The Journal of Nutrition
Inulin and Oligofructose: Health Benefits and Claims–A Critical Review

Diet, Nutrition, and Bone Health[1,2]

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Abstract

Osteoporosis is a debilitating disease that affects many older people. Fragility fractures are the hallmark of osteoporosis. Although nutrition is only 1 of many factors that influence bone mass and fragility fractures, there is an urgent need to develop and implement nutritional approaches and policies for the prevention and treatment of osteoporosis that could, with time, offer a foundation for population-based preventive strategies. However, to develop efficient and precocious strategies in the prevention of osteoporosis, it is important to determine which modifiable factors, especially nutritional factors, are able to improve bone health throughout life. There are potentially numerous nutrients and dietary components that can influence bone health, and these range from the macronutrients to micronutrients as well as bioactive food ingredients. The evidence-base to support the role of nutrients and food components in bone health ranges from very firm to scant, depending on the nutrient/component. This article initially overviews osteoporosis, including its definition, etiology, and incidence, and then provides some information on possible dietary strategies for optimizing bone health and preventing osteoporosis. The potential benefits of calcium, vitamin D, vitamin K_1, phytoestrogens, and nondigestible oligosaccharides are briefly discussed, with particular emphasis on the evidence base for their benefits to bone. It also briefly considers some of the recent findings that highlight the importance of some dietary factors for bone health in childhood and adolescence. J. Nutr. 137: 2507S–2512S, 2007.

Introduction

Osteoporosis is a global health problem that will take on increasing significance as people live longer and the world's population continues to increase in number (1). Thus, prevention of osteoporosis and its complications is an essential socioeconomic priority. There is an urgent need to develop and implement nutritional approaches (including functional foods) and policies for the prevention and treatment of osteoporosis. This article first briefly defines the principal disease of bone mass (i.e., osteoporosis) and considers its epidemiology and risk factors. It then focuses on the importance of certain dietary factors (in particular those that could be potential functional food ingredients for the prevention of osteoporosis) in bone health.

Osteoporosis: definition and epidemiology

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (2). For the purposes of clinical diagnosis, a working party of the World Health Organization has redefined osteoporosis according to bone mass, at least for women. Their diagnostic criteria for osteoporosis, based on bone mineral content (BMC)[3] or bone mineral density (BMD), include: normal, within 1 SD of the young adult reference mean for the population; osteopenia, between –1 and –2.5 SD of the young adult mean; osteoporosis more than –2.5 SD below the young adult mean; and established osteoporosis as the same mass definition but associated with a fragility fracture (3). Fragility fractures are the hallmark of osteoporosis and are particularly common in the spine, hip, and distal forearm, although they can occur throughout the skeleton.

Osteoporotic fractures constitute a major public health problem. Currently, in the United States alone, 10 million individuals already have osteoporosis, and a further 34 million more have low bone mass, placing them at increased risk from this disorder (4). Moreover, 1 in 8 European Union (EU) citizens over the age of 50 y will fracture their spine this year (1). The estimated remaining lifetime risk of fractures in Caucasian women at age 50 y, based on incidence rates in North America, is 17.5%, 15.6%, and 16% for hip, spine, and forearm, respectively; the remaining lifetime risk for any fragility fracture approaches 40% in women and 13% in men (5).

The incidence of vertebral and hip fractures increases exponentially with advancing age (6). This is of particular concern because it is projected that the number of elderly (80 y and older, in whom the incidence of osteoporotic fracture is greatest) in the EU population will grow from 8.9 million women and 4.5 million men in 1995, to 26.4 million women and

[1] Published in a supplement to *The Journal of Nutrition*. Presented at the conference ''5th ORAFTI Research Conference: Inulin and Oligofructose: Proven Health Benefits and Claims'' held at Harvard Medical School, Boston, MA, September 28–29, 2006. This conference was organized and sponsored by ORAFTI, Belgium. Guest Editors for the supplement publication were Marcel Roberfroid, Catholique University of Louvain, Brussels, Belgium and Randal Buddington, Mississippi State University, USA. *Guest Editor disclosure*: M. Roberfroid and R. Buddington, support for travel to conference provided by ORAFTI.

[2] Author disclosure: K. Cashman, no conflicts of interest.

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[3] Abbreviations used: BMC, bone mineral content; BMD, bone mineral density; EU, European Union; HRT, hormone replacement therapy.

17.4 million men in 2050 (1). Similar demographic changes have been forecast for the U.S. population (7). Because of the increase in incidence rates of osteoporotic fractures with age, these demographic changes and increasing life expectancy will have a huge impact on the number of fractures that can be expected to occur. For example, the number of hip fractures occurring each year in the EU alone is estimated to rise from current figures of 414,000 to 972,000 by 2050, representing an increase of 135% (1). Hip fracture patients have an overall mortality of 15–30% (8), the majority of excess deaths occurring within the first 6 mo after the fracture.

From an economic perspective, the expenses of hospital care and rehabilitation associated with osteoporotic fractures are a considerable fiscal drain for the health care system, exceeding those of other highly prevalent pathologies of the elderly, such as myocardial infarction (9). Osteoporosis costs national treasuries over €3500 million annually in hospital health care alone (1).

Risk factors for osteoporosis

Low bone mineral mass is the main factor underlying osteoporotic fracture (10). Bone mass in later life depends on the peak bone mass achieved during growth and the rate of subsequent age-related bone loss. Development of maximal bone mass during growth and reduction of loss of bone later in life are the 2 main strategies of preventing osteoporosis (11). Consequently, any factor that influences the development of peak bone mass or the loss of bone in middle-age will affect later fracture risk. Several factors are thought to influence bone mass. These can be broadly grouped into factors that cannot be modified, such as gender, age, body (frame) size, genetics and ethnicity, and those factors that can be modified, such as hormonal status (especially sex and calciotropic hormone status), lifestyle factors including physical activity levels, smoking and alcohol consumption patterns, and diet (including functional foods). The interaction of these genetic, hormonal, environmental and nutritional factors influences both the development of bone to peak bone mass at maturity and its subsequent loss. The remainder of this article will focus on a selected number of dietary components/nutrients that may influence bone health.

Diet, nutrition and bone health

Many of the nutrients and food components we consume as part of a Westernized diet can potentially have a positive or negative impact on bone health (see **Table 1**). They may influence bone by various mechanisms, including alteration of bone structure, the rate of bone metabolism, the endocrine and/or paracrine system, and homeostasis of calcium and possibly of other bone-active mineral elements (12). These dietary factors range from inorganic minerals (e.g., calcium, magnesium, phosphorus, sodium, potassium, and various trace elements) and vitamins (vitamins A, D, E, K, C, and certain B vitamins), to macronutrients, such as protein and fatty acids. In addition, the relative proportions of these dietary factors derived from different types of diets (vegetarian vs. omnivorous) may also affect bone health and thus osteoporosis risk. Furthermore, in recent years a number of bioactive food components have been proposed as being beneficial for bone health. A review of all of these dietary factors is beyond the scope of the present article.

Three important reports [the European Commission's *Report on Osteoporosis in the European Community: Action for Prevention* (1); the U.S. Surgeon General's *Report on Bone Health and Osteoporosis* (12); the World Health Organization's report on *Diet, Nutrition and the Prevention of Chronic Diseases* (13)] have stressed the importance of calcium and vitamin D in promoting bone health. Therefore, this section focuses on calcium and vitamin D but also briefly mentions selected nutrients/food components that also have important roles in bone health (such as vitamin K and dietary phytoestrogens). At present, however, the evidence base for these latter nutritional factors is less well developed (1,10,14).

TABLE 1 Potential nutritional determinants of bone health*

Beneficial factors	Potentially detrimental dietary factors
Nutrients	Dietary factors/nutrients
Calcium	Excess alcohol
Copper	Excess caffeine
Zinc	Excess sodium
Fluoride	Excess fluoride
Magnesium	Excess/insufficient protein
Phosphorus	Excess phosphorus
Potassium	Excess/insufficient vitamin A
Vitamin C	Excess n-6 PUFA
Vitamin D	
Vitamin K	
B vitamins	
n-3 Fatty acid	
Protein	
Novel bioactive food compounds	
Whey-derived peptides	
Phytoestrogens	
Nondigestible oligosaccharides (especially inulin-type fructans)	

* Some nutrients could be categorized as being both beneficial and detrimental depending on dietary exposure level: insufficient or in excess.

Dietary calcium and its absorption. Calcium is required for normal growth and development of the skeleton (15). Adequate calcium intake is critical to achieving optimal peak bone mass and modifies the rate of bone loss associated with aging (16). Over the past decade, convincing evidence has emerged with respect to effects of dietary calcium on bone health in all age groups (1). The role of calcium in bone health has been extensively reviewed elsewhere (1,15–18). Unfortunately, there are a significant proportion of some population groups failing to achieve the recommended calcium intakes in a number of Western countries (18).

Besides the amount of calcium in the diet, the absorption of dietary calcium in foods is also a critical factor in determining the availability of calcium for bone development and maintenance. There is therefore a need to identify food components and/or functional food ingredients that may positively influence calcium absorption to ensure that calcium bioavailability from foods can be optimized (18). This approach may be of particular value in individuals who fail to achieve the dietary recommended level of calcium and/or in those individuals with a low efficiency of intestinal absorption of calcium. Calcium in food occurs as salts or associated with other dietary constituents in the form of complexes of calcium ions (Ca^{2+}). Calcium must be released in a soluble, and probably ionized, form before it can be absorbed. Once in a soluble form, calcium is absorbed by 2 routes, transcellular and paracellular transport, and these have been reviewed elsewhere (19). In brief, the saturable transcellular pathway is a multistep process involving the entry of luminal Ca^{2+} across the microvillar membrane into the enterocyte, then movement through the cytosol (i.e., translocation to

the basolateral membrane), followed by active extrusion from the enterocyte into the lamina propria and, eventually, into the general circulation (see **Fig. 1**). The intracellular Ca^{2+} diffusion is thought to be facilitated by a cytosolic calcium-binding protein, calbindin D_{9K}, whose biosynthesis is dependent on vitamin D. Calbindin D_{9K} facilitates the diffusion of Ca^{2+} across the cell by acting as an intracellular calcium ferry or a chaperone. The active extrusion of Ca^{2+} at the basolateral membrane takes place against an electrochemical gradient and is mainly mediated by Ca-ATPase. The entry of Ca^{2+} across the apical membrane of the enterocyte is strongly favored electrochemically because the concentration of Ca^{2+} within the cell (10^{-7} to 10^{-6} mol/L) is considerably lower than that in the intestinal lumen (10^{-3} mol/L), and the cell is electronegative relative to the intestinal lumen. Therefore, the movement of Ca^{2+} across the apical membrane does not require the expenditure of energy. It is widely believed that a Ca^{2+} channel or integral membrane transporter [such as the transient receptor potential channel, subfamily V, member 6 (TRPV6), also known as calcium transporter (CaT1)] in the brush border membrane facilitates this entry into the enterocyte. Although each step in the transcellular movement of Ca^{2+} has a vitamin D-dependent component, calbindin D_{9K} is believed to be the rate-limiting molecule in vitamin D-induced transcellular calcium transport.

The paracellular route of calcium absorption involves a passive calcium transport through the tight junctions between mucosal cells (see **Fig. 1**); it is nonsaturable, essentially independent of nutritional and physiological regulation, and is concentration dependent (19). Most calcium absorption in humans occurs in the small intestine, although there is some small colonic component (typically believed not to be >10% of total calcium absorption). However, the large intestine may represent a site of increased importance for calcium absorption when acidic fermentation takes place (19). This is important if one remembers that consumption of prebiotics will lead to acidic fermentation in the large intestine. When dietary calcium is abundant, the paracellular pathway is thought to be predominant. In contrast, when dietary calcium is limited, the active, vitamin D-dependent transcellular pathway plays a major role in calcium absorption.

A number of food constituents have been suggested as potential enhancers of calcium absorption. Individual milk components, such as lactose, lactulose, and casein phosphopeptides have in the past attracted considerable attention, and these have been reviewed extensively elsewhere (20–22). In addition, there is a growing body of evidence to show that nondigestible oligosaccharides can improve calcium absorption in some life-stage groups. This evidence base has been reviewed elsewhere (19,23) and is the subject of 3 further articles in this Supplement (Abrams et al., Scholz-Ahrens and Schrezenmeir, V. Coxam).

Vitamin D. Vitamin D is found naturally in very few foods; endogenous synthesis of vitamin D, therefore, which occurs when skin is exposed to UVB radiation from sunlight during summer, is a principal determinant of vitamin D status. However, in latitudes above 40°N and 40°S (Rome, for example, is at latitude 42°N), the dermal photoconversion of the precursor 7-dehydrocholesterol to vitamin D occurs little if at all during most of the 3–4 winter mo, with this period being extended to 6 mo in more northern latitudes (24). Thus, during the winter months there is an increased reliance on dietary supply of vitamin D. Of concern, vitamin D intakes are low in many populations (25), placing many people at risk of low vitamin D status, with possible consequences for bone health.

Vitamin D deficiency is characterized by inadequate mineralization, or demineralization, of the skeleton. In children, severe vitamin D deficiency results in inadequate mineralization of the skeleton causing rickets, whereas in adults, it leads to a mineralization defect in the skeleton causing osteomalacia (15). In addition, the secondary hyperparathyroidism associated with low vitamin D status enhances mobilization of calcium from the skeleton (15). There is a considerable body of evidence that vitamin D deficiency is an important contributor to osteoporosis through less efficient intestinal absorption of calcium, increased bone loss, muscle weakness, and a weakened bone microstructure (26). Increasing vitamin D intake can significantly reduce risk of bone fracture in older people (26).

In light of the high prevalence of low vitamin D status among large population groups in Europe, the United States, and elsewhere (15,16,27), strategies are needed to address this public

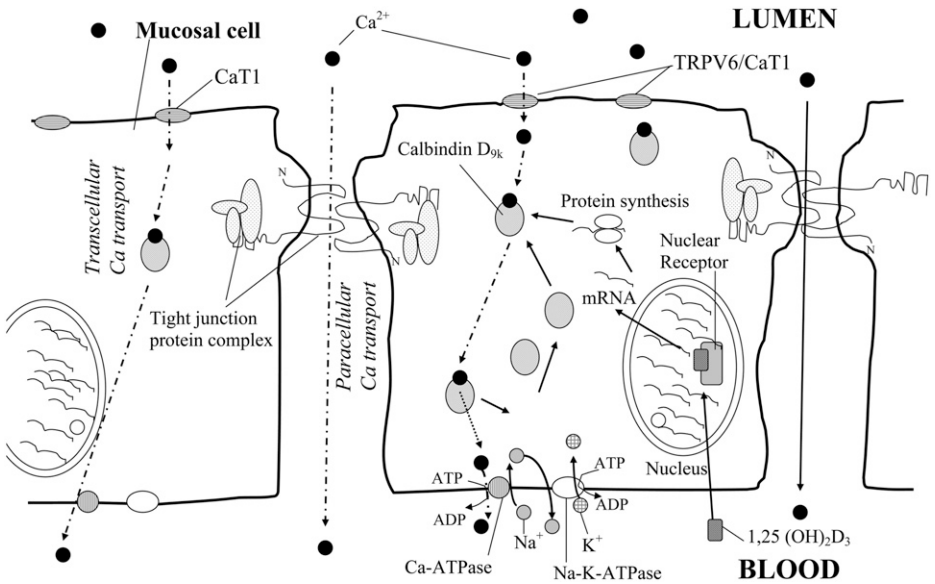

FIGURE 1 A schematic representation of transepithelial calcium transport in the intestine. The central feature is that calcium absorption occurs by 2 independent processes, namely transcellular and paracellular transport of calcium across the epithelium.

health problem, including development of vitamin D-containing functional foods.

Vitamin K

Recently, the identification of γ-carboxyglutamyl (Gla)-containing proteins in bone, notably osteocalcin and matrix Gla protein, has generated much interest in the role of vitamin K in bone metabolism and bone health (28). The circulating concentration of under-γ-carboxylated osteocalcin, a sensitive marker of vitamin K nutritional status (29), has been reported to be an indicator of hip fracture (30,31) and a predictor of BMD (15,32). Moreover, the findings of 2 large, prospective cohort studies [the Nurses' Health Study (33) and the Framingham Heart Study (34)] support an association between relative risk of hip fracture and vitamin K intake. In the Nurses' Health Study, vitamin K_1 intakes of <109 μg/d were associated with an increased risk of hip fracture in 72,327 women (33). In the Framingham Heart Study, elderly men and women in the highest quartile of vitamin K_1 intake (median 254 μg/d) had significantly lower adjusted relative risk of hip fracture than did those in the lowest quartile of intake (median 56 μg/d) (34).

The above mentioned studies, however, were observational in nature, and this inevitably raises the issue of causal relationships and proof of causality. In terms of proof of causality, there is a general consensus that there is a need for well-designed, randomized vitamin K_1 supplementation trials in adults to confirm observational findings and the role of vitamin K in bone metabolism and mass in healthy subjects (35). Clinical intervention studies presently being conducted or near completion in North America will help to elucidate this question and thus will substantiate whether vitamin K has the potential to be a functional food ingredient for bone health. Of interest, Braam et al. showed that relatively high-dose vitamin K_1 supplementation (1 mg/d) for 3 y, if coadministered with calcium, magnesium, zinc, and vitamin D, reduced postmenopausal bone loss at the femoral neck (36). The dose of vitamin K used in this study, however, is unlikely to be achieved by dietary means and would require either supplementation or the functional food approach.

Dietary phytoestrogens

Estrogen deficiency is a major contributory factor to the development of osteoporosis in women, and hormone replacement therapy (HRT) remains the mainstay for prevention of bone loss in postmenopausal women (37). Recently, as a consequence of poor uptake and adherence of HRT as well as potential concerns over an increased risk of malignancy and other side effects associated with the use of HRT, attention has been focused on the so-called dietary phytoestrogens as possible safe alternatives, or at least adjuncts, to HRT. Phytoestrogens are nonsteroidal compounds naturally occurring in foods of plant origin (especially soy-based foods) that structurally resemble natural estrogens and compete with them for binding estrogen receptors (38).

Currently, the data from human intervention studies are mixed in relation to potential beneficial effects of phytoestrogens on bone health (38). One of the most cited works in support of their potential beneficial effects for bone is that of Morabito et al. (39), who reported the findings of their randomized double-blind, placebo-controlled study in which the effects of purified genistein (a soy-based isoflavone) supplementation (56 mg/d) and continuous HRT for 12 mo on bone metabolism and BMD were evaluated and compared in early postmenopausal women. Genistein supplementation significantly increased BMD in the femur and lumbar spine, effects that appeared to be of similar magnitude to those achieved with HRT (39). The dose of genistein used in this study, however, far exceeds that naturally present in the normal Western diet (38) and could realistically be achieved only by supplementation or by the function food approach. A recent critical review of the health effects of soybean phytoestrogens in postmenopausal women concluded that there is a suggestion, but no conclusive evidence, that isoflavones from the sources studied so far have a beneficial effect on bone health (40). Further research is needed to clarify the role of dietary phytoestrogens in osteoporosis prevention.

Diet and bone health in childhood and adolescence

About 90% of total adult bone mass is accrued by age 20, and a significant proportion of this is achieved during puberty alone (18). Thus, gaining an understanding of the role of dietary components in bone metabolism and bone mass in these early life stages is important because finding new strategies to maximize the accretion of bone during growth may help reduce the risk of osteoporosis in later life.

The importance of dietary calcium to bone health in childhood and adolescence has been emphasized (1,12,15). There is some concern about the proportion of adolescents, particularly girls, who appear to be failing to meet the dietary recommended level of calcium (18). Adolescence also appears to be the life stage during the first 2 decades of life that has the highest prevalence of low vitamin D status (41). It is well established that prolonged and severe vitamin D deficiency leads to rickets in children (15). Less severe vitamin D deficiency, although it does not cause rickets, may prevent children and adolescents from reaching their genetically programmed height and peak bone mass (27). For example, results from studies in adolescents provide evidence of a possible adverse effect of vitamin D deficiency and insufficiency for bone health in children (42–44). A recent 12-mo intervention study with supplemental vitamin D shows the benefits to BMC in adolescent Finnish girls (45). There is a need to consider various strategies for increasing vitamin D status of adolescents.

Beyond the effect of calcium and vitamin D, there have been a number of recent studies that show the importance of other nutrients and food components. Kalkwarf et al. (46) investigated the relation between vitamin K intake (and status) and indices of bone health in children and adolescents (aged 3–16 y). Their findings suggest that better vitamin K status was associated with decreased bone turnover in healthy girls consuming a typical U.S. diet. However, vitamin K status was not consistently associated with BMC. O'Connor et al. (47) showed that better vitamin K status was associated with increased BMC in healthy peripubertal Danish girls, although no effects on bone metabolism were evident. Thus, there is a need for well-designed, randomized vitamin K_1 supplementation trials in children and adolescents to confirm epidemiological findings of an association between vitamin K status and bone health.

As mentioned previously, there is a growing body of evidence to show that nondigestible oligosaccharides (especially inulin-type fructans) can enhance calcium absorption. This is particularly the case in adolescents, and the studies illustrating this have been reviewed elsewhere (22,23). One recent study merits particular mention, namely that of Abrams et al. (48), who recently reported the findings of a 12-mo randomized, placebo-controlled intervention trial with an inulin-type fructan (Synergy) in 9- to 13-y-old boys and girls. They found that calcium absorption was significantly higher in the inulin-type fructan-supplemented group than in the placebo (maltodextrin) control group at 8 wk but also, interestingly, after 12 mo (48).

Furthermore, there was evidence that the additional calcium absorbed was retained within the body for use by skeletal tissue. The group receiving the inulin-type fructan had a greater increment in both BMC and BMD than did the control group (48). These findings strongly suggest that addition of selective nondigestible oligosaccharides to food represents an opportunity for increasing the uptake and utilization of calcium present in the diet.

It is also of interest that inulin-type fructans have been suggested to positively influence postmeal satiety and food intake (49), which might be of potential application in tacking childhood obesity, not only of importance for its own sake but also because childhood obesity has been shown to increase risk of childhood fracture (50).

The lack of effective treatments for degenerative diseases such as osteoporosis places increased emphasis on a preventative approach, including dietary strategies. In addition, it offers considerable opportunities for the development of functional foods. The development of nutritional policies as well as of functional foods for bone health must be based on a detailed understanding of the influence of dietary constituents on health. Particularly in the case of functional foods, their development must be supported by independent and appropriate scientific evidence to demonstrate efficacy with respect to claimed health benefits. Thus, more research on the role of diet on bone health is required. In addition, more emphasis should be placed on understanding the role of diet and nutrition on bone health during childhood and adolescence.

Literature Cited

1. European Commission. Report on osteoporosis in the European Community: action for prevention. Luxembourg: Office for Official Publications for the European Commission; 1998.
2. Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. Am J Med. 1993;94:646–50.
3. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series 843. Geneva: World Health Organization; 1994.
4. National Osteoporosis Foundation. http://www.nof.org/osteoporosis/diseasefacts.htm (accessed 4/12/06); 2006.
5. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? J. Bone Miner Res. 1992;7:1005–10.
6. Compston J. Osteoporosis. In: Campbell G, Compston J, Crisp A, editors. The management of common metabolic bone disorders. Cambridge, UK: Cambridge University Press; 1993. p. 29–62.
7. U.S. Census Bureau. http://www.census.gov/ (accessed 4/12/06); 2006.
8. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med. 1996;156:1521–25.
9. Schurch M, Rizzoli R, Mermillod B, Vasey H, Michel J, Bonjour J. A prospective study on socioeconomic aspects of fracture of the proximal femur. J Bone Miner Res. 1996;11:1935–42.
10. Prentice A. Is nutrition important in osteoporosis? Proc Nutr Soc. 1997;56:357–67.
11. Weaver CM. The growing years and prevention of osteoporosis in later life. Proc Nutr Soc. 2000;59:303–6.
12. Cashman KD. Diet and control of osteoporosis. In: Remacle C, Reusens B, editors. Functional foods, ageing and degenerative disease. Cambridge, UK: Woodhead Publishing Limited; 2004. p. 83–114.
13. U.S. Department of Health and Human Services. The 2004 Surgeon General's report on bone health and osteoporosis. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004.
14. World Health Organisation. Diet, nutrition and the prevention of chronic disease. Report of a joint WHO/FAO expert consulation. Technical Report Series 619. Geneva: World Health Organization; 2003.
15. Institute of Medicine. Dietary reference intakes: calcium, magnesium, phosphorus, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
16. National Institutes of Health. Optimal calcium intake. NIH Consens Statement. 1994;12:4.
17. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Hamel C, Ortiz Z, Peterson J, et al. Calcium supplementation on bone loss in postmenopausal women. Cochrane Database Syst Rev. 2004;1:CD004526.
18. Cashman KD. Calcium intake, calcium bioavailability and bone health. Br J Nutr. 2002;87:S169–77.
19. Cashman KD. Prebiotics and calcium bioavailability. Curr Issues Intest Microbiol. 2003;4:21–32.
20. Miller DD. Calcium in the diet: food sources, recommended intakes and nutritional bioavailability. Adv Food Nutr Res. 1989;33:103–56.
21. Flynn A, Cashman K. Calcium fortification of foods. In: Hurrel R, editor. Mineral fortification of foods. Surrey, UK: Leatherhead Food RA; 1999. p. 18–53.
22. Scholz-Ahrens KE, Schrezenmeir J. Effects of bioactive substances in milk on mineral and trace element metabolism with special reference to casein phosphopeptides. Br J Nutr. 2000;84:S147–53.
23. Cashman KD. A prebiotic substance persistently enhances intestinal calcium absorption and increases bone mineralization in young adolescents. Nutr Rev. 2006;64:189–96.
24. Webb AR, Kline LW, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab. 1988;67:373–78.
25. Andersen R, Molgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, Charzewska J, Flynn A, Jakobsen J, et al. Teenage girls and elderly women living in northern Europe have low winter vitamin D status. Eur J Clin Nutr. 2005;59:533–41.
26. Department of Health. Nutrition and bone health with reference to calcium and vitamin D. Dietary reference values for food energy and nutrients for the United Kingdom. Report in Health and Social Subjects no. 49. London: HM Stationery Office; 1998.
27. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers and cardiovascular disease. Am J Clin Nutr. 2004;80:1678S–88S.
28. Weber P. Vitamin K and bone health. Nutrition. 2001;17:880–87.
29. Sokoll LJ, Sadowski JA. Comparison of biochemical indexes for assessing vitamin K status in a healthy adult population. Am J Clin Nutr. 1996;63:566–73.
30. Szulc P, Chapuy MC, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. J Clin Invest. 1993;91:1769–74.
31. Vergnaud P, Garnero P, Meunier PJ, Breart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. J Clin Endocrinol Metab. 1997;82:719–24.
32. Szulc P, Arlot M, Chapuy MC, Duboeuf F, Muenier PJ, Delmas PD. Serum undercarboxylated osteocalcin correlates with hip bone mineral density in elderly women. J Bone Miner Res. 1994;9:1591–5.
33. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr. 1999;69:74–9.
34. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PWF, Ordovas J, Schaefer EJ, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr. 2000;71:1201–8.
35. Cashman KD. Vitamin K status may be an important determinant of bone health in early life. Nutr Rev. 2005;63:284–9.
36. Braam LA, Knapen MH, Geusens P, Brouns F, Hamulyak K, Gerichhausen MJ, Vermeer C. Vitamin K_1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. Calcif Tissue Int. 2003;73:21–6.
37. Gallagher JC. Role of estrogens in the management of postmenopausal bone loss. Rheum Dis Clin North Am. 2001;27:143–62.

38. Cotter A, Cashman KD. Genistein, a soy-based dietary phytoestrogen, appears to prevent early postmenopausal bone loss as effectively as hormone replacement therapy. Nutr Rev. 2003;61:346–51.
39. Morabito N, Crisafulli A, Vergara C, Gaudio A, Lasco A, Frisina N, D'Anna R, Corrado F, Pizzoleo MA, et al. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. J Bone Miner Res. 2002;17:1904–12.
40. Cassidy A, Albertazzi P, Lise Nielsen I, Hall W, Williamson G, Tetens I, Atkins S, Cross H, Manios Y, et al. Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women. Proc Nutr Soc. 2006;65:76–92.
41. Cashman KD. Vitamin D in childhood and adolescence. Postgrad Med J. 2007;83:230–5.
42. Outila TA, Karkkainen MUM, Lamberg-Allardt CJE. Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. Am J Clin Nutr. 2001;74:206–10.
43. Cheng S, Tylavsky F, Kroger H, Karkkainen M, Lyytikainen A, Koistinen A, Mahonen A, Alen M, Halleen J, et al. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. Am J Clin Nutr. 2003;78:485–92.
44. Lehtonen-Veromaa M, Mottonen T, Nuotio I, Irjala K, Leino A, Viikari J. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. Am J Clin Nutr. 2002;76:1446–53.
45. Viljakainen HT, Natri AM, Karkkainen M, Huttunen MM, Palssa A, Jakobsen J, Cashman KD, Molgaard C, Lamberg-Allardt C. A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention. J Bone Miner Res. 2006;21:836–44.
46. Kalkwarf HJ, Khoury JC, Bean J, Elliot JG. Vitamin K, bone turnover, and bone mass in girls. Am J Clin Nutr. 2004;80:1075–80.
47. O'Connor E, Mølgaard C, Michaelsen KF, Jakobsen J, Lamberg-Allardt CJE, Cashman KD. Serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, and its relationship to bone health indices in Danish girls. Br J Nutr. 2007;97:661–6.
48. Abrams SA, Griffin IJ, Hawthorne KM, Liang L, Gunn SK, Darlington G, Ellis KJ. A combination of prebiotic short- and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. Am J Clin Nutr. 2005;82:471–6.
49. Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. J Bone Miner Res. 2005;20:2090–6.
50. Archer BJ, Johnson SK, Devereux HM, Baxter AL. Effect of fat replacement by inulin or lupin-kernel fibre on sausage patty acceptability, post-meal perceptions of satiety and food intake in men. Br J Nutr. 2004;91:591–9.