietary protein's role in bone health.

Keywords: Bone biomarkers, Bone health, Bone mineral density, Dietary protein

Introduction

Protein makes up ~50% of bone volume and approximately one-third of its mass. It provides the structural matrix of bone, whereas calcium is the dominant mineral within that matrix. Collagen and a variety of non-collagenous proteins form the organic matrix of bone, so an adequate dietary protein intake would seem to be essential for optimal acquisition and maintenance of adult bone mass. Considerable attention has recently also focused on dietary protein's role in the mature skeleton, prompted in part by an increasing interest in nonpharmacological approaches to maintaining skeletal health in adult life and later adult years.

It is unclear whether dietary protein exerts a positive or negative effect on bone health. The positive association of dietary protein is based on the anabolic effects of protein on bone, via increase of insulin growth factor 1 (IGF-1) and the positive link between dietary protein and calcium absorption by the gastrointestinal track. Contrary protein rich diets are more acidic and thus may lead to bone demineralization[1-3]. Studies that examined the association between protein intake and bone health outcomes are limited. A meta-analysis published in 2017 found that although there were positive trends on BMD at most bone sites, only the LS showed moderate evidence to support benefits of higher protein intake. In light of several new studies and a plethora of available data on bone mineral density (BMD), bone biomarkers, and fracture outcomes, we undertook a comprehensive systematic review in an effort to clarify the impact of dietary protein on these bone health outcomes in healthy adults[4,5].

Materials and methods

The literature's analysis on the dietary protein in the context of bone health was based on the principles of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

The author has no conflict of interest.

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Data sources and searches

Three databases were searched (Medline, Cochrane Central Register of Controlled Trials and EMBASE). The searches were limited to the English language and human studies that examined the relations of protein intake (food or supplement sources) on bone health outcomes of interest.

We included all interventions trials and prospective cohort studies in healthy adults aged >18 years that examined the relations between varying doses of protein intake from any source and bone health outcomes. Any study with an intervention duration <6 months was excluded, and the bone health biomarkers of interest were limited to osteocalcin and collagen type 1 cross-linked C-terminal telopeptide (CTC) as measures of bone formation and bone turnover, respectively. The review concentrated primarily on publications from the last 10 years, but also included highly regarded older publications.

Data extracted included the following: study characteristics, baseline population characteristics, background diet data, dietary assessment methods, intervention (for intervention studies only), cofounders and effect modifiers used in statistical analysis.

Results

RCTs

Several RCTs examined the effect of protein intake in BMD at different body sites in different populations.

RCT's and BMD in lumbar spine

One RCT performed in 424 overweight and obese participants adults on a weight loss effort in 2015 prescribed dietary composition changes of increasing protein intake so as to reach 25% of total energy from protein/d, whereas the control group's diet consisted of 15% of total energy from protein/d and examined LS, TH, FN BMD changes in 24 months. Two-year changes in BMD were 0.005 (P=.04), -0.014 (P<.001), and -0.014 g/cm ^{2} (P<.001), at the spine, TH, and FN, respectively[6].

Another RCT performed in overweight middle-aged subjects (n=130, 59 males) in 2008 on a weight loss effort prescribed 1.4 g protein/ kg of body weight/d and 3 daily servings of dairy/day, whereas the lower-protein group's intervention consisted of 0.8 g protein /kg of body weight/d with 2 daily servings of dairy and examined LS, TH, TB BMD changes in 12 months. At 12 mo, high pro group BMD's was higher by 1.6% (0.3-3.0%) at TB, 2.1% (0.6-3.7%) at LS, and 1.4% (0.2-2.5%) at TH compared with the low protein group's BMD[7].

Another RCT in 323 overweight post-menopausal women in 2013 prescribed a diet plan with >90 g protein/d (High-Protein HP) whereas the control group's diet plan consisted of <80 g protein/d (High-Normal Protein HPN) and examined FN, LS, TH BMD, CTX and OC changes in 24 mths. ANCOVA showed no effect of the HP or HNP diet (P>0.05 for diet and diet-time interactions). A diet-by-time analysis showed that the HNP diet increased C-terminal telopeptide and osteocalcin (P≤0.001 for each) despite hypercalciuria (P=0.029)[8].

Another RCT performed in 208 older women and men with a body mass index between 19 and 32 kg/m ^{2} and a self-reported protein intake between 0.6 and 1.0 g/kg participated in the study. adults in 2015 were asked to incorporate either a 45-g whey protein or isocaloric maltodextrin supplement into their usual diet for 18 months and examined LS, TH, FN BMD, OC and CTX changes in 18 mths. There were no significant differences between groups for changes in L-spine BMD (primary outcome) or the other skeletal sites of interest. C-terminal telopeptide (P=.0414) was also higher in the protein group at the end of the study period[9].

An RCT performed in 82 healthy men in 2009 supplemented the intervention group with 13,2 gr milk-based protein and examined FN, LS and TH BMD changes in 12 mths. There were no main effects of fortified milk at any skeletal site[10].

Another RCT performed in patients >60 yrs with a recent hip fracture in 1998 prescribed 20gr of milk powder 5 d/wk and examined FN, LS and TB BMD, and OC changes in 12 mths. Compared with controls, patients who received protein supplements had an attenuation of the decrease in proximal femur bone mineral density (-2.29% +/- 0.75% and -4.71% +/- 0.77% at 12 months; difference, 2.42 percentage points [CI, 0.26 to 4.59 percentage points]; P=0.029)[11].

Another study performed in healthy overweight/obese post menopausal women in 2011 consisted of increasing protein intake so as to reach 30% of total energy from protein/d whereas the lower-protein group's diet consisted of 18% of total energy from protein/d, and examined FN, LS, TH, TB BMD and OC changes in 12 mths. HP compared with NP diet attenuated loss of BMD at the ultradistal radius, lumbar spine, and total hip and trabecular volumetric BMD and bone mineral content of the tibia. This is consistent with the higher final values of IGF-1 and IGFBP-3 and lower bone-resorption marker (deoxypyridinoline) in the HP group than in the NP group (p<.05). These data show that a higher dietary protein during weight reduction increases serum IGF-1 and attenuates total and trabecular bone loss at certain sites in postmenopausal women[12].

Overall a higher protein intake may cause less LS BMD loss than lower protein intake in older adults. Three RCTs (2 in older men and 1 in postmenopausal women) found this effect, whereas 4 (2 in healthy adults, 1 in postmenopausal women, and 1 in older adults with current hip fracture) found that protein intake had no significant effect on LS BMD. Studies in various populations are currently limited, varying doses and dietary compositions were used or prescribed, respectively, and there was medium risk of bias among the RCTs.

RCT's and BMD in femoral neck

A study performed in healthy post menopausal women in 2011 consisting of supplementing the intervention's daily menu with 30 gr of protein (skim milk and whey protein isolate) in comparison with the placebo group that received plain skim milk (2,1 gr protein) and examined FN and TH BMD changes in 24 mths. Quantitative computed tomographic (QCT) hip volumetric bone mineral density (vBMD) and a femoral neck engineering strength analysis were undertaken at baseline and at 2 years. There was a significant decrease in hip DXA aBMD and QCT vBMD over 2 years with no between-group differences[13].

Another RCT performed in lean, post-menopausal patients with recent femoral neck fracture in 2007 supplementing the intervention's group diet with an oral nutritional supplement containing 20 gr of milk-based protein examined TB, FN BMD and OC and CTX. The analyses showed an increase in total body BMD at 6 and 12 months in patients who received protein-rich supplementation. Osteocalcin increased in all groups while no significant changes were found for CTX[14].

Protein intake amount does not affect FN BMD loss. Although RCTs overall did not find protein intake to significantly affect FN BMD in various populations, studies in each population are limited, varying doses were used, and there was medium risk of bias.

RCT's and BMD in total hip

A study performed in 2014 in 79 hip fracture patients with a recent hip fracture, without severe cognitive impairment were randomized to treatment with bisphosphonates (risedronate 35 mg weekly) for 12 months (B; n=28), treatment with bisphosphonates along with nutritional supplementation (40 g protein, 600 kcal daily) for the first 6 months (BN; n=26), or to controls (C; n=25). All participants received calcium (1,000 mg) and vitamin D3 (800 IU) daily. Analysis of complete cases (70/79 at 6 months and 67/79 at 12 months) showed an increase in total hip BMD of 0.7% in the BN group, whereas the B and C groups lost 1.1% and 2.4% of BMD, respectively, between baseline and 6 months (P=0.071, between groups). There was no change in total body BMD between baseline and 12 months in the BN group, whereas the B group and C group both lost BMD, with C losing more than B (P=0.009)[15].

Protein intake amount does not affect TH BMD loss. Most of the RCTs did not find protein intake to significantly affect TH BMD in various populations, and only 2 studies found a difference. Studies in each population are also limited, varying doses were used, and there was medium risk of bias.

RCT's and BMD in total body

Another RCT performed in healthy overweight/obese adults in 2010 consisted of diet plans to achieve weight loss based on 500 kcal deficit of participant's estimated resting metabolic rate and in the intervention group the diet plan consisted of 2,2 gr of protein/kg of body weight/day, whereas the intervention group received diet plans consisted of 1,1 gr of protein/kg of body weight/ day and examined TB BMD changes in 13 mths. There was no significant change noted in bone mineral density by DEXA (HP 0.04±0.19 g/cm^2, p=0.210; SP -0.03±0.17 g/cm^2, p=0.320) in either group over one year[16].

Higher protein intake may cause less TB BMD loss than lower protein intake. Two RCTs (1 in postmenopausal women with FN fractures and 1 in men) found this effect, whereas 3 (1 in postmenopausal women, 1 in adults with recent hip fracture, and 1 in adults) found that protein intake had no significant effect on TB BMD. Multiple studies in various populations are currently limited, varying doses and dietary compositions were used or prescribed, respectively, and there was medium ROB among the RCTs.

Cohort studies

The prospective analysis published 2014 included 144,580 women aged 50-79 y at baseline in the Women Health Initiative (WHI) clinical trials (CTs) and observational study (OS) that recruited participants in 1993-1998 with follow-up through 2011. BMDs for total body, hip, and spine were measured at baseline and 3 and 6 y in 9062 women at 3 WHI clinics by using dual-energy X-ray absorptiometry. Protein intake was assessed via food-frequency questionnaire and calibrated by using biomarkers of energy and protein intakes. Each 20% increase in calibrated protein intake was associated with a significantly higher BMD for total body (mean 3-y change: 0.003 g/cm^2; 95% CI: 0.001, 0.005 g/cm^2) and hip (mean 3-y change: 0.002 g/cm^2; 95% CI: 0.001, 0.004 g/cm^2)[17].

Associations between protein intake and change in BMD were examined in 342 healthy men and women (aged > or = 65 y) who had completed a 3-y, randomized, placebo-controlled trial of calcium and vitamin D supplementation. Protein intake was assessed at the midpoint of the study with the use of a food-frequency questionnaire and BMD was assessed every 6 mo by dual-energy X-ray absorptiometry. The mean (+/-SD) protein intake of all subjects was 79.1 +/- 25.6 g/d and the mean total calcium intakes of the supplemented and placebo groups were 1346 +/- 358 and 871 +/- 413 mg/d, respectively. Higher protein intake was significantly associated with a favorable 3-y change in total-body BMD in the supplemented group (in a model containing terms for age, sex, weight, total energy intake, and dietary calcium intake) but not in the placebo group. The pattern of change in femoral neck BMD with increasing protein intake in the supplemented group was similar to that for the total body[18].

The relation between baseline dietary protein and subsequent 4-year change in bone mineral density (BMD) for 391 women and 224 men from the population-based Framingham Osteoporosis Study was examined. BMD (g/cm^2) was assessed in 1988-1989 and in 1992-1993 at the femur, spine, and radius. Usual dietary protein intake

was determined using a semiquantitative food frequency questionnaire (FFQ) and expressed as percent of energy from protein intake. BMD loss over 4 years was regressed on percent protein intake, simultaneously adjusting for other baseline factors: age, weight, height, weight change, total energy intake, smoking, alcohol intake, caffeine, physical activity, calcium intake, and, for women, current estrogen use. Mean protein intake was 68 g/day (+/-24.0; range, 14-175 g/day), and mean percent of energy from protein was 16% (+/-3.4; range, 7-30%). Lower protein intake was significantly related to bone loss at femoral and spine sites (p< or =0.04) with effects similar to 10 lb of weight. Persons in the lowest quartile of protein intake showed the greatest bone loss. Even after controlling for known confounders including weight loss, women and men with relatively lower protein intake had increased bone loss, suggesting that protein intake is important in maintaining bone or minimizing bone loss in elderly persons[19].

In 2008 a 30-month study investigating bone change and its determinants in 438 perimenopausal Chinese women was published investigating change in bone mineral density and its determinants in Hong Kong Chinese perimenopausal women. Bone mass, body composition, lifestyle measurements were obtained at baseline and at 9-, 18- and 30-month follow-ups. Among different parameters soy protein intake was protective for total body BMC[20].

The associations of total, animal, and vegetable protein with bone mineral density (BMD) were studied in a community-dwelling cohort of 572 women and 388 men aged 55-92 years (Rancho Bernardo, California). Protein intake was assessed by food frequency questionnaires in 1988-1992, and BMD, measured 4 years later. For every 15-g/day increase in animal protein intake, BMD increased by 0.016 g/cm^2 at the hip (p=0.005), 0.012 g/cm^2 at the femoral neck (p=0.02), 0.015 g/cm^2 at the spine (p=0.08), and 0.010 g/cm^2 for the total body (p=0.04). Conversely, a negative association between vegetable protein and BMD was observed in both sexes[21].

A longitudinal prospective study of up to 5 years on a convenience sample of 156 healthy college-aged women published in 2002 researched the bone mineral densities of the spine, forearm, and total body by dual- and single-photon absorptiometry in association with estimates of nutrient intake by repeated 7-day diet diaries. The median gain in bone mass for the third decade of life, expressed as a percentage per decade, was 4.8% for the forearm, 5.9% for lumbar bone mineral content, 6.8% for lumbar bone mineral density, and 12.5% for total body bone mass (P<.0001 in all cases). The rate of gain in bone density of the spine was negatively correlated with age and positively correlated with calcium/protein intake ratio (multiple r=.31; P=.004)[22].

At the Framingham Offspring Study, in 1280 men and 1639 women, the association of percentage of total energy intake from protein (protein intake %) with bone mineral density (BMD, g/cm^2) and bone loss at the femoral neck, trochanter and lumbar spine (L2-L4) and (ii) Ca as an effect modifier was investigated. In the cross-sectional analyses, protein intake % was positively associated with all BMD sites (P range: 0·02-0·04) in women but not in men. Significant interactions were observed with total Ca intake (<800 mg/d v. ≥800 mg/d) in women at all bone sites (P range: 0·002-0·02). Upon stratification, protein intake % was positively associated with all BMD sites (P range: 0·04-0·10) in women with low Ca intakes but not in those with high Ca intakes. In the longitudinal analyses, in men, higher protein intake % was associated with more bone loss at the trochanter (P= 0·01) while no associations were seen in women, regardless of Ca intake[23].

Cohort studies overall did not support this association between higher protein intake and LS BMD loss, although there may be risk of bias because of loss to follow-up or because it is unclear if they had adequate sample size and power to detect an association. Two cohort studies also found no association between protein intake and TH BMD loss, although it is important to note that the number of cohort studies included were limited with medium risk of bias. Some cohort studies found no association between higher protein intake and BMD loss, although 2 in older adults reported high protein intake to be associated with less BMD loss. Cohort studies overall supported this association between higher protein intake and less TB BMD loss.

Discussion / Conclusion

Based on the current research presented, there may be little benefit of increasing protein intake for bone health in healthy adults with an adequate protein intake but there is clearly no indication of any detrimental effect. A large number of the presented research had as primary aim weight loss and moreover showed protein intakes that meet protein intake recommendations. Results of the analysis could differ if persons with a low protein intake (<0,8 gr protein/day) were included. The opposing anabolic (uptake of calcium by the gut, impact on IGF-1) and catabolic actions of dietary protein (increase of acidic load of diet) may cancel each other out to some extent.

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