The Negative Effect of a High-Protein–Low-Calcium Diet

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Peter Burckhardt

Abstract

The interdependent influence of the protein and the calcium intake on bone health has been conclusively studied. For obtaining a positive bone effect from nutritional protein, an adequate calcium intake is required, and vice versa. A high-protein intake was first considered as potentially negative for bone, but this fear was not defendable anymore when it became evident that a high-protein intake increases urinary calcium excretion because it stimulates calcium absorption. Protein deficiency was shown to be detrimental to bone, not a high-protein intake. However, some large follow-up studies demonstrated that the combination of a high-protein intake with a low-calcium diet increases fracture risk. This particular nutritional profile seems to be rare, but some cross-sectional studies seem to confirm that.

Keywords

Protein intake • Protein/calcium ratio • Fracture risk

Introduction

At the first International Symposium on Nutritional Aspects of Osteoporosis (ISNAO) in 1992, E.S. Orwoll stated "… weather a relatively high intake of protein influences mineral and bone metabolism remains controversial," and "… commonly consumed diets, replete in phosphate but low in calcium, may be associated with potentially harmful metabolic changes" [1]. Although the eventual negative bone effect of a high protein stemmed mainly from animal studies, the doubt remained, but was already linked to a low-calcium diet. At the sixth ISNAO in 2006, R.P. Heaney recalled that "… protein-related benefit is dependent upon an adequate calcium intake" [2], and at the seventh ISNAO in 2009, A.L. Darling summarized her review on protein effects with the alarming sentence "high calcium intakes may offset any detriment caused by high protein intake, and low calcium intakes may make protein-induced detriment worse" [3].

This was formulated as a hypothesis. The purpose of this study is to gather the evidence for

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this statement. It will not discuss the various effects of dietary protein, such as providing substrates for bone matrix, stimulating IGF-1, and increasing calcium absorption and urinary calcium excretion [4], and it will not review the evidence for the various benefits of an adequate protein intake, such as higher BMD, slower bone loss, and smaller fracture risk in postmenopausal women and elderly people. Nor will it discuss the still controversial observation that high-protein intake may affect bone via acid load [5]. But it will analyze the literature in search of an answer to the question if a high-protein–low-calcium diet is detrimental to bone.

Definition of a High-Protein Intake

The impressive number of studies on the bone effects of dietary protein intake reviewed by [6] allows comparing the protein intakes recorded in the various studies (Fig. 12.1). For this comparison, all values were indicated in g/kg. When the total intake was indicated in g/day and the body weight was not given, a body weight (BW) of 70 kg was assumed. It appeared in general the protein intake was about 1 g/kg in most of the studies, with a lowest value at 0.8 g/kg, although the RDA is in general set at 0.8 g/kg. The three studies close or below 0.8 g/kg concerned vegetarians [7], or subjects with a high intake of vegetable proteins and for that with a relatively low total protein intake [8], and a study based on non-dairy proteins only [9]. Since there is no definition of a high-protein intake, the upper limit of "normal" or "adequate" could be arbitrarily fixed, for reasons of symmetry, at 1.2 g/kg, considering an intake above this figure as high, not as abnormal or inadequate.

Definition of the Optimal Calcium/Protein Ratio

In several studies, the ratio calcium intake/protein intake has been used for evaluating the combined effect of calcium and of protein on bone. However, there is no definition of a normal range for the calcium/protein ratio, although this ratio is used as a parameter in many studies. In order

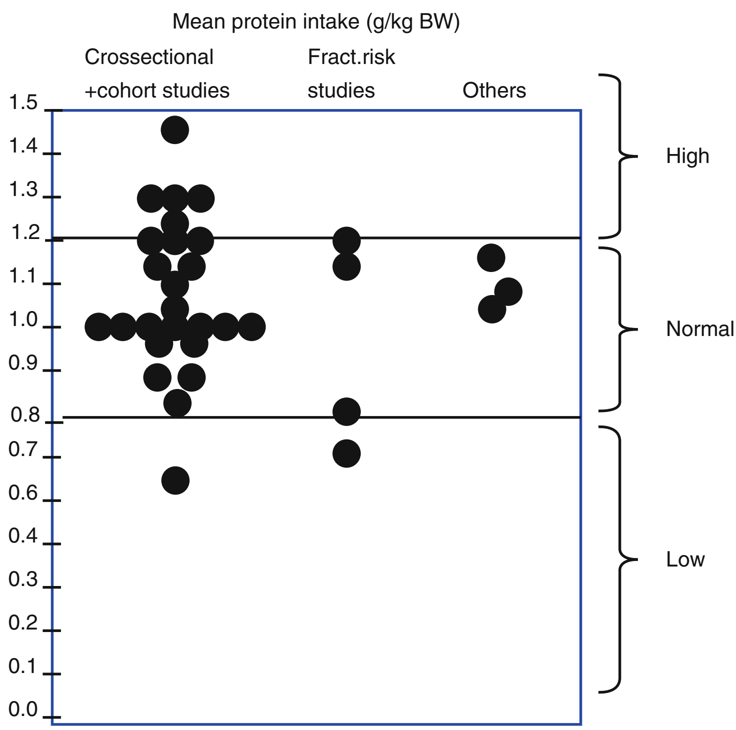

Fig. 12.1 Mean protein intake from the studies analyzed by Darling et al. When protein intake was given only in g/day, a mean body weight (BW) of 70 kg was taken for calculation of g/kg BW (Based on data from Darling et al. [6])

to define a minimal ratio, one could implement a calcium intake of 800 mg/day and a protein intake of 1.2 g/kg/day, which would result in a calcium/protein ratio of 11.1 mg/g for a BW of 60 kg and 8.3 mg/g for a BW of 80 kg. A ratio of eight could then be considered as the lowest acceptable value, but to the knowledge of this author, no official recommendation has been formulated. For assessing this ratio, one can calculate it for taller and for smaller subjects. For a young white US or a Dutch man with a BMI of 23 kg/m^2, both with a median height of 182 cm, an intake of 1.2 g protein/kg and of 800 mg calcium would give a calcium/protein ratio of 8.8, while the same calculation for a Japanese or Portuguese man (median height 172, resp. 171 cm) would give a ratio of 9.8, resp. 9.9. These values give the wrong impression to be close, but they should also be valid for taller and for smaller subjects. This is not the case. For historical reasons, the calcium recommendations are given in absolute values, while the recommendations for protein intake are adapted to BW. This explains why the same calculation using the same intake of calcium and of protein, performed for a tall US man at percentile 95, results in a ratio of 8.1 and for a small Japanese women at percentile 5 in a ratio of 13.4. This important variation of the ratio, which depends on BW, makes the ratio unfit for scientific use, unless it is applied to a homogenous population as seen, e.g., in rat experiments. To illustrate this statement, the reported or calculated calcium/protein ratios of the studies reviewed by [6] are presented on a diagram (Fig. 12.2). It becomes evident that the ratio cannot be used as a parameter which helps to evaluate the effects of various protein and calcium intakes.

Analysis of Published Studies in Search of a Negative Effect of a High-Protein–Low-Calcium Intake

Studies with Calcium Isotopes

Four studies from two groups demonstrated that a high-protein intake enhances calcium absorption [10–13]. All used very-high-protein intakes (average values of 1.6–2.1 g/kg), but the average calcium intakes were not or only moderately low (average values 600–800 mg/day). Therefore, no information on the effect of a high-protein–low-calcium intake could be drawn from these studies. But one study [13] came to the conclusion that the increase in calcium absorption might "nearly" compensate the increase in urinary calcium excretion. By that it evokes the possibility

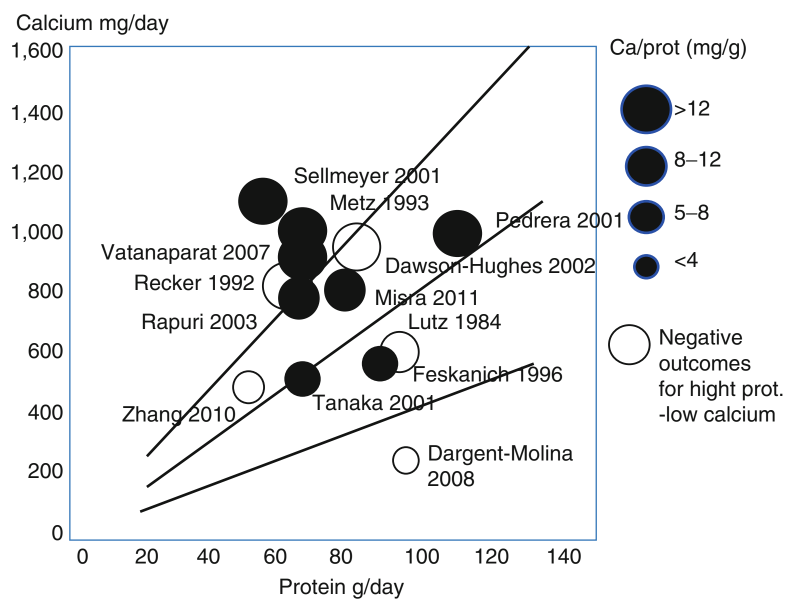

Fig. 12.2 The calcium/protein ratio taken from the studies analyzed by Darling et al. (Based on data from Darling et al. [6])

that a high-protein intake might lead to a negative calcium balance when the calcium intake is inadequately low.

Cross-Sectional and Cohort Studies

None of the numerous studies reviewed by [6] studied specifically the effect of a high-protein–low-calcium diet, neither the more recent study on the relation between protein intake and fracture risk by Misra et al. [14].

A special look on the five studies of Darling's meta-analysis with a protein intake above 1.2 g/kg [15–19] also did not reveal data of subgroup analysis with high-protein–low-calcium intakes, although the three Japanese studies among them reported rather low-calcium intakes (average values 458–660 mg/day). However, one of these studies [19] found a surprising negative correlation between protein intake and radial bone density. Calcium intake was high (±1,001 mg/day), and there was a positive correlation between the calcium/protein ratio and BMC.

The Exception of the Growing Bone

In children and adolescents too, adequate protein intake is essential for bone growth and strength, and the positive response to calcium supplementation is also influenced by the protein intake [20]. But the requirements seem to be different, since the three studies on young adults or peripubertal girls reported a positive correlation between the calcium/protein ratio and BMC or BMD [19, 21, 22]. All three studies showed a negative correlation between protein intake and bone measurements. Since the physiology of growth and development of peak bone mass is different from that of bone loss after menopause and in advanced age, it also can be assumed that the nutritional needs for building up bone are not the same as for preventing bone loss after menopause or in advanced age.

This is also demonstrated in a study of 15–17-year-old female ballet dancers ($N=127$) [23], where food intake was compared with BMC. The intake of nondairy proteins, assessed by portions (servings), was negatively correlated by bivariate analysis with femoral neck BMC ($p=0.008$, coeff. −0.089) and by multivariate analysis ($p=0.045$, coeff. −0.62), while the intake of dairy products was positively correlated with femoral neck BMC by bivariate analysis ($p=0.049$, coeff. 0.083) and by multivariate analysis ($p=0.067$, coeff. 0.069). In addition, dairy products were also positively correlated with lumbar spine BMC by bivariate analysis ($p=0.008$, coeff. 1.84) and by multivariate analysis ($p=0.015$, coeff. 1.69). The multivariate analysis ($p<0.02$) corrected for BW, pubertal stage, years since menarche, and hours of dancing. Even when the Caucasians and the Asians were analyzed separately by Spearman correlations, significant negative coefficients were found between nondairy protein intake and BMAD of the lumbar spine in Caucasians (−0.303, $p<0.05$) and with BMAD of the femoral neck in Asians (−0.301, $p<0.05$). Positive coefficients were found in Caucasians between the intake of dairy products and BMAD of the spine (+0.323, $p<0.01$) and the femoral neck (+0.249, $p<0.05$), while in Asians the coefficient was −0.305 ($p<0.05$) with the lumbar spine.

When the highest tertile of nondairy protein intake was combined with the lowest tertile of dairy intake, the mean Z-scores of lumbar BMD were −1.61 in Caucasians and −1.12 in Asians, compared to −0.57, resp. −004, with the highest tertile of dairy products ($p<0.02$, resp. <0.04). These results show again that in the growing skeleton and in young adults, a high-protein intake combined with a low-calcium intake is in negative correlation to bone mineral content.

Intervention Studies

Intervention studies, where the protein intake was modified, also could be a source of information on the effect of a high-protein–low-calcium diet. Most intervention studies showed no detrimental effect of a high-protein intake on bone metabolism, even when the calcium intake was low [24–28]. But these studies were probably too short for detecting a negative bone effect of a high-protein–low-calcium intake. Spencer et al. [29] approached this question in her early study but could not deliver statistics on such a particular subgroup from the small number of subjects studied. But Lutz [30] observed that calcium balance became more negative when the protein intake was doubled while the calcium intake was kept low at ±500 mg/day.

Cross-Sectional and Follow-Up Studies with Analysis of High-Protein–Low-Calcium Intake

The studies with and without calcium supplements [31] and the studies with specific analysis of the calcium intake [20, 32] pointed to the importance of an adequate calcium intake for developing a positive effect of protein on bone. In the study of Dawson-Hughes [31], calcium supplementation revealed a positive effect of the protein intake on bone loss in elderly men and women over 3 years, although calcium intake was not low without supplementation (±940 mg/day) and the highest tertile of protein intake was not very high (±87.6 g/day) [32]. Rapuri et al. concluded in their 3 years' follow-up study that high-protein intake was associated with higher BMD only when the calcium intake exceeded 408 mg/day. But whether the combination of high-protein with low-calcium intake was detrimental was not examined. Vatanparast et al. [20] made a similar conclusion, since in their study on young adults, protein intake predicted TB-BMC only in females who had a calcium intake >1,000 mg/day. They even stated "in the absence of sufficient calcium, protein doesn't confer as much benefit to bone" without showing the figures and without examining the issue of a high-protein–low-calcium intake.

Follow-Up Studies with Subgroup Analysis of High-Protein–Low-Calcium Diet

There are finally five studies which approached the question of the effect on bone of a high-protein–low-calcium diet (Table 12.1). The first one [33], based on NHANES 1999–2000, compared the fracture risk in nine groups of postmenopausal women: three tertiles of protein intake and three tertiles of calcium intake. The highest tertile of protein intake (>70 g) with the lowest calcium intake (<400 mg/day) did not show an increased fracture risk, but this group consisted in 43 subjects, which obviously was too small to obtain a reliable estimate of the odds ratio for fractures.

The study of Feskanich et al. [34] based on the Nurses' Health Study, showed in a 12-year follow-up an increase of the risk for forearm fractures by 31 % in the tertile with the highest protein intake (>90 g/day) combined with the lowest tertile of calcium intake (<541 mg/day), but this result was not significant.

In the large French epidemiologic study of Dargent-Molina et al. [35] in more than 35,000 subjects and a mean follow-up of more than 8 years, there was 51 % increase in the RR for fractures in the quartile with highest protein intake combined with quartile of the lowest calcium intake and of 46 % when the protein intake was weight adjusted. This subgroup had a calcium intake of <210 mg and a protein intake of >99.6 g, resp. 1.71 g/kg (extrapolated figures), which lets us assume that these extreme values only concern a small percentage of the population.

The large Norwegian follow-up study in 2,302 men and women over 10–12 years [9] also showed an increased hip fracture risk (+96 %, sign.) in women in the highest quartile of protein intake (>20.6 g nondairy animal protein) and the lowest calcium intake (<435 mg/day), while the same analysis in men (>21.6 g nondairy animal protein and <623 mg calcium) showed an increased RR of 1.67, which however was not significant. Here the proportion of subjects was indicated – 7.4 % of the women and 8.4 % of the men.

The last study, based on the Framingham offspring cohort, came to the same conclusion [36]. This 12-year follow-up study on 2,697 men and women showed that in the subjects with a calcium intake of >800 mg/day, a high-protein intake (tertile median 60 g/day animal protein, calcium intake 1,096 mg/day) lowered the fracture risk by 70 %, while in the subjects with a calcium intake

Table 12.1 Increased fracture risk with high-protein and low-calcium intake

Author	Ref.	Sex Mean age	Follow-up		Calcium mg/day	Protein g/day	g/kg BW	Ca/prot mg/g	Outcome
Feskanich et al. (1996)	[34]	F 46.5 years	12 years	Tertiles	<541?	>90	>1.15?	<6.0	Forearm fractures
Dargent-Molina et al. (2008)	[35]	F 56 years	8.4 years	Quartiles	<210	>99.9	>1.71	<2.1	Any low-impact fracture
Meyer et al. (1997)	[9]	M+F 47 years	11.4 years	Quartiles	<435	>20.6 nondairy	n.a.	n.a.	Hip fractures
Sahni et al. (2010)	[36]	M+F 55 years	33 years	Tertiles	±517	±60 animal	n.a.	8.6	Hip fractures

of <800 mg (±578 mg/day), the fracture risk was doubled (RR 2.02) in the tertile with the highest protein intake (median 60 g/day). This means that in presence of a sufficient calcium intake, a high-protein diet was protective, while in the presence of a low-calcium diet, a high-protein intake increased the fracture risk.

Conclusion

Normal protein intake is essential for preventing osteoporosis and decreasing fracture risk, especially hip fracture in advanced age. High-protein intake has never been shown to have a negative effect on bone in humans when integrated in an otherwise equilibrated diet. But several large and long-term follow-up studies demonstrated that a high-protein diet combined with a low-calcium intake is detrimental to bone, leading to an elevated fracture risk. Some cross-sectional studies, which analyzed this phenomenon, seem to confirm that. This particular nutritional profile is rare, but its negative impact should be known.

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