Benefits and safety of dietary protein for bone health—an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation

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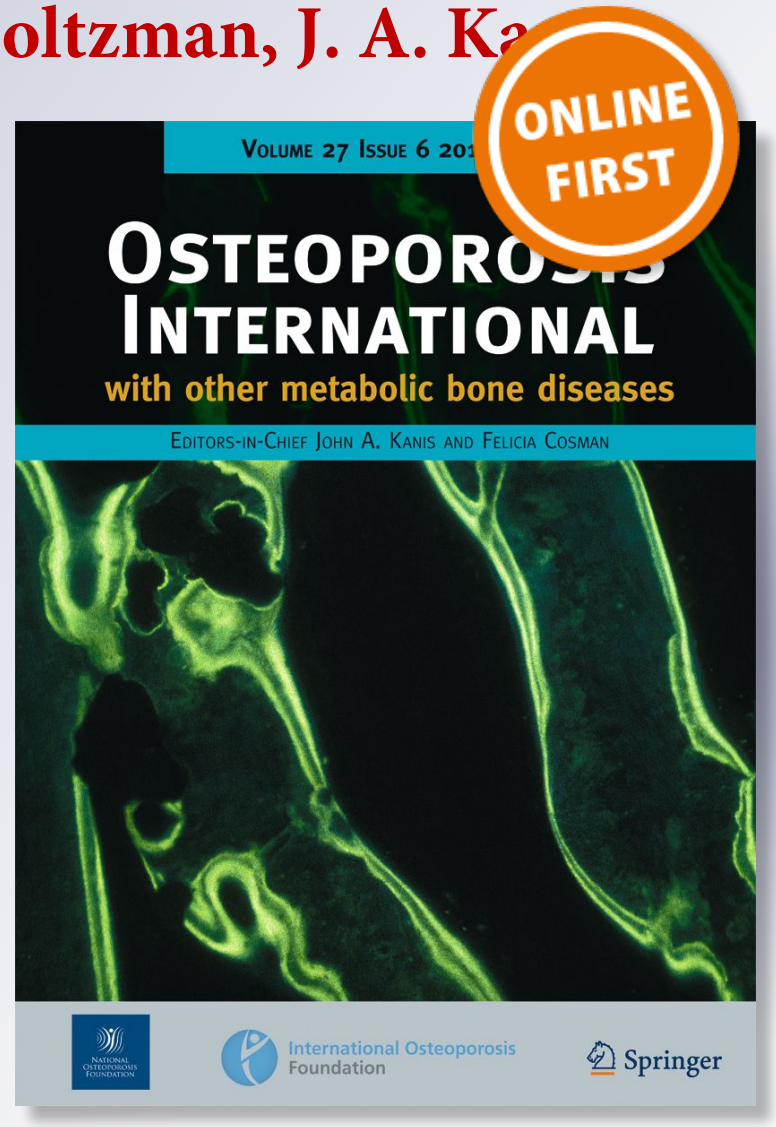
Osteoporosis International
With other metabolic bone diseases

ISSN 0937-941X

Osteoporos Int
DOI 10.1007/s00198-018-4534-5



Springer

Osteoporosis International
https://doi.org/10.1007/s00198-018-4534-5

REVIEW

Benefits and safety of dietary protein for bone health—an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation

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Received: 11 January 2018 / Accepted: 12 April 2018

Abstract

A summary of systematic reviews and meta-analyses addressing the benefits and risks of dietary protein intakes for bone health in adults suggests that dietary protein levels even above the current RDA may be beneficial in reducing bone loss and hip fracture risk, provided calcium intakes are adequate. Several systematic reviews and meta-analyses have addressed the benefits and risks of dietary protein intakes for bone health in adults. This narrative review of the literature summarizes and synthesizes recent systematic reviews and meta-analyses and highlights key messages. Adequate supplies of dietary protein are required for optimal bone growth and maintenance of healthy bone. Variation in protein intakes within the "normal" range accounts for 2–4% of BMD variance in adults. In older people with osteoporosis, higher protein intake (≥ 0.8-g/kg body weight/day, i.e., above the current RDA) is associated with higher BMD, a slower rate of bone loss, and reduced risk of hip fracture, provided that dietary calcium intakes are adequate. Intervention with dietary protein supplements attenuate age-related BMD decrease and reduce bone turnover marker levels, together with an increase in IGF-I and a decrease in PTH. There is no evidence that diet-derived acid load is deleterious for bone health. Thus, insufficient dietary protein intakes may be a more severe problem than protein excess in the elderly. Long-term, well-controlled randomized trials are required to further assess the influence of dietary protein intakes on fracture risk.

Keywords Acid-base homeostasis · Bone mineral density · Bone turnover · Dairy products · Fracture · Osteoporosis

IOF Committee of Scientific Advisors and Committee of National Societies

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Published online: 08 May 2018

Introduction

Adequate dietary protein intakes are necessary for optimal growth and maintenance of structure and function of many organs including the musculo-skeletal system [1]. In adults, the current Recommended Dietary Allowance (RDA) is 0.8 g of protein per kg of body weight [2]. For the elderly, higher intakes have been proposed, i.e., 1.0–1.2-g protein/kg body weight × day, and even 1.2–1.5 g/kg body weight × day for preserving muscle function [3]. This particularly concerns older subjects who are malnourished or at risk of malnutrition because of acute or chronic illness or injury.

Several recent extensive systematic reviews and meta-analyses have addressed the issue as to whether high dietary protein intakes would exert deleterious effects on bone and thus be associated with increased fracture risk [4–7]. Indeed, based on studies in which the administration of large amount of acid was increasing bone resorption, it has been claimed that a diet rich in compounds whose metabolism is generating acid would lead to low-grade metabolic acidosis, impairing thereby osteoblast function, stimulating osteoclast survival and activity, increasing bone resorption, and decreasing bone mass and strength (for review see [8]). This has raised numerous debates, sometimes more emotional than based on evidence [9]. Various systematic reviews and meta-analyses have specifically assessed dietary acid load and bone health [8, 10–13].

In light of these abundant series of data and analyses, the aim of the present paper is to summarize and synthesize these recent systematic reviews and meta-analyses, to complete them by an extensive narrative review of the literature and to highlight their take home messages. These analyses have concluded that there is no adverse effect of higher protein intakes on bone, with even benefits in attenuating age-related bone loss and reducing hip fracture risk and that a causal link between dietary acid load and osteoporosis is not supported by clinical evidence.

Methods

This commentary reflects the discussion of a working group that reviewed the current evidence linking bone health and dietary protein intakes up to 2017. It is based on an extensive narrative literature review, focusing on the most robust evidence such as a series of recent meta-analyses of bone outcomes, i.e., fracture and bone mineral density, in relation with dietary protein intakes, which formed the search criteria in PubMed. A special emphasis was given to the safety, in particular to acid-base homeostasis.

Dietary protein and fracture risk

No randomized controlled trial has examined the effect of dietary protein on fracture risk, irrespective of the fracture site. Rather, evidence is derived from prospective cohort studies. Four systematic reviews and meta-analyses have assessed this issue since 2009 (Table 1). Darling et al. found no significant reduction in hip fracture risk comparing the highest with the lowest quartile/quintile of dietary protein intakes in four cohort studies (RR 0.75; 95% CI 0.47–1.20) [4]. Separating animal and vegetable protein in these studies did not modify the conclusion (RR 0.83 [0.54–1.30] and 1.21 [0.82–1.79], for animal and vegetable proteins, respectively).

Wu et al. included 12 longitudinal cohort studies in their analysis, representing more than 400,000 subjects [5]. Pooling six cohorts with data on hip fracture risk, they found a relative risk of 0.89 [0.82–0.97] comparing the highest to the lowest quartile/quintile of dietary protein intakes. There was no effect on all fractures (four studies) or on limb fractures (two studies) of total protein intakes. For animal protein consumption, relative risk of all fractures and hip fracture was 0.79 [0.32–1.96] and 1.04 [0.70–1.54], respectively; for vegetable protein consumption, the corresponding values were 0.77 [0.52–1.12] and 1.00 [0.53–1.91]. The conclusion was that total dietary protein consumption could slightly decrease the risk of hip fracture.

In a 2017 systematic review, Shams-White et al. assessed the effects on bone health outcomes of dietary protein intakes with and without calcium in adults [6]. The systematic review included 16 randomized controlled intervention trials and 20 prospective cohort studies. Regarding fracture risk and dietary protein, the authors reviewed 12 cohort studies, five in postmenopausal women, two in men, and five in both men and women. Among the nine studies with data on hip fracture, six were interpreted as showing no association with dietary protein intakes and three with some inverse relationship between hip fracture risk and protein intakes. For overall fracture, there was no association in three studies, while a fourth study detected an inverse relation in the highest versus the lowest quintile of soy protein intakes [14]. The conclusion was that higher protein intakes had no adverse effects on bone.

In the systematic review and meta-analysis by Wallace and Frankenfeld [7], 60 randomized controlled trials and 13 prospective cohort studies conducted in healthy individuals older than 18 years and with dietary protein intakes at or above the RDA of 0.8-g/kg BW × day (or 10–15% of total caloric intake) were analyzed. To illustrate the magnitude of the difference between controls and higher protein intakes in the analysis of RCTs, mean protein intakes were 65.5 ± 19.6 and 113.0 ± 38.2 g/day, respectively. Meta-analysis of the cohort studies showed that high vs low dietary protein intakes were associated with a reduction of 16% of hip fracture risk, with a relative risk of 0.84 [0.73–0.95]. This refers to five studies out

Table 1 Summary of the systematic review and meta-analyses investigating the associations between protein intakes and hip fractures in observational studies in adults

Reference	Darling et al. 2009 [4]	Wu et al. 2014 [5]	Shams-White et al. 2017 [6]	Wallace et al. 2017 [7]
Type of review	Meta-analysis	Meta-analysis	Systematic review	Meta-analysis
Year of last search	2008	2014	2016	2017
Inclusion criteria	All relevant studies investigating the relation between protein and bone health in healthy human adults.	PCS examining protein consumption and fractures with relative risk estimates and 95% confidence intervals were reported or could be calculated by data reported.	RCT and PCS examining the effects of "high versus low" protein intake or dietary protein's synergistic effect with calcium ± vitamin D intake on bone health outcomes.	RCT and PCS examining the relationships between various protein intakes at or above the current U.S. RDA (0.8 g/kg/d or 10%–15% of total caloric intake) from any source.
Included studies hip fracture outcome				
- Beasley et al. 2014, women [19]		✓	✓	✓
- Cauley et al. 2016, men [20]			✓	
- Feskanich et al. 1996 [16]	✓	✓	✓	
- Fung et al., 2017, women and men [21]				✓
- Koh et al. 2009, women and men [23]			✓	
- Meyer et al. 1997, Women and Men [32]			✓	
- Misra et al. 2011, women and men [15]		✓	✓	✓
- Munger et al. 1999, women [26]	✓	✓	✓	✓
- Mussolino et al. 1998, men [27]	✓	✓	✓	✓
- Sahni et al. 2010, women and men [17]		✓	✓	
Conclusion	No significant difference in risk of hip fractures between the highest and lowest quintile/quartile of protein intake: RR 0.75 (0.47, 1.20)	11% decrease in hip fractures between the highest vs. the lowest category of total dietary protein consumption: RR 0.89 (0.82, 0.97)	Insufficient data for dose-response meta-analysis: 6 studies no association; 1 study in men: inverse association; 1 study in women and men: inverse association in women, not in men; 1 study in women and men: inverse association	16% decrease in hip fractures between high versus low intake of protein: RR 0.84 (0.73, 0.95)

RCT, randomized controlled trials; PCS, prospective cohort studies; RDA, recommended dietary allowance

of the 13, which included men (one), women (two), or both sexes (two) [15]. There was no difference in hip fracture outcome between animal and vegetable proteins. The conclusion was that dietary proteins at or above the current RDA could be beneficial for reducing hip fracture risk.

To further address the possible discrepancies between the meta-analyses results, an extensive narrative review of the various cohort studies (and two case-control studies) with fracture as outcome in relation to dietary protein intakes is presented in Table 2. Not all were included in the various meta-analyses. Three studies reported an increase in fracture risk in relation with dietary protein intakes over a follow-up of 7 to 12 years. In the large Nurses' Health Study, an increase of forearm fracture risk in the subjects with the highest protein intake of animal origin was found [16]. In the Framingham Offspring Study, higher hip fracture risk was detected in those with higher protein intake and a calcium intake in the lowest quartile [17]. In the Study of Osteoporotic Fractures (SOF), higher animal protein intake increased the risk of hip fractures (RR 2.84), while higher vegetable protein intake was protective (RR 0.30) [18].

In 13 cohort and one case-control studies, relative fracture risks or odds ratios were lower with higher dietary protein intakes [14, 15, 17, 19–29]. For 12 of these, a statistically significant lower value was reported and numerically lower, but not significant for two [22, 27] (Table 2). In the pooled Health Professionals Follow-up and Nurses' Health Study, the lower hazard ratio for hip fracture was similar in magnitude for total, animal, vegetable, and dairy proteins [21]. In two cohort studies, one for hip and one for all fragility fracture, a lower fracture risk was found in women but not in men [23, 24]. In contrast, in the Osteoporotic Fractures in Men Study (MrOS) cohort, hazard ratio was 0.84, 0.80, and 0.84 for total, dairy, and non-dairy animal proteins, respectively, while it was 0.99 for vegetable protein [25]. In a prospective study carried out on more than 40,000 women in Iowa, higher protein intake was associated with a reduced risk of hip fracture [26]. The protective effect was mostly observed with dietary protein of animal origin. In the Framingham Offspring Study, lower relative hip fracture risk (0.15) was detected in those with higher protein intakes and a calcium intake above 800 mg/day [17]. In a case-control study, increasing protein intake was associated with a lower hip fracture risk of 65% in the highest quartile in the 50- to 69-year-old age class [29]. Relative risk of all types of fractures was lower in those with a higher consumption of soy protein in the Shanghai Women's Health Study [14].

In five prospective cohort studies [16, 19, 30–32], there was no association between hip or all fragility fractures and dietary protein intakes, except a relative risk of 1.51 in the first quartile of calcium intake in one study [30].

Based on 4 systematic reviews with meta-analyses for 3 and a review of additional observational studies, it appears that hip fracture risk is modestly decreased with higher dietary protein intakes, provided calcium intakes are adequate.

Dietary protein and bone mineral density

The operational definition of osteoporosis is based on the value of areal bone mineral density (BMD), which is an important determinant of bone strength, hence of fracture risk [33]. The association between BMD and dietary protein intakes has been investigated in three recent systematic reviews and meta-analyses [4, 6, 7]. In Darling's review, 15 cross-sectional studies reported a significant positive association between BMD and dietary intakes at at least one skeletal site, whereas 18 studies did not show any association. Variations in protein intakes between approximately 0.8 and 1.2 g/kg body weight/day, thus above the RDA, accounted for 2 to 4% of BMD variance in adults [4]. In two out of five cohort studies, femoral neck bone loss was lower with higher dietary protein intakes. Among 18 intervention studies with various supplements, populations, and durations, nine had BMD as outcome. Three reported a significant difference with protein supplements as compared with controls at at least one skeletal site. Pooling three studies in a meta-analysis, a significant effect of protein supplements was observed at the lumbar spine level. There was no difference when looking at soy protein (three studies) or milk basic protein (two studies).

In an extensive analysis, Shams-White et al. [6] extracted data from 20 prospective cohort studies and 16 randomized controlled trials. Regarding cohort studies conducted for an up to 4.6-year follow-up period, six out of seven for lumbar spine and three out five for femoral neck did not show any significant association between BMD changes and dietary protein intakes. For one with lumbar spine and two with femoral neck, BMD decrease over time was less in those in the highest category of dietary protein intakes. In a meta-analysis of five RCT with lumbar spine BMD as outcome, higher protein intake was associated with + 0.52% change difference (95% CI 0.06–0.97). For femoral neck, six studies were pooled, without any difference between high protein intakes and controls.

In five cohort studies extracted from the 13 included in their review, Wallace and Frankenfeld reported a higher lumbar spine BMD in relation to dietary protein intakes in two studies [7]. For femoral neck, three out of five studies did show some improvement in BMD in the highest versus the lowest category of dietary protein, with a follow-up duration of 1 and 4 years. Regarding intervention trials, three assessed protein supplements on lumbar spine, with one showing an improvement in BMD with protein intakes at 163% of RDA for 26 weeks. For femoral neck, one out of two trials having

Table 2 Relationship between osteoporotic fracture risk and dietary protein intakes (cohort studies; *: case-control studies)

Reference	Population	*N*	Mean protein intake	Follow-up duration (years)	Outcome (fracture)	Effects of proteins
Positive association						
Feskanich et al. 1996 [16]	Women (35–59 y) Nurses' Health Study	85,900	79.6 g/day (median)	12	Forearm	Quintile 5 vs quintile 1 of protein intake (g/day): RR **1.22** (total), **1.25** (animal)
Sahni et al. 2010 [17]	Men (55.3 ± 9.9 years) and women (54.9 ± 9.8 y) Framingham Offspring Cohort	3656	79.0 g/day in men 75.7 g/day in women	12	Hip	Tertile 3 vs tertile 1 of protein intake (g/day): HR **2.84** (animal protein, if calcium intake < 800 mg/day)
Sellmeyer et al. 2001 [18]	Women (> 65 years) Study of Osteoporotic Fractures	1035	49.8 g/d	7	Hip	Quintile 5 vs quintile 1 of energy-adjusted protein intake: RR **2.7** (animal), **0.30** (vegetable)
Inverse relationship						
Beasley et al. 2014 [19]	Postmenopausal Women (50–79 y) WHI Study	144,580	15% total kcal intake (median) (calibrated)	6	Forearm Hip	Per 20% increase in daily calibrated protein intake: HR **0.93** HR **0.91**
Cauley et al. 2016 [20]	Men (≥ 65 years) MrOS study	5876	16.1% total energy intake	8.6	Hip	HR **0.82** per SD increase of protein intakes (2.9% of energy intake) in multivariate-adjusted model.
Fung et al. 2017 [21]	Men & postmenopausal women ≥ 50 years, Health Professionals Follow-up & Nurses' Health Study	35,439 men 74,443 women	91.3 (M) and 74.4 (W) g/d	32	Hip	Per 10-g increase of protein intake (pooled data): HR **0.96** (total), **0.95** (animal), **0.88** (vegetable), **0.91** (dairy protein)
Huang et al. 1996 [22]	Women ≥ 45 years NHANES I Study	2513	56.6 g/day	16	Hip	HR 0.89 (NS, age adjusted) per SD increase of protein intake:
Koh et al. 2009 [23]	Women & men (45–74 y) Singapore Chinese Health Study	63,257	2.7–7.6 g/day interquartile range soy protein	> 8	Hip	Quartile 4 vs quartile 1 of soy proteins: HR **0.79** (women), 1.11 (NS) (men)
Langsetmo et al. 2015 [24]	Men and women ≥ 50 year CaMos Study	4570	56.9 g/day (median)	13	All fragility	Quartile 3 (14.1–15.7%) vs quartile 1 of % of total energy intake in age-adjusted models: RR **0.71** (women), 0.66 (NS) (men) No heterogeneity by source of proteins.
Langsetmo et al. 2017 [25]	Men (73.6 ± 5.9 years) MrOS Study	5875	16.1% total energy intake	10.5–11.2	Major osteoporotic Hip	Per one SD increase of proteins intakes as % of total energy intake in multi-adjusted models: HR **0.92** (total), 0.89 (dairy), 0.92 (non-dairy animal), 0.96 (vegetable) HR **0.84** (total), **0.80** (dairy), **0.84** (non-dairy animal), 0.99 (vegetable)
Misra et al. 2011 [15]	Men and women (75 years) Framingham Osteoporosis Study	946	68 g/day	15	Hip	Quartile 3 vs quartile 1 of energy-adjusted protein intake: HR **0.56** (NS for women only)
Munger et al. 1999 [26]	Postmenopausal women (55–69 years) Iowa Women's Health Study	32,050	1.2 g/kg × day	3	Hip	Quartile 4 vs quartile 1 of energy-adjusted protein intake in multivariate-adjusted models: RR **0.44** (total), **0.31** (animal), 1.92 (vegetable)
Mussolino et al. 1998 [27]	Men (44–74 years) NHANES I	2879	80.6 g/day	22	Hip	Per SD increase of proteins intakes: RR: 0.55 (NS)
Sahni et al. 2010 [17]		3656	79.0 in men 75.7 in women	12	Hip	Tertile 3 vs tertile 1 of protein intake (g/day): HR **0.15** (animal protein, if calcium intake ≥ 800 mg/d

Table 2 (continued)

Reference	Population	*N*	Mean protein intake	Follow-up duration (years)	Outcome (fracture)	Effects of proteins
	Men (55.3 ± 9.9 years) and women (54.9 ± 9.8 years) Framingham Offspring Cohort					
Thorpe et al. 2008 [28]	Peri- & postmenopausal women (≥ 45 year)	1865		25	Forearm	RR **0.44** (meat > 4×/week vs never), **0.42** (cheese > 3×/week vs < 1×/week). 0.79 (vegetable 1×/d vs < 3×/week, NS)
* Wengren et al. 2004 [29]	Men and women (50–89 years)	2501	1.2 g/kg × day		Hip	Quartile 4 vs quartile 1 of energy-adjusted protein intake in multivariate-adjusted models in 50–69 years group: OR **0.35** (total), **0.43** (animal), **0.52** (vegetable) in 50–69 years group: all NS
Zhang et al. 2005 [14]	Postmenopausal women (40–70 years) Shanghai Women's Health Study	24,403	8.5 g/day median soy protein intake	5	All	Quintile 5 vs quintile 1 of soy protein intake: RR **0.63**
No association						
Beasley et al. 2014 [19]	Postmenopausal women (50–79 years) WHI Study	144,580	15% total kcal intake (median) (calibrated)	6	All Hip	Per 20% increase in daily calibrated protein intake: HR 0.99 HR 0.91
Dargent-Molina et al. 2008 [30]	Postmenopausal women (40–65 years) E3N Study	36,217	1.45 ± 0.43-g/kg BW	12	All	Quartile 4 vs quartile 1 of energy-adjusted protein intake in multivariate-adjusted models: RR 1.06 (total), 1.10 (animal), 0.95 (vegetable) RR **1.51** (total) in 1st quartile of calcium intake Quartile 4 vs quartile 1 of body-weight adjusted protein intake in multivariate-adjusted models: RR 1.02 (total) RR **1.46** (total) in first quartile of calcium intake
Feskanich et al. 1996 [16]	Women (35–59 years) Nurses' Health Study	85,900	79.6 g/day (median)	12	Hip	Quintile 5 vs quintile 1 of protein intake (g/day): RR 0.96 (total), 0.98 (animal protein), 1.11 (vegetable) RR 0.90 (vegetable)
Key et al. 2007 [31]	Men and women (20–89 y) EPIC Study	34,696	72.4 g/day	5.2	All	Protein intake > 90 g/day vs < 55 g/day: Incidence rate ratio 0.97 (women), 1.29 (men) (NS)
Meyer et al. 1997 [32]	Men and women (47.1 years)	19,752	0.8 g/kg × day	11.4	Hip	Quartile 4 vs quartile 1 of non-dairy animal protein intake: HR 0.96 (women), 1.3 (men) (NS)
* Nieves et al. 1992 [99]	Women (50–103 years)	329	< 24 to ≥ 55 g/day		Hip	Quintile 5 vs quintile 1 of protein intake (g/day) in multivariate-adjusted model: OR 1.04

In bold: statistically significant values. NHANES: National Health and Nutrition Examination Survey. CaMos: Canadian Multicentre Osteoporosis Study. EPIC: European Prospective Investigation of Cancer

assessed BMD changes showed an improvement with protein at 150% of RDA after 104 weeks.

In a randomized placebo controlled trial, conducted in vitamin D and calcium replete patients with a recent hip fracture, a protein supplement of 20 g per day for 6 months led to a 50% reduction in proximal BMD decrease at 1 year [34]. In terms of mechanisms involved, an estimation of bone strength of peripheral skeleton sites, using finite element analysis, showed a dose-dependent positive association between predicted failure load and total, animal, and dairy protein intakes [35].

BMD, which is an important determinant of bone strength, appears to be positively associated with dietary protein intakes.

Dietary protein-calcium interaction

When assessing fracture risk, three studies found some interaction between protein and calcium intakes for fracture risk [17, 30, 32], and one did not for forearm fracture [19]. Two studies detected higher hip fracture risk in subjects with a calcium intake in the lowest quartile or lower than 800 mg/day [17, 32]. In another study, higher fracture risk in relation with higher protein intakes was observed in the lowest quartile of calcium intake but not in the higher calcium quartiles [30]. In their systematic review, Shams-White et al. reported four cohort studies in which an interaction between protein and calcium-vitamin D on BMD at various sites was assessed [6]. A significant interaction was found in a calcium-vitamin D intervention trial [36]. Only in the calcium-vitamin D supplemented group, higher protein intake was associated with better femoral neck and total body BMD outcomes. Thus, a negative, respectively positive association between fracture risk or BMD and dietary proteins seems to require adequate calcium intakes. Conversely, in the same trial, the positive effects of calcium-vitamin D supplementation on femoral neck BMD was more evident in the highest dietary protein tertile [36]. There was an estimated + 2.8% points difference in femoral neck BMD between the higher and lower dietary protein tertiles.

Dairy products are a source of both proteins and calcium, since 1 l of milk provides 32 g of proteins and 1200 mg of calcium. In certain countries, yogurts are enriched in milk powder, leading to an up to 50% increased content of these nutrients as compared with yoghurt prepared from plain milk. For Swiss cheese, protein and calcium contents are 26 g/100 g and 890 mg/100 g, respectively [37]. Numerous studies have addressed the hypothesis of a favorable influence of both protein and calcium supplementation on bone health variables, through dairy products administration, in randomized controlled trials [38–68] (Table 3). These trials were relatively small, including between 11 and 408 subjects, precluding thus the assessment of fracture risk. The length of follow-up was between 1 week and 2.5 years, with a large variety of studied populations and outcomes. Altogether, dairy products, some being fortified with calcium or vitamin D, were consistently associated with a decrease in circulating PTH, an increase in IGF-I, and a decrease in bone resorption markers. In 13 studies, BMD changes were assessed. In 10 of them, a blunted decrease and even an increase in BMD were observed in response to dairy products, depending on the age of the subjects. The effects of dairy products specifically attributable to fermented compounds have been recently reviewed [69] and are in agreement with those of other dairies. It remains to be established whether pre- and probiotics contained in fermented dairy products provide additional benefits.

Protein and calcium combined in dairy products have beneficial effects on calciotropic hormones, bone turnover markers and BMD. The benefit of dietary proteins on bone outcomes seems to require adequate calcium intakes.

Effects of dietary protein on acid-base status and bone

There has been much debate on the "acid-ash hypothesis," which theorizes that metabolism of high protein intake (particularly of animal origin with sulfur containing amino acids) leads to increased acid production and increased bone resorption, in turn producing hypercalciuria, bone loss, and osteoporosis (for review see [8]). However, transient changes from steady state experimental data should be distinguished. The hypothesis that bone contributes to acid-base homeostasis was supported by experiments in healthy subjects or in patients with chronic renal failure indicating that the administration of large doses of ammonium chloride led to a marked decrease in serum bicarbonate, an increase in urinary calcium excretion, and a negative calcium balance [70], which was attributed to the mobilization of calcium carbonate from bone mineral to buffer the acid load. Conversely, the administration of potassium bicarbonate to healthy postmenopausal women [71] or to patients with chronic renal failure and metabolic acidosis [72] was associated with an improvement in calcium balance. Several studies have assessed the effects of potassium bicarbonate or potassium citrate on urinary calcium excretion, bone turnover markers, and a few on BMD [73–76]. In a dose-finding study evaluating the effect of potassium bicarbonate supplementation on bone turnover, calcium excretion, and nitrogen excretion, daily doses of 1 (median dose 81 mmol/day) and 1.5 mmol/kg (median dose 122 mmol/day) of potassium

Table 3 Controlled intervention studies with dairy products or dairy proteins on bone mineral density and biological markers associated with bone metabolism in adults

Reference	Population	*N*	Dairy product	Intervention	Control	Duration	Outcomes	Effects of intervention
Bonjour et al. 2008 [40]	Postmenopausal women	30	Milk	Semi-skimmed milk 500 ml	Cross-over	6 weeks	BTM, PTH	↘ PTH, ↘ CTX, ↘ P1NP, ↘ Oc
Bonjour et al. 2009 [41]	Institutionalized women ≥ 65 years old with low vit D status and Ca intake < 700 mg/day	37	Soft white cheese	2 servings of soft white cheese fortified with Vit D (+ 1.25 μg/100 g) and milk extracted Ca (total Ca achieved 151 mg/100 g)	No soft white cheese consumption (cross-over study)	6 weeks	Vit D, BTM	↗ vit D, ↗ IGF-I, ↘ PTH, ↘ CTX and TRAP5b, ↗P1NP
Bonjour et al. 2012 [42]	Postmenopausal women with low spontaneous supply of Ca and vit D	71	Milk + soft white cheese	Skimmed-milk and soft white cheese fortified with Vit D (2.5 μg/day) and Ca (400 mg/day)	Usual diet	6 weeks	IGF-I, BTM	Greater ↗ IGF-I and ↘ TRAP5b
Chee et al. 2003 [43]	Postmenopausal (> 5 years) women (55–65 years)	173	Milk powder	Milk powder with 1200-mg/day Ca	Usual diet	24 months	Vit D, BMD	↗ vit D, ↘ spine and hip BMD loss, benefit still evident 21 months after the study end
Ting et al. 2007 [62]								
Daly et al. 2006 [44, 45]	Community living Caucasian men (50–87 years)	111	Milk	Fortified milk with Ca (1000 mg/day) and vit D (800 IU/day)	Usual diet	24 months	Vit D, PTH, BMD, bone geometry (QCT)	↘ hip and radius BMD loss, femur endocortical bone loss (in men > 62 years), ↗ vit D and ↘ PTH
Gui et al. 2012 [46]	Postmenopausal women without osteoporosis (45–65 years)	141	Milk	Milk/soymilk with 250 mg/day Ca	Usual diet	18 months	BMD	↘ BMD loss at the hip with milk, not soymilk. No difference at the spine.
Heaney et al. 2002 [47]	Postmenopausal white women with Ca intake < 600 mg/day	29	Yoghurt	Three servings of yoghurt/day	Three servings of a nutrition-poor snack	7–11 days	Urine NTX	↘ urine NTX
Hinton et al. 2010 [100]	Obese men + women (40.8 ± 0.6 years)	113	Dairy	Energy restricted diet (1200 kcal/day; 10% wt loss) followed by recommended dairy diets (≥ 3/day)	Energy restricted diet (1200 kcal/day; 10% wt loss) followed by low dairy diet (≤ 1/day)	12 weeks; 24 weeks dairy vs control	Whole body BMC, BMD vit D, PTH, Ca	No effects of intervention.
Josse et al. 2010 [48]	Young women (23.2 ± 2.8 years)	20	Fat-free milk	2 × 500 ml, immediately and 1 h after exercise	Isocaloric carbohydrates	12 weeks	Vit D, PTH,	↗ vit D, ↘ PTH
Kristensen et al. 2005 [49]	Healthy young men (22–29 years)	11	Milk	2.5 L/d of cola + low-Ca basic diet	2.5 L/day of semi-skimmed milk + low-Ca basic diet (cross-over study)	10 days	BTM	↗ PTH, Oc, CTX, and NTX with cola diet, not milk diet.
Kruger et al. 2006 [50]	Premenopausal women 20–35 years	82	Milk	High Ca skim milk (1000 mg/day of extra Ca) ± vit K1 (80 μg/day)	Usual diet	16 weeks	BTM	↘ CTX, Oc, and NTX independently of vit K1
Kruger et al. 2010 [52]	Postmenopausal women	120	Milk powder	Milk powder fortified with 1200-mg Ca, 96-mg magnesium, 2.4-mg zinc and 9.6-μg vit D/day	Powdered control rice-based drink	16 weeks	Vit D, PTH, BTM	↗ vit D, ↘ PTH, CTX, Oc, P1NP
Kruger et al.	Postmenopausal women	63	Milk		Powdered rice-based drink	12 wk	Vit D, PTH, BTM	↗ Vit D and ↘ CTX and P1NP

Table 3 (continued)

Reference	Population	*N*	Dairy product	Intervention	Control	Duration	Outcomes	Effects of intervention
2012 [51]				Milk fortified with 900 mg Ca, 96 mg magnesium, 2.4 mg zinc and 6.4 μg Vit D /d				
Kukuljan et al. 2009 [53]	Men (50–79 years) without Vit D deficiency	180	Milk	Milk fortified with 1000-mg/day Ca and 800 IU/day vit D ± exercise	Usual diet	12/18 months	BMD + bone structure and strength with QCT	No difference
Lau et al. 2001 [54, 55]	Postmenopausal women	185	Milk powder	Milk powder containing 800-mg/day Ca	Usual diet	24 months	BMD, vit D, PTH, BTM	Lower ↘ BMD, ↗ vit D, ↘ PTH
Liu et al. 2011 [56]	Pregnant women (24–31 years) with habitual low Ca intake.	36	Milk powder	Milk powder (containing 350 mg Ca); milk powder (containing 350-mg Ca) + 600-mg Ca/day	Usual diet	20 weeks gestational age to 6 weeks postpar-tum	BMD, BTM	↗ BMD whole body and spine, not hip; ↘ urinary hydroxyproline, ↗ Oc
Manios et al. 2007 [57]	Postmenopausal women	101	Milk and yoghurt	Milk and yoghurt fortified with 1200 mg Ca and 7.5-μg vit D + counseling	Two groups: Ca-supplements 1200 mg/day; usual diet	5 months	IGF-I, BTM	Greater ↗ IGF-I and ↘ PTH and CTX in dairy intervention group compared to Ca supplementation alone. Greater ↗ BMD in pelvis, spine and total-body
Moschonis et al. 2010 [59]	Postmenopausal women (55–65 years)	66	Milk and yoghurt	Milk and yoghurt fortified with 1200-mg Ca and 7.5/22.5-μg vit D + counseling	Usual diet	30 months	BMD	More favorable changes in arms, total spine and total body BMD, trend for ↗ spine BMD
Moschonis et al. 2011 [58]	Postmenopausal women	115	Milk and yoghurt	Milk and yoghurt fortified with 800-mg Ca + 10-μg vit D ± vit K	Usual diet	12 months	BMD	↗ total body BMD, ↗ spine BMD in Vit K treated groups
Sukumar et al. 2011 [101]	Postmenopausal women (58.0 ± 4.4 years), BMI between 25 and 40 kg/m^2, caloric restriction during a 1-year weight-loss trial	47	Whey protein + dairy, meat, fish, legumes proteins.	Caloric restriction + high protein diet (whey protein 6 g/day + dairy, meat, fish, legumes proteins) + 1.2 g/day calcium + multivitamin with 400 IU vit D.	Identical to intervention with exception of normal protein diet and no whey protein supplement.	12 months	aBMD, vBMD, IGF-1,IGFBP-3, vit D, PTH, DPD	↘ loss of aBMD at radius, spine and hip, and of tibia total and trabecular vBMD; higher IGF-1, IGFBP-3 and lower deoxypyridinoline in intervention group at 12 mo.
Tenta et al. 2011 [60]	Osteopenic postmenopausal women (55–65 years)	40	Milk and yoghurt	Milk and yoghurt fortified with Ca (1200 mg/day) and vit D (7.5 to 30 μg/day)	Usual diet	30 months	Vit D, BTM, BMD	Prevented ↘ vit D in winter. ↘ CTX and RANKL; trend for total body BMD.
Thorpe et al. 2008 [61]	Overweight men (59) and women (30–65 y)	130	Dairy products	Protein 1.4-g/kg BW and three servings dairy	Protein 0.8-g/kg BW and two servings dairy	12 months	BMD, urinary calcium	↘ BMD decrease and urinary Ca
Toxqui et al. 2014 [63]	Young iron-deficient or iron-sufficient women (18–35 years)	150	Milk	Milk fortified with iron 15 mg/d ± vit D 5 μg/day	Usual diet	16 weeks	Vit D, PTH, BTM	↗ vit D and ↘ BTM with milk fortified with vit D
Trombetti et al. 2016 [64]	Young women with anorexia nervosa (22.5 ± 4.5 years)	62	Fermented dairy	Fortified fresh cheese (15-g protein)	Fresh cheese (3-g protein)	4 weeks	IGF-I, BTM, PTH	↗ IGF-I and IGF-I/IGF-BP3
Woo et al. 2007	Women (20–35 years)	408	Milk powder	Milk powder with 1000-mg Ca, 80-μg vit K	Usual diet	24 months	BMD, BTM	

Table 3 (continued)

Reference	Population	*N*	Dairy product	Intervention	Control	Duration	Outcomes	Effects of intervention
[66]								No difference between groups (↗ BMD and ↘ BTM) except spine BMD at 6 months
Zou et al. 2009 [68]	Healthy young women (19.6 ± 0.6 years)	81	Milk + whey protein	Milk ± MBP (milk basic protein fraction)	Usual diet	8 months	BMD, BTM	↘ bone resorption with milk but no effect of MBP
Whey protein[a]								
Aoe et al. 2001 [39]	Healthy women (28.8 ± 8.7 years)	27	Whey proteins	MBP (milk basic protein fraction)	Placebo	6 months	BMD calcaneus, BTM	↗ BMD, ↘ urine NTX, and deoxypyridinoline,
Aoe et al. 2005 [38]	Postmenopausal women	27	Whey proteins	MBP (milk basic protein fraction)	Placebo	6 months	BMD, BTM	↗ spine BMD gain, ↘ NTX,
Ballard et al. 2006 [102]	Healthy women and men (18–25 years)	52	Casein + whey	Protein supplement (42 g protein casein + whey) + exercise (5×/week)	Carbohydrate control + xercise (5×/week	6 onths	Whole body BMC (DXA), tibia vBMD (pQCT)	Effects NS.
Kerst-etter et al. 2015 [103]	Healthy adults (women > 60 years; men > 70 years)	208	Whey	45-g whey powder; minimum Ca intake 1200 mg/day	Isocaloric maltodextrin; minimum Ca intake 1200 mg/day	18 months	LS, FN, hip BMD (DXA), Femur & spine QCT, PTH, IGF-I, CTX, P1NP, osteocalcin, vit D.	No difference for BMD changes, ↗ IGF-I, and CTX in intervention group at 18 months.
Uenishi et al. 2007 [65]	Healthy young women (21.3 ± 1.2 years)	35	Whey protein	MBP (milk basic protein fraction)	Placebo	6 months	BMD, BTM	↗ spine BMD gain, ↘ NTX, ↗ Oc
Wright et al. 2017 [104]	Overweight/obese adults (49 ± 8 years)	186/103	Whey protein	400-kcal supplement with 20, 40, 60-g whey protein; regular diet and exercise	400-kcal supplement without whey protein; regular diet and exercise	36 weeks	BMC, BMD	No difference between groups.
Yama-mura et al. 2002 [105]	Healthy women (28.8 ± 8.7 years)	33	Whey proteins	40-mg/day MBP	Placebo	6 months	Radial BMD	↗ radial BMD
Zhu et al. 2011 [67]	Postmenopausal protein-replete women (70–80 years)	219	Whey protein	High-protein drink containing 30 g of whey protein + 600-mg Ca	Placebo drink containing 2.1 g of protein + 600-mg Ca	2 years	BMD, hip QCT (estimated bone strength), IGF-I	↗ IGF-I but no effect on BMD and bone strength

BMD: bone mineral density; MBP: milk basic protein fraction; Ca: Calcium; BTM: bone turnover markers; QCT: quantitative computerized tomography; BW: body weight; Oc: osteocalcin

[a] Mean spontaneous calcium intakes were 529–627 mg/day for [38, 39], and calcium supplements were 400–636 mg/day for [67, 102–104]

bicarbonate were compared to placebo [76]. A reduction in 24-h urinary N-telopeptides (NTX) was observed for the low dose group ($p = 0.012$). Both treatment groups had lower urinary calcium excretion, while no effect was observed on urinary nitrogen excretion for either dose group. Reviewed in a meta-analysis [77], results of these various studies can be summarized as follows. Alkali administration is associated with a reduction in net acid excretion, in urinary calcium excretion, in urinary NTX, but with no change in bone formation markers. These data were interpreted as an increase in calcium balance. In a previous study, potassium bicarbonate administration has been shown to increase intestinal calcium absorption [78].

Regarding changes in BMD evaluated over a 2-year period, two randomized placebo-controlled intervention trials have addressed this question. In a 2-year randomized controlled trial, including 276 healthy postmenopausal women, aged 55 to 65 years, Macdonald et al. did not find any difference with postassium citrate supplementation on spine or hip BMD nor on bone turnover markers [73]. In contrast, a similar dose of potassium citrate (60 vs 55 mEq/day) in 201 healthy men and women, older than 65 years, was associated with a higher 1.7 and 1.6% change vs placebo, for spine and femoral neck areal BMD, respectively, over 2 years [74]. Distal radius and tibia volumetric trabecular density was increased as well by this intervention. Pooling the BMD values of these two trials in a meta-analysis did not allow the difference to reach a level of statistical significance [77].

While the administration of substantial amounts of acid or alkali is able to slightly influence blood pH and possibly bone metabolism [79, 80], the question is whether diet-derived acid load is able to modify even slightly extracellular pH [81]. Furthermore, it has been claimed that the source of proteins, animal versus vegetable, would differentially affect calcium metabolism. This is based on the hypothesis that animal proteins would generate more sulfuric acid from sulfur-containing amino acids than a strict vegetarian diet. A strict vegetarian diet with protein derived from grains and legumes may deliver as many millimoles of sulfur per gram proteins as would a purely meat-based diet [82]. It is unlikely that the bone is exposed to marked changes in extracellular pH in relation to animal protein or grains consumption within the limits of a balanced diet. A diet low in fruits and vegetables appears to be associated with a higher fracture risk [83–87]. This may be the reflection of other deficiencies or life style habits. In an intervention randomized controlled trial, BMD did not change in subjects receiving a diet-rich in fruits and vegetables, hence presumably rich in alkali [73]. The issue is further complicated by the fact that vegetable intake-induced decrease in bone resorption has been shown to be independent from acid-base changes [88] and that potassium but not sodium bicarbonate (i.e., the same anion) reduces urinary calcium excretion. On the other hand, a prospective cohort study (EPIC) with 7947 men and 26,749 women, aged 20–89 years, found that fracture risk was higher in vegans with low (< 525 mg/day) calcium intakes but was not different between meat eaters, fish eaters, and lactoovovegetarians [89].

To characterize dietary acid load, i.e., endogenous acid production, various calculations have been used. Potential renal acid load (PRAL) [82] is proportional to protein and phosphorus intakes and inversely related to potassium, calcium, and magnesium intakes. Estimated net endogenous acid production (renal net acid excretion) (NEAP) [90] is based on the ratio of protein over potassium intakes.

The associations between bone health outcomes and measured net acid excretion (NAE) have been assessed in several meta-analyses (Table 4). In 25 analyzed studies, diet-derived acid load was manipulated by dietary intakes, such as sulfur-containing amino acids, protein, meat, grain or fruits and vegetables, or acidic or alkaline salts, such as ammonium chloride, potassium bicarbonate, or potassium citrate [10]. A positive linear relationship was found between changes in urinary calcium excretion and changes in net acid excretion in urine, over a wide range of acidic or alkaline urine. It should be noted that food-related variation in urinary acid excretion represents a physiological and homeostatic response to dietary acid load. However, an association between urinary calcium and acid excretion does not imply that the source of calcium is primarily an increased bone resorption, thereby contributing to the development of osteoporosis. Another possibility is that acidosis or alkalosis alters renal tubular reabsorption of calcium. Under these conditions, acidosis-mediated hypercalciuria may be a compensatory mechanism to maintain calcemia in the presence of a renal calcium leak [91]. Alternatively, higher protein intakes have been shown to be associated with higher intestinal calcium absorption. Of note is the fact that aromatic amino acids are stimulating the hepatic synthesis of IGF-I, which in turn increases calcitriol synthesis and intestinal calcium absorption [92]. The resulting hypercalciuria represents thereby more an increase in the calcium throughput than a mobilization of bone mineral [93, 94]. In another meta-analysis, changes in calcium balance or bone resorption marker NTX were assessed in relation with changes of NAE, induced by varying the intakes of meat, soy, and lentils [12]. There was no evidence from balance studies that increasing the diet-derived acid load promotes changes in bone turnover, skeletal bone mineral loss, or osteoporosis.

Phosphate is considered an acid-producing nutrient [95]. The role of dietary phosphate supplements, under various forms, on bone health variables was addressed in a meta-analysis [11]. Analyzing 12 studies including 30 intervention arms manipulating phosphate intakes, it was shown

Table 4 Summary of the systematic reviews and meta-analyses investigating the acid ash hypothesis in relation with bone outcomes

Reference	Objective	N studies	Conclusion
Fenton et al. 2008 [10]	- To estimate the quantity of NAE and calciuria associated with the modern diet - To assess the association between NAE and calcium excretion	25 studies	- Linear association between changes in calcium excretion in response to experimental changes in NAE. - This finding is not evidence that the source of the excreted calcium is bone or that this hypercalciuria contributes to the development of osteoporosis.
Fenton et al. 2009 [11]	- To assess the effect of supplemental dietary phosphate on urine calcium, calcium balance, and markers of bone metabolism - To assess whether these affects are altered by the level of calcium intake AND the degree of protonation of the phosphate.	12 studies	- Contrary to the acid ash hypothesis, higher phosphate intakes were associated with decreased urine calcium and increased calcium retention. - There is no evidence that higher phosphate intakes are detrimental for bone health
Fenton et al. 2009 [12]	- To assess the effect of changes in NAE, by manipulation of healthy adult subjects' acid-base intakes, on urine calcium, calcium balance, and a marker of bone metabolism, N-telopeptides.	5 studies	- Despite a significant linear relationship between an increase in NAE and urinary calcium, no relationship between a change of NAE and a change of calcium balance or N-telopeptides. - This meta-analysis does not support the concept that the calciuria associated with higher NAE reflects a net loss of whole body calcium.
Fenton et al. 2011 [13]	-Systematic review to evaluate causal relationships between dietary acid load and osteoporosis using Hill's criteria.	- 36 studies with bone health outcomes in healthy adults. - 19 in vitro cell studies which examined the hypothesized mechanism.	- A causal association between dietary acid load and osteoporotic bone disease is not supported by evidence - No evidence that an alkaline diet is protective of bone health.

NAE, net acid excretion

that higher phosphate intakes were associated with decreased rather than increased urinary calcium excretion and with increased calcium balance. This was observed under both high and low calcium intakes. In three studies, changes in net acid excretion in response to dietary phosphate supplements were measured. In all three, net acid excretion was increased. Two studies have reported BMD measurement in relation to dietary phosphate intakes. In a 12-month randomized controlled trial, 1800 mg of calcium either as tricalcium phosphate or calcium carbonate, together with teriparatide and vitamin D, similarly increased spine and hip BMD irrespective of the calcium salt anion [96]. In a cross-sectional study performed in premenopausal women and in men, phosphate intake was slightly positively associated with tibia bone mineral content and cross-sectional cortical bone area in men. In women, this association disappeared with the inclusion of calcium in the model, and phosphate intake was negatively associated with the bone formation marker P1NP [97]. However, a diet rich in phosphate and low in calcium is likely to induce a secondary hyperparathyroidism, which may be deleterious for the skeleton.

A systematic review and meta-analysis studied 22 randomized controlled trials, two meta-analyses, and 12 prospective longitudinal observational studies on bone health outcomes in healthy adults, in whom acid or alkali intakes were modified by supplements or observed through food intakes record [13]. None of the intervention studies provided direct evidence of osteoporosis progression (fragility fractures or altered bone strength). Neither did they show adverse effects of phosphate, milk, and grain foods on bone. In this study, Hill's criteria for evaluating causation were applied to the potential associations between bone health outcomes and diet acid load in prospective cohort studies, i.e., temporality, strength of the evidence, biological gradient, plausibility, consistency of the data, and experimental confirmation. The authors failed to detect arguments in favor of the hypothesis that a diet-derived acid load would be deleterious on bone.

In a cross-sectional study in community-dwelling women and men older than 70 years, there was no association between osteoporosis diagnosis nor fracture history with NEAP or PRAL, irrespective of the presence of chronic kidney disease [98], again not supporting the hypothesis of dietary acid load increasing fracture risk. However, additional data in advanced renal failure would be required.

There appears to be no direct evidence of osteoporosis progression, fragility fractures or altered bone strength, with the acid load from a balanced diet origin.

Conclusions

Although acid loading or a high protein diet is associated with increased urinary calcium excretion, which may be related to higher intestinal calcium absorption, higher protein intakes, whatever their origin (animal or vegetable), do not appear to contribute to the development of osteoporosis or to increase fracture risk. With intakes above the current RDA, dietary protein is rather beneficial in reducing bone loss and fracture risk, especially at the hip, provided calcium intakes are adequate. Insufficient dietary protein intakes may be a much more severe problem than protein excess.

Funding information The writing of this paper was supported by a grant from the Dairy Research Consortium (Dairy Farmers of Canada, Centre national interprofessionnel de l'économie laitière (CNIEL), National Dairy Council, Dairy Australia Ltd., Dutch Dairy Association, Danish Dairy Research Foundation), who did not intervene in data analysis, interpretation or conclusions.

Compliance with ethical standards

Conflicts of interest RR received fees for lectures or advisory boards from Radius Health, Danone, Nestlé and Effrx/Labatec. EB received a research grant from Danone. JPB has nothing to disclose. VC received a grant from Rousselot and belongs to the advisory board of Triballat Institute. DG has nothing to disclose. JAK reports grants from Amgen, Eli Lilly, and Radius Health; non-financial support from Medimaps and Asahi; and other support from AgNovos. JL has nothing to disclose. LR has received institutional research grants from the Danish Dairy Research Foundation. SS has received institutional grants from Dairy Management, Inc. and is a member of the Nutrition Research Scientific Advisory Committee, National Dairy Council. CW received fees for lectures, advising, or grants from Pharmavite, Pfizer, ILSI, Alliance for Potato Research and Education, Tate & Lyle, Danone, and General Mills. HW received research grants from Dairy Farmers of Canada and the Dairy Research Cluster Initiative (Dairy Farmers of Canada, Agriculture and Agri-Food Canada, the Canadian Dairy Network and the Canadian Dairy Commission). JYR received fees for consulting from IBSA-Genevrier, Mylan, Radius Health, Pierre-Fabre and for lectures from IBSA-Genevrier, Mylan, CNIEL, Dairy Research Council.

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