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SYSTEMATIC REVIEW

Protein intake, calcium balance and health consequences

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High-protein (HP) diets exert a hypercalciuric effect at constant levels of calcium intake, even though the effect may depend on the nature of the dietary protein. Lower urinary pH is also consistently observed for subjects consuming HP diets. The combination of these two effects was suspected to be associated with a dietary environment favorable for demineralization of the skeleton. However, increased calcium excretion due to HP diet does not seem to be linked to impaired calcium balance. In contrast, some data indicate that HP intakes induce an increase of intestinal calcium absorption. Moreover, no clinical data support the hypothesis of a detrimental effect of HP diet on bone health, except in a context of inadequate calcium supply. In addition, HP intake promotes bone growth and retards bone loss and low-protein diet is associated with higher risk of hip fractures. The increase of acid and calcium excretion due to HP diet is also accused of constituting a favorable environment for kidney stones and renal diseases. However, in healthy subjects, no damaging effect of HP diets on kidney has been found in either observational or interventional studies and it seems that HP diets might be deleterious only in patients with preexisting metabolic renal dysfunction. Thus, HP diet does not seem to lead to calcium bone loss, and the role of protein seems to be complex and probably dependent on other dietary factors and the presence of other nutrients in the diet.
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Introduction

The ingestion of protein-rich diets has been associated with modifications of urinary calcium and acid excretions suspected to reflect a state of slight acidosis inducing an environment favorable for demineralization of the skeleton and development of kidney stones. The metabolism of dietary proteins contributes to endogenous acid production, mainly through oxidation of sulfur amino acids and phosphoproteins. However, different results also support a positive relation between protein intake and bone health. In this review, we attempted to summarize the effects of high-protein (HP) diets on bone health and renal function, also considering the relationships between dietary protein intake, acid–base status and calcium metabolism. To identify the related literature, searches were conducted in the MEDLINE database through PubMed using the following keywords: high-protein diets, dietary proteins, protein intake, meat intake, acid–base balance, renal net acid excretion, hypercalciuria, calcium balance, urinary calcium, calcium excretion, calcium absorption, bone health, bone mass and fractures. Reference lists were reviewed for supplemental relevant studies. An attempt was also made to interpret the differences in the reported effects with regard to variations in dietary intakes.

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Protein intake, urinary calcium and acid excretions and calcium balance

Dietary protein and urinary calcium and acid excretions

Controlled feeding studies showed a hypercalciuric effect of HP diets when supplemental proteins were added in the form of purified proteins (casein, lactalbumin, wheat gluten, dried white eggs), with urinary calcium excretion being increased by 0.7–2.2 mg/g of supplemental ingested protein, at constant levels of calcium intake (Johnson *et al.*, 1970; Anand and Linkswiler, 1974; Kim and Linkswiler, 1979; Schuette *et al.*, 1980; Hegsted and Linkswiler, 1981; Hegsted

Table 1 Main reported effects of HP diets on urinary acid excretion in association with increased calcium urinary excretion, depending on the type and amount of dietary proteins

Author	*Changes in urine pH*[a]	*Changes in RNAE (mEquiv./day)*[a]	*Changes in urinary TA (mEquiv./day)*[a]	*Changes in urinary Ca excretion*[a]	*Type of supplemental P in HP diet compared with LP diet*	*Changes in protein intake (g/day)*[b]	*Study design*	n
Lutz (1984)	↓ (−0.8)	↑ (+40)	↑ (+10)	↑ (+94%)	Purified P (C, LA, WG)	+58 (44 vs 102)	CF-CO	6
Trilok and Draper (1989)	↓	↑ (+15)	↑ (+5)	↑ (+50–70%)	Purified P (C, LA, WG, WE)	+60 (50 vs 110)	CF-CO	8
Schuette *et al.* (1980)		↑ (+15)	↑ (+10)	↑ (+84%)	Purified P (LA, WG)	+65 (45 vs 110)	CF-CO	11
Hegsted and Linkswiler (1981)		↑ (+43)	↑ (+11)	↑ (+88%)	Purified P (C, LA, WG, WE)	+77 (46 vs 123)	CF-CO with 1st diet period = 60days 2nd diet period = 15 days	6
Schuette and Linkswiler (1982)		↑ (+86)	↑ (+32)	↑ (+53%)	Purified P (C, LA, WG, WE)	+90 (55 vs 145)	CF-CO	8
Roughead *et al.* (2003)	↓ (−0.1)		↑ (+4)	=	Meat	+50 (68 vs 117)	CF-CO	15
Reddy *et al.* (2002)	↓ (−0.5)			↑ (+56%)	Meat (Atkins diet vs usual diet)	+73 (91 vs 164)	1 week *ad libitum* with FR and 1 week with CF-CO	10
Schuette *et al.* (1982)		↑ (+40)	↑ (+12)	↑ (+28%)	Meat	+90 (55 vs 145)	CF-CO	8
Hunt *et al.* (2009)	↓ (−0.3)		↑ (+10)	↑ (+11%)	Meat and milk	+55 (58 vs 113)	CF-CO, diets with two levels of Ca	27
Hunt *et al.* (2009)	↓ (−0.4)		↑ (+13)	↑ (+18%)	Meat and milk	+55 (58 vs 113)	CF-CO, diets with two levels of Ca	27
Remer and Manz (1994)	↓ (−1.2)	↑ (+112)		↑ (+126%)	Animal P	+71 (49 vs 120)	CF-CO	6
Schuette *et al.* (1982)		↑ (+48)	↑ (+19)	↑ (+71%)	Meat and dairy products	+90 (55 vs 145)	CF-CO	8
Kerstetter *et al.* (2006)		↑ (+18)		↑ (+47%)	Meat, fish and dairy products	+90 (45 vs 135)	CF-CO	20
Frank *et al.* (2009)	↓ (−0.7)				Animal P	+93 (88 vs 181)	FE with recommendations to achieve the dietary intervention goals and daily FR-CO	24
Wagner *et al.* (2007)	↓ (−0.8 to −0.4)			↑ (+100%)	Meat and dairy products	+1.5g/kg per day	CF-CO	24
Kerstetter *et al.* (2006)		↑ (+28)		↑ (+26%)	Soy P	+90 (45 vs 135)	CF-CO	20

Abbreviations: C, casein; CF, controlled feeding study (all the food was provided to the subjects); CO, cross-over design (either randomized or not randomized); FE, free eating; FR, food records; G, gelatin; HP, high protein; LA, lactalbumin; LP, low protein; RNAE, renal net acid excretion; TA, titratable acids; WE, dried white eggs; WG, wheat gluten.

[a]Changes in parameters values under HP diet compared with LP diet: ↑ indicates an increase in the parameter values, ↓ indicates a decrease in the parameter values, = indicates no significant changes in the parameter values.

[b]Difference in the amount of proteins in the HP diet compared with the LP diet (amount of proteins in the LP diet vs amount of proteins in the HP diet).

et al., 1981; Zemel *et al.*, 1981; Schuette and Linkswiler, 1982; Lutz, 1984; Trilok and Draper, 1989; Pannemans *et al.*, 1997; Wagner *et al.*, 2007) (Table 1). Increased urinary calcium excretion was also observed in omnivorous than in vegetarian women (Ball and Maughan, 1997) or in subjects following an Atkins diet (Reddy *et al.*, 2002). However, other studies reported no change in the level of urinary calcium with the consumption of high-meat diets compared with low-meat diets (Spencer *et al.*, 1978, 1983, 1988). The hypercalciuric effect of HP diets certainly depends on the nature of the dietary protein, and food with HP contents, such as meat or dairy products, also contain components that limit urinary calcium excretion. For instance, phosphorus exerts a hypocalciuretic effect that counteracts the hypercalciuretic effect of protein intake. When protein and calcium intakes are held constant, an increase in phosphorus intake causes a decrease in urinary calcium between 40 and 65% depending on the level of protein intake (Hegsted *et al.*, 1981).

HP diets were also associated with a higher acid excretion, as reflected by a decrease in urine pH and an increase in total renal net acid excretion. In controlled feeding studies, comparing diets with low and high levels of proteins, urinary pH was reduced by 0.3–0.8 Units when protein intake was increased by 40–60 g/day (Lutz, 1984; Trilok and Draper, 1989; Reddy *et al.*, 2002; Roughead *et al.*,

2003). Increases in renal net acid excretion ranging from 0.4 to 1 mEquiv. were reported for ingestion of 1 g supplemental proteins (Schuette *et al*., 1980; Hegsted and Linkswiler, 1981; Schuette and Linkswiler, 1982; Lutz, 1984; Reddy *et al*., 2002). The level of supplemental acid excretion induced by higher protein intakes may depend on the nature of the ingested proteins. For instance, renal net acid excretion was shown to be positively correlated with non-dairy (Hu *et al*., 1993) and total (Frassetto *et al*., 1998) animal protein intake but not with plant protein intake (Frassetto *et al*., 1998).

However, the increased renal acid load under HP diets is not necessarily associated with modifications of the systemic acid load. Plasma pH and bicarbonate concentration remain within normal ranges when increasing the protein intake up to 164 g/day (Reddy *et al*., 2002) or 2 g/kg (Wagner *et al*., 2007). The preservation of the systemic acid–base equilibrium suggests that protein-induced acid loads can be adequately handled by the kidney through excretion of excess produced acid and by activation of buffer systems.

Protein intake and calcium balance

Calcium balance is defined as calcium intake minus the sum of urinary and fecal calcium excretions. Although there is a large consensus over the increase in urinary calcium excretion with increase in protein intake, the effect of HP diets on whole-body calcium is less clear (Table 2). In some studies, HP diets, associated with increased levels of urinary calcium, resulted in lower and negative calcium balances compared with low protein (LP) diets (Johnson *et al*., 1970; Anand and Linkswiler, 1974; Kim and Linkswiler, 1979; Allen *et al*., 1979b; Hegsted *et al*., 1981; Schuette and Linkswiler, 1982; Lutz, 1984), with a decrease in daily calcium balance ranging from 1 to 1.6 mg/g of supplemental ingested proteins. Other studies reported no changes in calcium balance with HP diets, either with no changes in urinary calcium excretion and calcium absorption when proteins were given as meat (Spencer *et al*., 1983; Draper *et al*., 1991) or with a decrease in fecal calcium excretion, which compensates for the increase in urinary calcium when supplemental proteins were added to the diet as purified proteins (Cummings *et al*., 1979; Pannemans *et al*., 1997).

The discrepancies among the reported effects of HP diets on calcium balance may be partly explained by the difficulties in measuring whole-body calcium balance. First, fecal calcium losses which need to be measured over a 5–10-day period to be representative of the diet, are up to 10 times greater than urinary calcium losses, and an error in fecal calcium determination can strongly skew the estimation of calcium balance. In addition, dietary factors, such as calcium and phosphorus intakes, also modulate calcium balance. At high levels of protein intake, an increase in phosphorus intake causes the calcium balance to change from negative to positive (Hegsted and Linkswiler, 1981). A HP and high phosphorus intake was associated with a positive calcium balance with high calcium intakes but with a negative balance with low calcium intake (Schuette and Linkswiler, 1982). These effects are of particular importance as an increase in protein intake from ordinary food is generally accompanied by an increase in phosphorus intake, as meat and dairy products are also rich in phosphorus, and it may explain why smaller changes in calcium balance are usually observed in studies in which HP intakes consist in high-meat or high-dairy products instead of purified proteins.

Protein intake and modulations of calcium metabolism

Modulation of calcium renal handling

The hypercalciuric effect of dietary proteins likely results from an alteration of calcium renal handling (Table 3). A two- or three-fold increase in protein intake causes a 6–20% increase in glomerular filtration rate (Kim and Linkswiler, 1979; Allen *et al*., 1979b; Schuette *et al*., 1980; Hegsted and Linkswiler, 1981; Hegsted *et al*., 1981; Zemel *et al*., 1981), thus resulting in an increased filtered load of calcium. In parallel, the fractional tubular reabsorption is decreased by 0.9–2% when the protein intake is increased by 100–200% (Kim and Linkswiler, 1979; Hegsted and Linkswiler, 1981; Hegsted *et al*., 1981; Zemel *et al*., 1981). These modulations of the renal function seem to be due to a direct effect of proteins on renal cells, as the circulating level of the major regulatory hormone of calcium metabolism, namely the parathyroid hormone, does not vary with the increase in protein intake (Kim and Linkswiler, 1979; Allen *et al*., 1979b; Schuette *et al*., 1980).

Alterations of calcium renal handling could also be caused by the increased acid excretion associated with HP intakes. Urinary calcium excretion was reported to be higher by $\sim$100 mg/day under an acid-forming diet compared with a base-forming diet (Buclin *et al*., 2001). Meta-analysis of studies in which the acid–base intake was manipulated through changes in food intake or supplementation shows a positive correlation between urinary net acid excretion and urinary calcium, with a 0.9–1.4 mg increase in urinary calcium for a 1mEquiv. increase in acid excretion (Fenton *et al*., 2008, 2009). The relationship between acid and calcium excretion is further supported by the fact that addition of base to the diet in the form of sodium bicarbonate partially negates the hypercalciuretic effect of the HP diet (Lutz, 1984). More specifically, increased urinary calcium excretion under HP diet is often attributed, at least partially, to the increase in urine excretion of sulfate which results from the increased metabolism of sulfur amino acids (Schuette *et al*., 1980). However, sulfur amino acids added to a LP diet, with amounts similar to that present in a HP diet, cause an increase in urinary calcium that account for only 44% of the increase caused by the HP diet (Zemel *et al*., 1981), suggesting that other factors, such as ammonia excretion, are involved in protein-induced hypercalciuria. Hormones such as insulin, growth hormones and glucocorticoids, which affect calcium excretion, may also be

Table 2 Main reported effects of diets with different levels of protein on calcium balance, calcium intestinal absorption and calcium urinary excretion

	Changes reported in HP diets compared with LP diets			*Method used for measure of Ca intestinal absorption*	*Dietary intakes*				*Study characteristics*			
	Urinary Ca excretion (mg/g added P)	*Intestinal Ca absorption (mg/day)*	*Ca balance (mg/day)*[a]		*Proteins in LP vs HP diets (g/day)*[b]	*Type of supplemental P in HP diet compared with LP diet*	*Calcium (mg/day)*[c]	*Phosphorus (mg/day)*[c]	*Design*[d]	n	*Duration*	*Particularities*
Increase in urinary calcium excretion												
Trilock *et al.* (1989)	+1				50–110	Purified P (C, LA, WG, WE)	=(800)	=(800)	CF-CO	8	7 days	
Zemel *et al.* (1981)	+2				70–120	Purified P (C, LA, WG, WE)	=(500)	=(1100)	CF-CO	8	12 days	
Licata (1981)	+0.9				28–115	Complex P (meat)	=(800)	=(1500)	CF-CO	6	7 days	
Ball and Maughan (1997)	+1.7				55–70	Complex P (vegetarian vs omnivorous diets)	=(1000)	=(1250)		33		Evaluation of protein intake by food reports
Remer *et al.* (1994)	+1.4				49–120	Complex P (animal)	?	?	CF-CO	6	5 days	
Wagner *et al.* (2007)	+0.7				35–140	Complex P (meat)	?	?	CF-CO	24	7 days	
Increase in urinary calcium excretion with no change in intestinal calcium absorption and decrease in calcium balance (mainly observed under supplementation with purified proteins)												
Anand and Linkswiler (1974)	+1.4	NS	−151 (<0)	Balance	47–142	Purified P (C, LA, WG, G)	=(500)	=(800)	CF-CO	9	15 days	
Lutz *et al.* (1984)	+1.6	NS	−76 (<0)	Balance	44–102	Purified P (C, LA, WG)	=(500)	=(900)	CF-CO	6	15 days	Postmenopausal women
Hegsted and Linkswiler (1981)	+1.3	NS	−107 (<0)	Balance	46–123	Purified P (C, LA, WG, WE)	=(500)	=(900)	CF-CO	6	15–60 days	
Kim and Linkswiler (1979)	+1.6	NS	−141 (<0)	Balance	47–142	Purified P (C, LA, WG)	=(500)	=(1110)	CF-CO	6	10 days	
Hegsted *et al.* (1981)[d]	+1.8	NS	−140 (<0)	Balance	50–150	Purified P (C, LA, WG, WE)	=(500)	=(1010)	CF-CO	8	12 days	
Schuette *et al.* (1980)	+1.3	NS	−70 (<0)	Balance	45–110	Purified P (C, LA)	=(750)	=(1100)	CF-CO	11	12 days	Older subjects (>45 years)
Walker and Linkswiler (1972)	+2.2	NS	−97 (<0)	Balance	47–142	Purified P (C, LA, WG, G)	=(800)	=(1000)	CF-CO	9	14 days	
Johnson *et al.* (1970)	+1.7	NS	−94 (<0)	Balance	47–142	Purified P (C, LA, WG, G)	=(1400)	=(1400)	CF-CO	6	45 days	
Allen *et al.* (1979b)	+0.6	NS	−100 (<0)	Balance	100–260	Purified P (soy P isolate)	=(1400)	=(2300)	CF-CO	6	47 days	
Schuette *et al.* (1982)[e]	+0.9	NS	−78 (<0)	Balance	55–146	Purified P (C, LA, WG, WE)	=(600)	>(1660)	CF-CO	8	10–15 days	
Reddy *et al.* (2002)	+1.2	NS	−130 (<0)	Dual tracer stable isotope	91–164	Complex proteins (meat)	=(850)	>(2000)	CF-CO	10	14 days	
Increase in urinary calcium excretion with no change in intestinal calcium absorption or in calcium balance: increases in urinary excretion are smaller and these effects are mainly observed when higher protein levels are reached by addition of food rich in proteins (meat, dairy products … as opposed to purified proteins) with a concomitant increase in phosphorus intake, suggesting a compensating effect of dietary phosphorus in the diet												
Hegsted *et al.* (1981)[d]	+0.3	NS	NS (=0)	Balance	50–150	Purified P (C, LA, WG, WE)	=(500)	=(2525)	CF-CO	8	12 days	
Ceglia *et al.* (2009)	+0.6	NS	?	Dual tracer stable isotope	30–100	Complex P (meat)	=(600)	>(1125)	CF-CO	23	10 days	Older subjects (>50 years)

Table 2 *Continued*

	Changes reported in HP diets compared with LP diets			*Method used for measure of Ca intestinal absorption*	*Dietary intakes*				*Study characteristics*			
	Urinary Ca excretion (mg/g added P)	*Intestinal Ca absorption (mg/day)*	*Ca balance (mg/day)*[a]		*Proteins in LP vs HP diets (g/day)*[b]	*Type of supplemental P in HP diet compared with LP diet*	*Calcium (mg/day)*[c]	*Phosphorus (mg/day)*[c]	*Design*[d]	n	*Duration*	*Particularities*
Kerstetter *et al.* (2006)[f]	+0.7	NS	?	Dual tracer stable isotope	45–135	Complex P (animal)	=(800)	>(1290)	CF-CO	20	4 d	Eight postmenopausal women
Kerstetter *et al.* (2006)[f]	+0.4	NS	?	Dual tracer stable isotope	45–135	Complex P (vegetal)	=(800)	>(1520)	CF-CO	20	4 d	Eight postmenopausal women
Schuette *et al.* (1982)[e]	+0.5	NS	NS (=0)	Balance	55–146	Complex P (meat)	=(600)	>(1660)	CF-CO	8	10–15 d	
Hunt *et al.* (2009)[g]	+0.4	NS	NS	Radiotracer	58–113	Complex P (meat + milk)	=(1510)	>(1960)	CF-CO	27	7 wks	
Increase in urinary calcium excretion with increase in intestinal calcium absorption and no change in calcium balance: the increase in calcium absorption compensates for the increase in calcium urinary excretion												
Lutz (1981)	+1.4		NS (<0)	Balance	50–110	Purified P (LA, WG)	=(710)	=(1080)	CF-CO	8	15 days	Postmenopausal women
Pannemans *et al.* (1997)	+0.7		NS (=0)	Balance	80–140	Purified P (C, WG, soyabean)	>(1200)	>(1800)	CF-CO	28	3 weeks	Two groups of subjects differing in age
Kerstetter *et al.* (2005)	+1	+1.3	NS (<0)	Dual tracer stable isotope	67–136	Complex P (animal and vegetal)	=(800)	=(2200)	CF-CO	10	10 days	
Kerstetter *et al.* (1998)	+1	+0.9	NS	Dual tracer stable isotope	46–135	Complex P (meat + dairy products)	=(800)	>(1170)	CF-CO	7	5 days	
Hunt *et al.* (2009)[g]	+0.4	+0.3	NS	Balance	58–113	Complex P (meat + milk)	=(675)	>(1780)	CF-CO	27	7 weeks	
Cummings *et al.* (1979)	+0.7	+0.6	NS (>0)	Balance	63–136	Complex P (meat)	=(980)	?	CF-CO	4	3 weeks	
Schuette *et al.* (1982)[e]	+1.2	+2.1	NS (=0)	Balance		Complex P (meat + dairy products)	>(1370)	>(2060)	CF-CO	8	10–15 days	
No change in calcium homeostasis												
Draper *et al.* (1991)	NS	NS	NS (<0)	Balance	55–146	Complex P (meat)	=(650)	>	CF	8	15 days	Postmenopausal women
Hunt *et al.* (1995)	NS	NS	NS (>0)	Balance	55–110	Complex P (meat)	=(750)	>(1700)	CF-CO	14	7 weeks	Postmenopausal women
Spencer *et al.* (1983)	NS	NS	NS (=0)	Radiotracer	76–142	Complex P (meat)	=(800)	>(1300)	CF-CO	7	18–130 days	
Roughead *et al.* (2003)	NS	NS		Radiotracer	68–117	Complex P (meat)	=(600)	>(1700)	CF-CO	15	8 weeks	Postmenopausal women

Abbreviations: C, casein; CF, controlled feeding study (all the food was provided to the subjects); CO, cross-over design (either randomized or not randomized); G, gelatin; HP, high protein; LA, lactalbumin; LP, low protein; NS, no significant changes in Ca balance; WE, dried white eggs; WG, wheat gluten; ? indicates that information was not provided in the article.

[a]Estimated as Ca balance under HP diet −Ca balance under LP diet; <0 indicates negative Ca balance under the HP diet.

[b]= indicates that the level of calcium or phosphorus intake was held constant across protein levels by supplementation; '>' indicates higher level of calcium or phosphorus intake with the HP diet.

[c]The lowest and the highest levels of protein intake are reported if >2 levels of protein intake were investigated.

[d]Results from the same study, under two different levels of phosphorus intake.

[e]Results from the same study, with different type of supplemental proteins.

[f]Results from the same study, with two different types of supplemental proteins (animal vs vegetal).

[g]Results from the same study, under two different levels of Ca intake.

Table 3 Main reported effects of HP diets on renal handling of calcium

	Changes in GFR[a]	*Changes in FTR*[a]	*Changes in urinary Ca*[a]	*Dietary intakes*			*Study design*	*Subjects*			*Duration of diet*
				Changes in protein intake (g/day)[a]	*Type of added P in HP diet compared with LP diet*	*Calcium (mg/day)*[b]		n	*Sex*	*Age*	
Increase in GFR[c]											
Allen *et al.* (1979b)	+14%		+47%	+160	Soy P	=(1400)	CF-CO	6	♂		47 days
Kerstetter *et al.* (2006)	+10%		+47%	+90	Soy P	=(800)	CF-CO	20	♀	12 young (30 years) and 8 older (60 years)	4 days
Kerstetter *et al.* (2006)	+14%		+26%	+90	Animal P	=(800)	CF-CO	20	♀	12 young (30 years) and 8 older (60 years)	4 days
Kerstetter *et al.* (1998)	+15%		+64%	+89	Animal P	=(800)	CF-CO	7	♀	Young (25 years)	5 days
Wagner *et al.* (2007)	+3%		+100%	+1.5 g/kg per day	Animal P	?	CF-CO	24	♀/♂	Young (25–40 years) and older (55–70 years)	1 week
Frank *et al.* (2009)	+13%			+93	Animal P	?	FE-CO	24	♂	Young (20–30 years)	7 days
Increase in GFR and decrease in FTR associated with an increase in urinary calcium											
Schuette *et al.* (1980)	+20%	−0.9%	+84%	+65	Purified P[d]	=(750)	CF-CO	11	♀/♂	44–86 years	12 days
Hegsted and Linkswiler (1981)	+12%	−0.9%	+88%	+77	Purified P[d]	=(500)	CF-CO	6	♀	Young	60 or 15 days
Kim *et al.* (1979)	+10%	−1%	+100%	+95	Purified P[d]	=(515)	CF	6	♂	Young	10 days
Zemel *et al.* (1981)	+6%	−2%	+100%	+100	Purified P[d]	=(500)	CF-Fact.	8	♂	Young	12 days
Hegsted *et al.* (1981)	+16%	−1.7%	+114%	+100	Purified P[d]	=(500)	CF-CO	8	♂		12 days
Hegsted *et al.* (1981)	+8%	−1%	+29%	+100	Purified P[d]	=(500)	CF-CO	8	♂		12 days
No change in GFR											
Kerstetter *et al.* (2005)	NS		+47%	+69	Animal and vegetal P	=(800)	CF-CO	10	♀	Young (20–40 years)	10 days
Modulations of renal function in the postprandial phase, after a HP meal challenge											
Burodom (2010)	+64%			+0.8g/kg	Animal P (chicken)			11	♀/♂		
Burodom (2010)	+58%			+0.8g/kg	Animal P (egg white)			11	♀/♂		
Allen *et al.* (1979a)	NS			+36g	Animal P (dairy P)	=(400)		9	♀/♂		
Allen *et al.* (1981)		NS		+30g		=(400)		11	♀/♂		

Abbreviations: CF, controlled feeding study (all the food was provided to the subjects); CO, cross-over design (either randomized or not randomized); fact., factorial design; FTR, fractional tubular reabsorption; GFR, glomerular filtration rate; HP, high protein; LP, low protein; NS, no significant changes; ? indicates that information was not provided in the article.

[a]Changes in HP compared with LP diets (values in HP diet−values in LP diet).

[b]= indicates that the level of calcium intake was held constant across protein levels by supplementation; '>' indicates higher level of calcium or phosphorus intake with the HP diet.

[c]Results from studies without assessment of FTR.

[d]Casein, lactalbumin, wheat gluten, dried white eggs added in the HP diet to reach the high level of protein intake.

involved in the hypercalciuretic effect of proteins (Allen *et al.*, 1981; Zemel *et al.*, 1981).

Modulations of intestinal dietary calcium absorption

The oldest hypothesis for the increased urinary calcium induced by HP diet was that dietary proteins enhanced calcium intestinal absorption. However, the effect of HP diet on calcium intestinal absorption is unclear (Table 2).

McCance *et al.* (1942) first observed that subjects consuming a LP diet (<70 g/day) had a 20% decrease of intestinal calcium absorption compared with those consuming a HP diet (>145 g/day). These first findings were confirmed by

some intervention studies (Lutz and Linkswiler, 1981; Schuette and Linkswiler, 1982), whereas others studies were unable to demonstrate any effect of dietary protein on intestinal calcium absorption (Schuette *et al.*, 1980; Hegsted and Linkswiler, 1981; Hegsted *et al.*, 1981). However, in these studies, calcium absorption was estimated using the balance method, that is, by measuring the difference between calcium intake and fecal calcium losses. As quantifying fecal calcium losses is technically difficult and small changes in absorption may go undetected by this method, the results should be interpreted with caution. Moreover, true absorption might be underestimated as it is impossible to dissociate endogenous fecal calcium excretion from dietary calcium.

More recently, methods using calcium isotopes, such as the actual gold-standard double-tracer method (Heaney, 2000) or the radiotracer method, offer a more reliable way to assess intestinal calcium absorption, but results about the effect of dietary proteins on calcium absorption are still contradictory. Under comparable experimental conditions, some intervention studies found that a HP diet (1.5–2 g/kg compared with 0.5–1 g/kg proteins consumed each day) induced an increase in calcium absorption associated with an increased calcium excretion in premenopausal and postmenopausal women (Kerstetter *et al.*, 1998, 2005; Hunt *et al.*, 2009), whereas other studies found no effect of HP intake on calcium absorption, despite an increased calcium excretion (Kerstetter *et al.*, 2006; Ceglia *et al.*, 2009). A longitudinal observational study and interventions studies, using the radiotracer method to assess calcium balance, also did not find any effect of a HP diet on calcium intestinal absorption; but in these studies, no effect of the dietary protein was found on calcium excretion (Spencer *et al.*, 1983; Dawson-Hughes and Harris, 2002; Roughead *et al.*, 2003). The level of dietary calcium might modulate the effect of protein intake on calcium absorption and contribute to explain the conflicting results. Indeed, Hunt *et al*. (2009) showed that HP compared with LP intakes increased calcium absorption with low (700 mg/day) but not with high (1500 mg/day) dietary calcium intakes.

The possible mechanism for enhanced intestinal calcium absorption in response to dietary protein is unclear. Calcium absorption occurs primarily in the duodenum where gastric acid secretion permits to obtain a pH <6.0 necessary for the solubilization of calcium salts from ingested food (Goss *et al.*, 2007). Gastric acid production is not only stimulated by the parasympathetic nervous system but also by chemical signals, nutrients, including Ca^{2+} (Hade and Spiro, 1992; Geibel and Wagner, 2006) and some amino acids (Konturek *et al.*, 1978; Strunz *et al.*, 1978). Thus, the dietary protein might increase calcium solubility by stimulating gastric acid production (DelValle and Yamada, 1990; Schulte-Frohlinde *et al.*, 1993). Furthermore, some products of protein digestion, such as casein, seem to enhance calcium intestinal absorption through direct interactions with calcium (Ferraretto *et al.*, 2001; Erba *et al.*, 2002).

Data on variations of calcium intestinal absorption are of particular importance to determine changes in calcium balance under HP diets. Indeed, although urinary calcium is often reported as a marker of calcium metabolism, it is not an exact indicator of whole-body calcium loss as there may also be differences in calcium intestinal absorption that compensate for changes in calcium excretion.

Mobilization of bone calcium and net calcium retention

According to the acid-ash hypothesis, HP diets causes an excess acid load, which would be neutralized by the release of bicarbonate ions from the bone matrix, a mechanism that is accompanied by a loss of Na^+, K^+ and a small amount of Ca^{2+} (Green and Kleeman, 1991), and consequently, the increase in bone resorption is reflected by the increase in urinary calcium excretion (Barzel and Massey, 1998; Remer, 2000; Frassetto *et al.*, 2001; New, 2003) (Table 4). The acid load would also decrease osteoblastic activity and increase osteoclastic activity, resulting in net bone resorption with mobilization of calcium (Bushinsky, 1989; Krieger *et al.*, 1992; Alpern and Sakhaee, 1997). However, no convincing experimental data support this theory. Results on changes in urinary hydroxyproline, a marker of collagen metabolism, in response to HP diets are controversial, with some studies reporting elevation of urinary excretion of hydroxyproline with HP diets (Kim and Linkswiler, 1979; Schuette and Linkswiler, 1982), whereas other did not observe any change (Allen *et al.*, 1979b; Hunt *et al.*, 1995).

Protein intake and bone health

No clinical support for detrimental effects of protein intake on bone health

Protein intake was shown to be positively correlated with bone mass in several skeletal sites in every category of the population, from children to elderly men and women (Hirota *et al.*, 1992; Geinoz *et al.*, 1993; Devine *et al.*, 1995; Cooper *et al.*, 1996; Feskanich *et al.*, 1996; Teegarden *et al.*, 1998; Hannan *et al.*, 2000; Sellmeyer *et al.*, 2001; Whiting *et al.*, 2002; Ilich *et al.*, 2003; Alexy *et al.*, 2005; Budek *et al.*, 2007; Chen *et al.*, 2007; Chevalley *et al.*, 2008; Thorpe *et al.*, 2008). In their systematical review, Darling *et al*. (2009) noted that a large majority of the cross-sectional surveys or cohort studies reviewed reported either no association or a beneficial association between proteins and bone mineral density (BMD), and only one survey found a negative correlation between proteins and body mineral content. They conclude that dietary proteins, if not significantly favorable, are at least not detrimental to bone density. In addition, a recent longitudinal study including 540 premenopausal women found no adverse effect of increased protein intakes (from 5 to 25% of the energy intake) on BMD (Beasley *et al.*, 2010).

Studies frequently cited to support the deleterious effect of HP diet on bone health are retrospective analyses of hip

Table 4 Controversial results about the effects of HP diets on calcium metabolism and bone resorption

	Changes in markers of bone resorption (in urine)[a]	*Changes in markers of bone formation (in serum)*[a]	*Changes in regulators of Ca metabolism (in serum)*[a]			*Changes in urinary Ca*	*Diet*		*Study design*	*Subjects*			*Duration of the diet*
			PTH	*1.25-$(OH)_2$-D*	*IGF-1*		*Changes in protein intake (g/day)*[b]	*Calcium intake (mg/day)*[c]		n	*Sex*	*Age (years)*	
Decrease in markers of bone resorption under HP diets → despite their calciuretic effect, HP diets decrease bone catabolism													
Heaney *et al.* (1999)	↓ in NTX	= b-ALP	↓ (9%)	↓	↑ (10%)	↑	+20 (dairy P)	>(1500)	FE—PR	101		>55	12 weeks
Hunt *et al.* (2009)	↓ in DPD	= b-ALP; = OC	=	=	↑ (23%)	↑ (18%)	+55	=(675)	CF-CO	27	♀	60	7 weeks
Hunt *et al.* (2009)	↓ in DPD	= b-ALP; = OC	=	=	↑ (35%)	↑ (11%)	+55	=(1510)	CF-CO	27	♀	60	7 weeks
Ince *et al.* (2004)	↑ in NTX		↓ (8%)	=		↑ (47%)	−20 (P restriction)	=(820)	FE and CF—CT	42	♀	20–40	1 week
No change in markers of bone resorption → HP diets increase urinary calcium excretion but do not seem to alter calcium metabolism													
Schurch *et al.* (1998)	= DPD	= OC	=	=	↑ (84%)		+20	=(650)	FE—PR	33		>60	6 months
Ceglia *et al.* (2009)	= NTX	= OC	↓ (15%)		↑ (25%)	↑ (38%)	+70	=(600)	CF-CO	23	♀/♂	>50	10 days
Kerstetter *et al.* (2006)	= NTX		↓ (60%)			↑ (47%)	+90 (animal P)	=(800)	CF-CO	20	♀	30 and 60	4 days
Kerstetter *et al.* (2006)	= NTX		↓ (63%)			↑ (26%)	+90 (soy P)	=(800)	CF-CO	20	♀	30 and 60	4 days
Reddy *et al.* (2002)	= NTX; = DPD	↓ in OC; = b-ALP	=			↑ (56%)	+73	=(850)	FE and CF—CO	10			2 weeks
Allen *et al.* (1979b)	= HYP		=			↑ (47%)	+160	=(1400)	CF-CO	6	♂	23–30	47 days
Roughead *et al.* (2003)	= NTX	= b-ALP; = OC	=	=	=	=	+50	=(600)	CF-CO	15	♀	>50	8 weeks
Hunt *et al.* (1995)	= HYP	↓ in b-ALP; = OC	=	=		=		=(750)	CF-CO	14	♀	63	7 weeks
Increase in markers of bone resorption → increase in HP intake (by addition of purified P) may increase bone resorption.													
Kim *et al.* (1979)	↑ in HYP		=			↑ (100%)	+95 (purified P)	=(515)	CF	6	♂	21–29	10 days
Effects on regulators of Ca homeostasis (without evaluation of changes in markers of bone resorption)													
Kerstetter *et al.* (1998)			↓ (33%)	↓ (18%)		↑ (64%)	+89	=(800)	CF-CO	7	♀	25	5 days
Licata *et al.* (1981)			↓ (37%)			↑ (84%)	+87	=(800)	CF-CO	6	♀/♂	41	7 days
Lutz *et al.* (1981)			=	=		↑ (91%)	+60	=(710)	CF-CO	8	♀	>50	15 days
Schuette *et al.* (1980)			=	=		↑ (84%)	+65	=(750)	CF-CO	11	♀/♂	44–86	12 days
Kerstetter *et al.* (2005)			=			↑ (47%)	+69	=(800)	CF-CO	10	♀	20–40	10 days

Abbreviations: b-ALP, bone-specific alkaline phosphatase; CF, controlled feeding study (all the food was provided to the subjects); CO, cross-over design; CT, controlled trial; DPD, deoxypyridinoline; FE, free eating; HP, high protein; HYP, hydroxyproline; LP, low protein; IGF-1, insulin-like growth factor-1; NTX, N-terminal telopeptide; PR, parallel randomized design; PTH, parathyroid hormone; OC, osteocalcin; 1.25-$(OH)_2$-D, 1.25-Dihydroxycholecalciferol.

[a]Changes in parameters values under HP diet compared with LP diet: ↑ indicates an increase in the parameter values, ↓ indicates a decrease in the parameter values, = indicates no significant changes in the parameter values.

[b]Changes in HP compared with LP diets (values in HP diet-values in LP diet).

[c]= indicates that the level of calcium intake was held constant across protein levels by supplementation; '>' indicates higher level of calcium or phosphorus intake with the HP diet.

fracture incidence in postmenopausal women of different countries (Abelow *et al*., 1992; Frassetto *et al*., 2000), which found that the highest rate of hip fractures occurred in industrialized Western countries, which have the highest animal protein intake. However, there are several obvious limitations to these studies as noted by Bonjour (2005). First, countries with the highest incidence of hip fractures are also those with the longest life expectancy, which is an important determinant of the risk of osteoporotic fracture (Kannus *et al*., 1996). The protein intake was then estimated from the whole population but not for the specific studied group. Finally, interethnic differences in risk of osteoporotic

fracture are well known and may be attributable to many factors such as bone structure, genotype or lifestyle (Nelson and Megyesi, 2004; Lei *et al*., 2006). Other epidemiological data provide some weak evidence that fracture incidence was related to higher protein intake. In the 12-year Nurses' Health Study carried out in the United States, women who consumed >95 g protein/day had an increased risk of forearm fracture but not of hip fracture (Feskanich *et al*., 1996). In a retrospective Norwegian survey, an elevated risk of hip fracture was associated with high non-dairy protein intake only when calcium intake was low (Meyer *et al*., 1997). A major limitation of both studies was the use of a mailed food frequency questionnaire at a limited number of occasions and limited evaluation of other lifestyle and dietary factors that may have contributed to fracture risk. On the contrary, many other prospective studies have found a clear negative association between protein intake and risk of hip fracture in the elderly (Huang *et al*., 1996; Munger *et al*., 1999; Wengreen *et al*., 2004; Misra *et al*., 2010). In a meta-analysis of cohort studies, Darling *et al*. (2009) found no association between protein intake and risk fracture. In addition, in intervention studies, oral protein supplementations significantly improved clinical outcomes after hip fractures in the elderly (Delmi *et al*., 1990; Tkatch *et al*., 1992; Schurch *et al*., 1998).

Impact of calcium intake on the relationship between protein intake and bone health

There is some evidence that the beneficial effect of protein intake on bone mineral mass is better expressed when supplies of both calcium and vitamin D are adequate (Heaney, 2001, 2002; Dawson-Hughes, 2003). In Norwegian women, protein intake was not correlated with the risk of hip fractures, except when the protein intake was the highest and the calcium intake the lowest (Meyer *et al*., 1997). In a 3-year intervention study in men and women older than 65 years, no relation was found between protein intake and BMD in the placebo group (which had a normal calcium intake), whereas HP diets had a beneficial effect on BMD in the calcium-supplemented group (Dawson-Hughes and Harris, 2002).

Taken together, the studies regarding protein intake and bone health suggest that high-dietary protein intake promotes bone growth and retards bone loss and that LP diet is associated with higher risk of hip fractures. The positive effects of dietary protein intake on bone health seem to be dependent, at least in part, on calcium intake. Furthermore, maintenance of adequate bone strength and density with aging is highly dependent on the maintenance of adequate muscle mass and muscle mass is in turn dependent on adequate intake of high-quality protein (Wolfe, 2006; Heaney and Layman, 2008).

Mechanisms supporting the beneficial effect of protein on bone health

Mechanisms by which the protein positively affects bone health mainly implied insulin-like growth factor-1 (IGF-1). Intake of proteins induces production and action of IGF-1 in both animal and human studies (Schurch *et al*., 1998; Heaney *et al*., 1999; Arjmandi *et al*., 2003; Dawson-Hughes, 2003; Ceglia *et al*., 2009). IGF-1 is a major regulator of bone metabolism that can act as a systemic and local regulator of osteoblastic function (Mohan *et al*., 1992; Langdahl *et al*., 1998) and as a coupling factor in bone remodeling by activating both bone resorption and bone formation (Rubin *et al*., 2002). As reviewed by Bonjour *et al*. (1997) and Thissen *et al*. (1994), the impact of dietary protein on IGF-1 and the impact, in turn, of IGF-1 on bone health has a key role in the prevention of osteoporosis. In adult rats, a LP diet was shown to decrease plasma IGF-1 level and to induce negative bone balance with a decreased formation and an increased resorption (Ammann *et al*., 2000; Bourrin *et al*., 2000a, b). This effect was reversed by amino-acid supplementation (Ammann *et al*., 2000).

Protein intake, kidney function and kidney stone formation

The potentially harmful effects of dietary proteins on renal function are believed to be due to the 'overwork' induced by such diets on the kidneys. Indeed, as shown previously, HP diets cause elevation of glomerular filtration rate and hyperfiltration (Kim and Linkswiler, 1979; Schuette *et al*., 1980; Hegsted and Linkswiler, 1981; Hegsted *et al*., 1981; Zemel *et al*., 1981; Brenner *et al*., 1982; Bilo *et al*., 1989; Metges and Barth, 2000; Tuttle *et al*., 2002; Frank *et al*., 2009; Burodom, 2010). In animal models, HP diets induce a renal hypertrophy (Addis, 1926; Wilson, 1933; Hammond and Janes, 1998) but not systematically (Robertson *et al*., 1986; Collins *et al*., 1990; Lacroix *et al*., 2004), and to our knowledge, the link between protein-induced renal hypertrophy or hyperfiltration and the initiation of renal disease in healthy individuals has not been clearly shown. Only one recent study showed in pigs that a long-term HP diet (4 or 8 months) resulted in enlarged kidneys and increased evidence of renal damages (Jia *et al*., 2010). In their review, Martin *et al*. (2005), concluded that there is no significant evidence of an association between HP intakes and the initiation or progression of renal disease in healthy individuals. For instance, in an observational study, high animal protein intake was correlated with a decline in renal function in women with preexisting renal disease, but not in women with normal renal function (Knight *et al*., 2003). In long interventional studies, including overweight or obese healthy subjects, without preexisting renal dysfunction, the HP diet did not adversely affect renal function, whether it increased glomerular filtration rate and kidney size (Skov *et al*., 1999) or whether it did not (Brinkworth *et al*., 2010). However, HP diets have been shown to accelerate renal deterioration in patients with kidney dysfunction, and protein restriction is a common strategy to postpone the progression of renal diseases (Klahr, 1989; Pedrini *et al*.,

1996; Robertson *et al*., 2007). Martin *et al*. (2005) suggest that in healthy people, renal hypertrophy increased glomerular filtration rate, and hyperfiltration induced by HP intakes might be normal physiological adaptations to the increased demand on kidney due to its role as an acid buffer. Taken together, these results suggest that HP diets might not have an adverse effect on healthy people but may accelerate renal diseases in people with renal dysfunction.

Another potentially harmful effect of HP consumption, especially animal proteins, concerns its relation with kidney stone formation. HP intake induces an increase in calcium and acid excretion, which are considered as potentially lithogenic substances (Robertson *et al*., 1979; Wasserstein *et al*., 1987). Prospective studies found an elevated risk of stone formation with high animal protein intakes in men or women with no history of kidney stones (Curhan *et al*., 1993, 1997), whereas others reported an unchanged or reduced risk (Hirvonen *et al*., 1999; Curhan *et al*., 2004). High intakes of animal protein (meat) were shown to adversely affect markers of stone formation in male recurrent stone formers, whereas no changes were observed in healthy individuals (Nguyen *et al*., 2001). It is possible that, as for renal disease, proteins are harmful only in patients with a preexisting dysfunction (Jaeger *et al*., 1983; Hess, 2002). Furthermore, although calcium from supplementation may be associated with an increase risk of stone formation (Curhan *et al*., 1997), a higher intake of dietary calcium has been shown to decrease the risk of kidney stone formation in healthy subjects (Curhan *et al*., 1993, 1997, 2004). As high calcium intakes reduced the absorption of oxalate, another impor-

Table 5 Main effect of high fruit and vegetable intake and potassium on calcium and acid–base balance and on bone and renal health

Effect of a diet rich in fruits and vegetables	
On bone health	
● Positive association between fruit and vegetable intake and BMD and bone mass	New *et al*. (1997); Tucker *et al*. (1999); New *et al*. (2000); Tucker *et al*. (2001); New (2003); Hardcastle *et al*. (2011)
● Inhibitory activity of vegetable on bone resorption	
→ Not mediated by base excess: pharmacologically active compounds? Effect of K *per se*?	Muhlbauer *et al*. (2002)
On renal health	
● Positive correlation between diets with high intake of fruits, vegetables, whole grains, nuts and dairy products and low intake of red and processed meat (that is, low PRAL index) and higher excretion of urinary citrate	Trinchieri *et al*. (2006); Taylor *et al*. (2010)
→ Reduction of stone risk	
→ *Beneficial effect of fruits and vegetables on bone and renal health: effect of base excess and/or of nutrients composition (K)*	
Effect of potassium	
On calcium balance	
● Reduction of urinary Ca excretion and positive Ca balance with short-term administration of $KHCO_3$ in healthy adults	Lemann *et al*. (1989); Lemann *et al*. (1993); Sebastian *et al*. (1994); Whiting *et al*. (1997)
● No systematic effect of short-term administration of $NaHCO_3$ on urinary Ca excretion	
→ Possible effect of K *per se* and not only of bicarbonate	Lutz (1984); Lemann *et al*. (1989)
● Dietary K is associated with urinary Ca excretion, but without any effect on Ca balance as Ca intestinal absorption is also reduced	
→ Possible different effects depending of the source of K	Rafferty *et al*. (2005)
On bone health	
● Positive association between high intake of K and BMD and bone mass	New *et al*. (1997); Tucker *et al*. (1999); New *et al*. (2000); Tucker *et al*. (2001)
On renal health	
● Prevention of calcium oxalate stones by potassium-magnesium citrate supplementation in at-risk patients	Ettinger *et al*. (1997); Zerwekh *et al*. (2007)
Possible mechanisms of K	
● Effect on calcium balance	
→ Stimulation of renal phosphate reabsorption capacity, leading to lower serum 1.25-dihydroxycholecalciferol concentration and consequent decrease intestinal Ca absorption	Jaeger *et al*. (1983); Rafferty and Heaney (2008)
● Effect on acid–base balance	
→ Neutralization of excess sulfate ions providing by sulfur amino acid	Markovich *et al*. (1999)
→ Modulation of various processes activated by acidosis	Caudarella *et al*. (2003); Tosukhowong *et al*. (2005)
● Effect on stone formation	
→ Positive effector of citrate excretion	Marangella *et al*. (2004); Demigne *et al*. (2004)
→ Modulation of various processes activated by acidosis	Caudarella *et al*. (2003); Tosukhowong *et al*. (2005)

Abbreviations: BMD, bone mineral density; PRAL, potential renal acid load.

tant risk factor for kidney stone formation, increasing calcium intake could decrease urinary oxalate excretion and thus offset the stone-promoting effect of the increase in urinary calcium (Heaney, 2006). This result suggests that dairy products might be beneficial for preventing kidney stone formation in healthy subjects.

Impact of other dietary factors on bone health and kidney function

The effect of proteins also depends on the presence of other nutrients in the diet (Table 5). High intakes of fruits and vegetables are associated with bone health in adult and elderly men and women (New *et al*., 1997, 2000; Tucker *et al*., 1999, 2001; New, 2002, 2003; Hardcastle *et al*., 2011) and with a reduced risk of stone formation in high-risk patients (Trinchieri *et al*., 2006; Taylor *et al*., 2010). This beneficial effect of fruits and vegetables is probably due to their high content in potassium and magnesium.

In healthy adults, potassium bicarbonate has been shown to be hypocalciuric (Lemann *et al*., 1993; Sebastian *et al*., 1994; Whiting *et al*., 1997) and positively associated with bone health (New *et al*., 1997; Tucker *et al*., 1999). However, it is not known whether the effect of potassium salts on calcium excretion, bone and kidney is due to the alkalinization effect of bicarbonate or due to the effect of potassium *per se*. Administration of $KHCO_3$ reduced urinary calcium excretion, but administration of other salts bicarbonate ($NaHCO_3$) did not have a systematic effect on calcium balance in healthy subjects (Lutz, 1984; Lemann *et al*., 1989). In rats, administration of various vegetable extracts was shown to induce an inhibition of bone resorption *in vivo*, independently of their base content (Muhlbauer *et al*., 2002). These data suggest a possible role of potassium *per se*. In a cohort study of ~650 premenopausal and postmenopausal women, an inverse relation between dietary potassium and urinary calcium was found without any effect on calcium balance as reduced calciuria was offset by a reduction in intestinal calcium absorption (Rafferty *et al*., 2005). In addition, potassium was identified as a major stimulator of urinary excretion of citrate, which is an inhibitor of calcium stone formation (Demigne *et al*., 2004; Marangella *et al*., 2004) (Crystallization …). Ingestion of alkali as potassium and magnesium citrate reduced the risk of renal stone formation during a 3-year period in a randomized controlled trial (Ettinger *et al*., 1997) or during a 5-week bed rest at risk period (Zerwekh *et al*., 2007). The alkalinic content and potassium richness of fruits and vegetables are positively linked to reduced calcium excretion, bone health and reduced kidney stones formation in high-risk patients.

Conclusions

Although HP diets induce an increase in net acid and urinary calcium excretion, they do not seem to be linked to impaired calcium balance and no clinical data support the hypothesis of a detrimental effect of HP diet on bone health, except in the context of inadequate calcium supply. Thus, it is more likely that excess urinary calcium excretion with HP diets does not originate from bone calcium loss but from an increased intestinal absorption. The increase of acid and calcium excretion due to HP diets is also accused of constituting a favorable environment for kidney stones and renal diseases, but no damaging effect of HP diets on kidney has been found in healthy subjects and HP diets might be deleterious only in patients with a preexisting metabolic renal dysfunction. However, HP diets often contain low amounts of fruits and vegetables, which yet appear to be beneficial to bone health and kidney function. Consequently, to assess effects of dietary intakes on calcium balance, bone health and kidney function, nutrients but also possible deficiencies have to be taken into account.

Conflict of interest

The authors declare no conflict of interest.

References

Abelow BJ, Holford TR, Insogna KL (1992). Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. *Calcif Tissue Int* **50**, 14–18.

Addis T (1926). The effect of some physiological variables on the number of casts, red blood cells and white blood cells and epithelial cells in the urine of normal individuals. *J Clin Invest* **2**, 417–421.

Alexy U, Remer T, Manz F, Neu CM, Schoenau E (2005). Long-term protein intake and dietary potential renal acid load are associated with bone modeling and remodeling at the proximal radius in healthy children. *Am J Clin Nutr* **82**, 1107–1114.

Allen LH, Bartlett RS, Block GD (1979a). Reduction of renal calcium reabsorption in man by consumption of dietary-protein. *J Nutr* **109**, 1345–1350.

Allen LH, Block GD, Wood RJ, Bryce GF (1981). The role of insulin and parathyroid hormone in the protein-induced calciuria of man. *Nutr Res* **1**, 3–11.

Allen LH, Oddoye EA, Margen S (1979b). Protein-induced hypercalciuria: a longer term study. *Am J Clin Nutr* **32**, 741–749.

Alpern RJ, Sakhaee K (1997). The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. *Am J Kidney Dis* **29**, 291–302.

Ammann P, Bonjour JP, Rizzoli R (2000). Essential amino acid supplements increase muscle weight, bone mass and bone strength in adult osteoporotic rats. *J Musculoskelet Neuronal Interact* **1**, 43–44.

Anand CR, Linkswiler HM (1974). Effect of protein intake on calcium balance of young men given 500 mg calcium daily. *J Nutr* **104**, 695–700.

Arjmandi BH, Khalil DA, Smith BJ, Lucas EA, Juma S, Payton ME *et al*. (2003). Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. *J Clin Endocrinol Metab* **88**, 1048–1054.

Ball D, Maughan RJ (1997). Blood and urine acid-base status of premenopausal omnivorous and vegetarian women. *Br J Nutr* **78**, 683–693.

Barzel US, Massey LK (1998). Excess dietary protein can adversely affect bone. *J Nutr* **128**, 1051–1053.

Beasley JM, Ichikawa LE, Ange BA, Spangler L, LaCroix AZ, Ott SM *et al*. (2010). Is protein intake associated with bone mineral density in young women? *Am J Clin Nutr* **91**, 1311–1316.

Bilo HJ, Schaap GH, Blaak E, Gans RO, Oe PL, Donker AJ (1989). Effects of chronic and acute protein administration on renal function in patients with chronic renal insufficiency. *Nephron* **53**, 181–187.

Bonjour JP (2005). Dietary protein: an essential nutrient for bone health. *J Am Coll Nutr* **24** (6 Suppl), 526S–536S.

Bonjour JP, Schurch MA, Chevalley T, Ammann P, Rizzoli R (1997). Protein intake, IGF-1 and osteoporosis. *Osteoporos Int* **7** (Suppl 3), S36–S42.

Bourrin S, Ammann P, Bonjour JP, Rizzoli R (2000a). Dietary protein restriction lowers plasma insulin-like growth factor I (IGF-I), impairs cortical bone formation, and induces osteoblastic resistance to IGF-I in adult female rats. *Endocrinology* **141**, 3149–3155.

Bourrin S, Toromanoff A, Ammann P, Bonjour JP, Rizzoli R (2000b). Dietary protein deficiency induces osteoporosis in aged male rats. *J Bone Miner Res* **15**, 1555–1563.

Brenner BM, Meyer TW, Hostetter TH (1982). Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* **307**, 652–659.

Brinkworth GD, Buckley JD, Noakes M, Clifton PM (2010). Renal function following long-term weight loss in individuals with abdominal obesity on a very-low-carbohydrate diet vs high-carbohydrate diet. *J Am Diet Assoc* **110**, 633–638.

Buclin T, Cosma M, Appenzeller M, Jacquet AF, Decosterd LA, Biollaz J *et al*. (2001). Diet acids and alkalis influence calcium retention in bone. *Osteoporos Int* **12**, 493–499.

Budek AZ, Hoppe C, Ingstrup H, Michaelsen KF, Bugel S, Molgaard C (2007). Dietary protein intake and bone mineral content in adolescents-The Copenhagen Cohort Study. *Osteoporos Int* **18**, 1661–1667.

Burodom A (2010). Renal response to egg white protein loading in healthy young adults. *J Med Assoc Thai* **93**, 824–829.

Bushinsky DA (1989). Net calcium efflux from live bone during chronic metabolic, but not respiratory, acidosis. *Am J Physiol Renal Physiol* **256**, F836–F842.

Caudarella R, Vescini F, Buffa A, Stefoni S (2003). Citrate and mineral metabolism: kidney stones and bone disease. *Front Biosci* **8**: s1084–s1106.

Ceglia L, Harris SS, Abrams SA, Rasmussen HM, Dallal GE, Dawson-Hughes B (2009). Potassium bicarbonate attenuates the urinary nitrogen excretion that accompanies an increase in dietary protein and may promote calcium absorption. *J Clin Endocrinol Metab* **94**, 645–653.

Chen YM, Teucher B, Tang XY, Dainty JR, Lee KK, Woo JL *et al*. (2007). Calcium absorption in postmenopausal Chinese women: a randomized crossover intervention study. *Br J Nutr* **97**, 160–166.

Chevalley T, Bonjour JP, Ferrari S, Rizzoli R (2008). High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys. *J Bone Miner Res* **23**, 131–142.

Collins DM, Rezzo CT, Coffman TM, Klotman PE (1990). Chronic high protein feeding does not reduce glomerular-filtration rate (GFR) in the normal rat. *Kidney Int* **37**, 501–501.

Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL *et al.* (1996). Dietary protein intake and bone mass in women. *Calcif Tissue Int* **58**, 320–325.

Cummings JH, Hill MJ, Jivraj T, Houston H, Branch WJ, Jenkins DJA (1979). Effect of meat protein and dietary fiber on colonic function ad metabolism .1. Changes in bowel habit, bile-acid excretion, and calcium-absorption. *Am J Clin Nutr* **32**, 2086–2093.

Curhan GC, Willett WC, Knight EL, Stampfer MJ (2004). Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med* **164**, 885–891.

Curhan GC, Willett WC, Rimm EB, Stampfer MJ (1993). A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* **328**, 833–838.

Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ (1997). Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Int Med* **126**, 497–504.

Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA (2009). Dietary protein and bone health: a systematic review and meta-analysis. *Am J Clin Nutr* **90**, 1674–1692.

Dawson-Hughes B (2003). Interaction of dietary calcium and protein in bone health in humans. *J Nutr* **133**, 852S–854S.

Dawson-Hughes B, Harris SS (2002). Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr* **75**, 773–779.

Delmi M, Rapin CH, Bengoa JM, Delmas PD, Vasey H, Bonjour JP (1990). Dietary supplementation in elderly patients with fractured neck of the femur. *Lancet* **335**, 1013–1016.

DelValle J, Yamada T (1990). Amino acids and amines stimulate gastrin release from canine antral G-cells via different pathways. *J Clin Invest* **85**, 139–143.

Demigne C, Sabboh H, Remesy C, Meneton P (2004). Protective effects of high dietary potassium: nutritional and metabolic aspects. *J Nutr* **134**, 2903–2906.

Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL (1995). A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* **62**, 740–745.

Draper HH, Piche LA, Gibson RS (1991). Effects of a high protein intake from common foods on calcium-metabolism in a cohort of postmenopausal women. *Nutr Res* **11**, 273–281.

Erba D, Ciappellano S, Testolin G (2002). Effect of the ratio of casein phosphopeptides to calcium (w/w) on passive calcium transport in the distal small intestine of rats. *Nutrition* **18**, 743–746.

Ettinger B, Pak CYC, Citron JT, Thomas C, AdamsHuet B, Vangessel A (1997). Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* **158**, 2069–2073.

Fenton TR, Eliasziw M, Lyon AW, Tough SC, Hanley DA (2008). Meta-analysis of the quantity of calcium excretion associated with the net acid excretion of the modern diet under the acid-ash diet hypothesis. *Am J Clin Nutr* **88**, 1159–1166.

Fenton TR, Lyon AW, Eliasziw M, Tough SC, Hanley DA (2009). Meta-analysis of the effect of the acid-ash hypothesis of osteoporosis on calcium balance. *J Bone Miner Res* **24**, 1835–1840.

Ferraretto A, Signorile A, Gravaghi C, Fiorilli A, Tettamanti G (2001). Casein phosphopeptides influence calcium uptake by cultured human intestinal HT-29 tumor cells. *J Nutr* **131**, 1655–1661.

Feskanich D, Willett WC, Stampfer MJ, Colditz GA (1996). Protein consumption and bone fractures in women. *Am J Epidemiol* **143**, 472–479.

Frank H, Graf J, Graf J, Amann-Gassner U, Bratke R, Daniel H *et al*. (2009). Effect of short-term high-protein compared with normal-protein diets on renal hemodynamics and associated variables in healthy young men. *Am J Clin Nutr* **90**, 1509–1516.

Frassetto L, Morris Jr RC, Sellmeyer DE, Todd K, Sebastian A (2001). Diet, evolution and aging—the pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. *Eur J Nutr* **40**, 200–213.

Frassetto LA, Todd KM, Morris Jr RC, Sebastian A (1998). Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr* **68**, 576–583.

Frassetto LA, Todd KM, Morris Jr RC, Sebastian A (2000). Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable foods. *J Gerontol A Biol Sci Med Sci* **55**, M585–M592.

Geibel JP, Wagner C (2006). An update on acid secretion. *Rev Physiol Biochem Pharmacol* **156**, 45–60.

Geinoz G, Rapin CH, Rizzoli R, Kraemer R, Buchs B, Slosman D *et al*. (1993). Relationship between bone mineral density and dietary intakes in the elderly. *Osteoporos Int* **3**, 242–248.

Goss SL, Lemons KA, Kerstetter JE, Bogner RH (2007). Determination of calcium salt solubility with changes in pH and P(CO(2)), simulating varying gastrointestinal environments. *J Pharm Pharmacol* **59**, 1485–1492.

Green J, Kleeman CR (1991). Role of bone in regulation of systemic acid-base balance. *Kidney Int* **39**, 9–26.

Hade JE, Spiro HM (1992). Calcium and acid rebound: a reappraisal. *J Clin Gastroenterol* **15**, 37–44.

Hammond KA, Janes DN (1998). The effects of increased protein intake on kidney size and function. *J Exp Biol* **201** (Pt 13), 2081–2090.

Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP (2000). Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res* **15**, 2504–2512.

Hardcastle AC, Aucott L, Reid DM, Macdonald HM (2011). Associations between dietary flavonoid intakes and bone health in a Scottish population. *J Bone Miner Res* **26**, 941–947.

Heaney RP (2000). Dietary protein and phosphorus do not affect calcium absorption. *Am J Clin Nutr* **72**, 758–761.

Heaney RP (2001). Protein intake and bone health: the influence of belief systems on the conduct of nutritional science. *Am J Clin Nutr* **73**, 5–6.

Heaney RP (2002). Protein and calcium: antagonists or synergists? *Am J Clin Nutr* **75**, 609–610.

Heaney RP (2006). Calcium intake and disease prevention. *Arq Bras Endocrinol Metabol* **50**, 685–693.

Heaney RP, Layman DK (2008). Amount and type of protein influences bone health. *Am J Clin Nutr* **87**, 1567S–1570S.

Heaney RP, McCarron DA, Dawson-Hughes B, Oparil S, Berga SL, Stern JS *et al*. (1999). Dietary changes favorably affect bone remodeling in older adults. *J Am Diet Assoc* **99**, 1228–1233.

Hegsted M, Linkswiler HM (1981). Long-term effects of level of protein intake on calcium metabolism in young adult women. *J Nutr* **111**, 244–251.

Hegsted M, Schuette SA, Zemel MB, Linkswiler HM (1981). Urinary calcium and calcium balance in young men as affected by level of protein and phosphorus intake. *J Nutr* **111**, 553–562.

Hess B (2002). Nutritional aspects of stone disease. *Endocrinol Metab Clin North Am* **31**, 1017–1030, ix and x.

Hirota T, Nara M, Ohguri M, Manago E, Hirota K (1992). Effect of diet and lifestyle on bone mass in Asian young women. *Am J Clin Nutr* **55**, 1168–1173.

Hirvonen T, Pietinen P, Virtanen M, Albanes D, Virtamo J (1999). Nutrient intake and use of beverages and the risk of kidney stones among male smokers. *Am J Epidemiol* **150**, 187–194.

Hu JF, Zhao XH, Parpia B, Campbell TC (1993). Dietary intakes and urinary excretion of calcium and acids: a cross-sectional study of women in China. *Am J Clin Nutr* **58**, 398–406.

Huang Z, Himes JH, McGovern PG (1996). Nutrition and subsequent hip fracture risk among a national cohort of white women. *Am J Epidemiol* **144**, 124–134.

Hunt JR, Gallagher SK, Johnson LK, Lykken GI (1995). High-meat versus low-meat diets–effects on zinc-absorption, iron status, and calcium, copper, iron, magnesium, manganese, nitrogen, phosphorus, and zinc balance in postmenopausal women. *Am J Clin Nutr* **62**, 621–632.

Hunt JR, Johnson LK, Fariba Roughead ZK (2009). Dietary protein and calcium interact to influence calcium retention: a controlled feeding study. *Am J Clin Nutr* **89**, 1357–1365.

Ilich JZ, Brownbill RA, Tamborini L (2003). Bone and nutrition in elderly women: protein, energy, and calcium as main determinants of bone mineral density. *Eur J Clin Nutr* **57**, 554–565.

Ince BA, Anderson EJ, Neer RM (2004). Lowering dietary protein to U.S. Recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. *J Clin Endocrinol Metab* **89**, 3801–3807.

Jaeger P, Bonjour JP, Karlmark B, Stanton B, Kirk RG, Duplinsky T *et al*. (1983). Influence of acute potassium loading on renal phosphate transport in the rat kidney. *Am J Physiol Renal Physiol* **245** (5 Pt 1), F601–F605.

Jia Y, Hwang SY, House JD, Ogborn MR, Weiler HA, O K *et al*. (2010). Long-term high intake of whole proteins results in renal damage in pigs. *J Nutr* **140**, 1646–1652.

Johnson NE, Alcantara EN, Linkswiler H (1970). Effect of level of protein intake on urinary and fecal calcium and calcium retention of young adult males. *J Nutr* **100**, 1425–1430.

Kannus P, Parkkari J, Sievanen H, Heinonen A, Vuori I, Jarvinen M (1996). Epidemiology of hip fractures. *Bone* **18** (1 Suppl), 57S–63S.

Kerstetter JE, O'Brien KO, Caseria DM, Wall DE, Insogna KL (2005). The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. *J Clin Endocrinol Metab* **90**, 26–31.

Kerstetter JE, O'Brien KO, Insogna KL (1998). Dietary protein affects intestinal calcium absorption. *Am J Clin Nutr* **68**, 859–865.

Kerstetter JE, Wall DE, O'Brien KO, Caseria DM, Insogna KL (2006). Meat and soy protein affect calcium homeostasis in healthy women. *J Nutr* **136**, 1890–1895.

Kim Y, Linkswiler HM (1979). Effect of level of protein intake on calcium metabolism and on parathyroid and renal function in the adult human male. *J Nutr* **109**, 1399–1404.

Klahr S (1989). The modification of diet in renal disease study. *N Engl J Med* **320**, 864–866.

Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC (2003). The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. *Ann Int Med* **138**, 460–467.

Konturek SJ, Tasler J, Cieszkowski M, Jaworek J (1978). Comparison of intravenous amino acids in the stimulation of gastric secretion. *Gastroenterology* **75**, 817–824.

Krieger NS, Sessler NE, Bushinsky DA (1992). Acidosis inhibits osteoblastic and stimulates osteoclastic activity *in vitro*. *Am J Physiol Renal Physiol* **262** (3 Pt 2), F442–F448.

Lacroix M, Gaudichon C, Martin A, Morens C, Mathe V, Tome D *et al*. (2004). A long-term high-protein diet markedly reduces adipose tissue without major side effects in Wistar male rats. *Am J Physiol Regul Integr Comp Physiol* **287**, R934–R942.

Langdahl BL, Kassem M, Moller MK, Eriksen EF (1998). The effects of IGF-I and IGF-II on proliferation and differentiation of human osteoblasts and interactions with growth hormone. *Eur J Clin Invest* **28**, 176–183.

Lei SF, Chen Y, Xiong DH, Li LM, Deng HW (2006). Ethnic difference in osteoporosis-related phenotypes and its potential underlying genetic determination. *J Musculoskelet Neuronal Interact* **6**, 36–46.

Lemann Jr J, Gray RW, Pleuss JA (1989). Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. *Kidney Int* **35**, 688–695.

Lemann Jr J, Pleuss JA, Gray RW (1993). Potassium causes calcium retention in healthy adults. *J Nutr* **123**, 1623–1626.

Licata AA (1981). Acute effects of increased meat protein on urinary electrolytes and cyclic adenosine-monophosphate and serum parathyroid-hormone. *Am J Clin Nutr* **34**, 1779–1784.

Lutz J (1984). Calcium balance and acid-base status of women as affected by increased protein intake and by sodium bicarbonate ingestion. *Am J Clin Nutr* **39**, 281–288.

Lutz J, Linkswiler HM (1981). Calcium metabolism in postmenopausal and osteoporotic women consuming two levels of dietary protein. *Am J Clin Nutr* **34**, 2178–2186.

Marangella M, Bagnis C, Bruno M, Vitale C, Petrarulo M, Ramello A (2004). Crystallization inhibitors in the pathophysiology and treatment of nephrolithiasis. *Urol Int* **72** (Suppl 1), 6–10.

Markovich D, Wang H, Puttaparthi K, Zajicek H, Rogers T, Murer H *et al*. (1999). Chronic K depletion inhibits renal brush border membrane Na/sulfate cotransport. *Kidney Int* **55**, 244–251.

Martin WF, Armstrong LE, Rodriguez NR (2005). Dietary protein intake and renal function. *Nutr Metab (Lond)* **2**, 25.

McCance RA, Widdowson EM, Lehmann H (1942). The effect of protein intake on the absorption of calcium and magnesium. *Biochem J* **36**, 686–691.
Metges CC, Barth CA (2000). Metabolic consequences of a high dietary-protein intake in adulthood: assessment of the available evidence. *J Nutr* **130**, 886–889.
Meyer HE, Pedersen JI, Loken EB, Tverdal A (1997). Dietary factors and the incidence of hip fracture in middle-aged Norwegians. A prospective study. *Am J Epidemiol* **145**, 117–123.
Misra D, Berry SD, Broe KE, McLean RR, Cupples LA, Tucker KL *et al*. (2010). Does dietary protein reduce hip fracture risk in elders? The Framingham osteoporosis study. *Osteoporos Int* **22**, 345–349.
Mohan S, Strong DD, Lempert UG, Tremollieres F, Wergedal JE, Baylink DJ (1992). Studies on regulation of insulin-like growth factor binding protein (IGFBP)-3 and IGFBP-4 production in human bone cells. *Acta Endocrinol (Copenh)* **127**, 555–564.
Muhlbauer RC, Lozano A, Reinli A (2002). Onion and a mixture of vegetables, salads, and herbs affect bone resorption in the rat by a mechanism independent of their base excess. *J Bone Miner Res* **17**, 1230–1236.
Munger RG, Cerhan JR, Chiu BC (1999). Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. *Am J Clin Nutr* **69**, 147–152.
Nelson DA, Megyesi MS (2004). Sex and ethnic differences in bone architecture. *Curr Osteoporos Rep* **2**, 65–69.
New SA (2002). Nutrition Society Medal lecture. The role of the skeleton in acid-base homeostasis. *Proc Nutr Soc* **61**, 151–164.
New SA (2003). Intake of fruit and vegetables: implications for bone health. *Proc Nutr Soc* **62**, 889–899.
New SA, Bolton-Smith C, Grubb DA, Reid DM (1997). Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. *Am J Clin Nutr* **65**, 1831–1839.
New SA, Robins SP, Campbell MK, Martin JC, Garton MJ, Bolton-Smith C *et al*. (2000). Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? *Am J Clin Nutr* **71**, 142–151.
Nguyen QV, Kalin A, Drouve U, Casez JP, Jaeger P (2001). Sensitivity to meat protein intake and hyperoxaluria in idiopathic calcium stone formers. *Kidney Int* **59**, 2273–2281.
Pannemans DLE, Schaafsma G, Westerterp KR (1997). Calcium excretion, apparent calcium absorption and calcium balance in young and elderly subjects: influence of protein intake. *Br J Nutr* **77**, 721–729.
Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH (1996). The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Int Med* **124**, 627–632.
Rafferty K, Davies KM, Heaney RP (2005). Potassium intake and the calcium economy. *J Am Coll Nutr* **24**, 99–106.
Rafferty K, Heaney RP (2008). Nutrient effects on the calcium economy: emphasizing the potassium controversy. *J Nutr* **138**, 166S–171S.
Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CYC (2002). Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. *Am J Kidney Dis* **40**, 265–274.
Remer T (2000). Influence of diet on acid-base balance. *Semin Dial* **13**, 221–226.
Remer T, Manz F (1994). Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr* **59**, 1356–1361.
Robertson JL, Goldschmidt M, Kronfeld DS, Tomaszewski JE, Hill GS, Bovee KC (1986). Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. *Kidney Int* **29**, 511–519.
Robertson L, Waugh N, Robertson A (2007). Protein restriction for diabetic renal disease. *Cochrane Database Systematic Review*. Article number: (4): CD002181.
Robertson WG, Heyburn PJ, Peacock M, Hanes FA, Swaminathan R (1979). The effect of high animal protein intake on the risk of calcium stone-formation in the urinary tract. *Clin Sci (Lond)* **57**, 285–288.
Roughead ZK, Johnson LK, Lykken GI, Hunt JR (2003). Controlled high meat diets do not affect calcium retention or indices of bone status in healthy postmenopausal women. *J Nutr* **133**, 1020–1026.
Rubin J, Ackert-Bicknell CL, Zhu L, Fan X, Murphy TC, Nanes MS *et al*. (2002). IGF-I regulates osteoprotegerin (OPG) and receptor activator of nuclear factor-kappa B ligand *in vitro* and OPG *in vivo*. *J Clin Endocrinol Metab* **87**, 4273–4279.
Schuette SA, Linkswiler HM (1982). Effects on Ca and P metabolism in humans by adding meat, meat plus milk, or purified proteins plus Ca and P to a low protein diet. *J Nutr* **112**, 338–349.
Schuette SA, Zemel MB, Linkswiler HM (1980). Studies on the mechanism of protein-induced hypercalciuria in older men and women. *J Nutr* **110**, 305–315.
Schulte-Frohlinde E, Schmid R, Schusdziarra V (1993). Effect of a postprandial amino acid pattern on gastric acid secretion in man. *Z Gastroenterol* **31**, 711–715.
Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP (1998). Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Ann Int Med* **128**, 801–809.
Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris Jr RC (1994). Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* **330**, 1776–1781.
Sellmeyer DE, Stone KL, Sebastian A, Cummings SR (2001). A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. *Am J Clin Nutr* **73**, 118–122.
Skov AR, Toubro S, Bulow J, Krabbe K, Parving HH, Astrup A (1999). Changes in renal function during weight loss induced by high vs low-protein low-fat diets in overweight subjects. *Int J Obes Relat Metab Disord* **23**, 1170–1177.
Spencer H, Kramer L, DeBartolo M, Norris C, Osis D (1983). Further studies of the effect of a high protein diet as meat on calcium metabolism. *Am J Clin Nutr* **37**, 924–929.
Spencer H, Kramer L, Osis D (1988). Do protein and phosphorus cause calcium loss? *J Nutr* **118**, 657–660.
Spencer H, Kramer L, Osis D, Norris C (1978). Effect of a high-protein (meat) intake on calcium-metabolism in man. *Am J Clin Nutr* **31**, 2167–2180.
Strunz UT, Walsh JH, Grossman MI (1978). Stimulation of gastrin release in dogs by individual amino acids. *Proc Soc Exp Biol Med* **157**, 440–441.
Taylor EN, Stampfer MJ, Mount DB, Curhan GC (2010). DASH-style diet and 24-hour urine composition. *J Am Soc Nephrol* **5**, 2315–2322.
Teegarden D, Lyle RM, McCabe GP, McCabe LD, Proulx WR, Michon K *et al*. (1998). Dietary calcium, protein, and phosphorus are related to bone mineral density and content in young women. *Am J Clin Nutr* **68**, 749–754.
Thissen JP, Ketelslegers JM, Underwood LE (1994). Nutritional regulation of the insulin-like growth factors. *Endocr Rev* **15**, 80–101.
Thorpe DL, Knutsen SF, Beeson WL, Rajaram S, Fraser GE (2008). Effects of meat consumption and vegetarian diet on risk of wrist fracture over 25 years in a cohort of peri- and postmenopausal women. *Public Health Nutr* **11**, 564–572.
Tkatch L, Rapin CH, Rizzoli R, Slosman D, Nydegger V, Vasey H *et al*. (1992). Benefits of oral protein supplementation in elderly patients with fracture of the proximal femur. *J Am Coll Nutr* **11**, 519–525.
Tosukhowong P, Tungsanga K, Phongudom S, Sriboonlue P (2005). Effects of potassium-magnesium citrate supplementation on

cytosolic ATP citrate lyase and mitochondrial aconitase activity in leukocytes: a window on renal citrate metabolism. *Int J Urol* **12**, 140–144.

Trilok G, Draper HH (1989). Sources of protein-induced endogenous acid production and excretion by human adults. *Calcif Tissue Int* **44**, 335–338.

Trinchieri A, Lizzano R, Marchesotti F, Zanetti G (2006). Effect of potential renal acid load of foods on urinary citrate excretion in calcium renal stone formers. *Urol Res* **34**, 1–7.

Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP (1999). Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr* **69**, 727–736.

Tucker KL, Hannan MT, Kiel DP (2001). The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. *Eur J Nutr* **40**, 231–237.

Tuttle KR, Puhlman ME, Cooney SK, Short RA (2002). Effects of amino acids and glucagon on renal hemodynamics in type 1 diabetes. *Am J Physiol Renal Physiol* **282**, F103–F112.

Wagner EA, Falciglia GA, Amlal H, Levin L, Soleimani M (2007). Short-term exposure to a high-protein diet differentially affects glomerular filtration rate but not acid-base balance in older compared to younger adults. *J Am Diet Assoc* **107**, 1404–1408.

Walker RM, Linkswiler HM (1972). Calcium retention in the adult human male as affected by protein intake. *J Nutr* **102**, 1297–1302.

Wasserstein AG, Stolley PD, Soper KA, Goldfarb S, Maislin G, Agus Z (1987). Case-control study of risk factors for idiopathic calcium nephrolithiasis. *Miner Electrolyte Metab* **13**, 85–95.

Wengreen HJ, Munger RG, West NA, Cutler DR, Corcoran CD, Zhang J *et al.* (2004). Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah. *J Bone Miner Res* **19**, 537–545.

Whiting SJ, Anderson DJ, Weeks SJ (1997). Calciuric effects of protein and potassium bicarbonate but not of sodium chloride or phosphate can be detected acutely in adult women and men. *Am J Clin Nutr* **65**, 1465–1472.

Whiting SJ, Boyle JL, Thompson A, Mirwald RL, Faulkner RA (2002). Dietary protein, phosphorus and potassium are beneficial to bone mineral density in adult men consuming adequate dietary calcium. *J Am Coll Nutr* **21**, 402–409.

Wilson HE (1933). An investigation of the cause of renal hypertrophy in rats fed on a high protein diet. *Biochem J* **27**, 1348–1356.

Wolfe RR (2006). The underappreciated role of muscle in health and disease. *Am J Clin Nutr* **84**, 475–482.

Zemel MB, Schuette SA, Hegsted M, Linkswiler HM (1981). Role of the sulfur-containing amino-acids in protein-induced hypercalciuria in men. *J Nutr* **111**, 545–552.

Zerwekh JE, Odvina CV, Wuermser LA, Pak CYC (2007). Reduction of renal stone risk by potassium-magnesium citrate during 5 weeks of bed rest. *J Urol* **177**, 2179–2184.