J Bone Miner Metab (2008) 26:416–424
DOI 10.1007/s00774-007-0846-9


REVIEW ARTICLE

**Germán Vicente-Rodríguez · Juan Ezquerra
María Isabel Mesana · Juan Miguel Fernández-Alvira
Juan Pablo Rey-López · José Antonio Casajus
Luis Alberto Moreno**

# Independent and combined effect of nutrition and exercise on bone mass development

Received: August 10, 2007 / Accepted: December 24, 2007

**Abstract** Food intake provides the necessary components for adequate metabolic functions in bone. Calcium, phosphorus, vitamin D, magnesium, proteins, and fluoride are some of the most important nutrients in this regard. These have different effects on bone mass. Additionally, exercise has been shown to elicit osteogenic responses in bone development; indeed, it seems to potentiate, for example, the effect of calcium supplementation on bone mass. However, the nutrition–exercise–bone mass relationship is complex and needs further in-depth investigation. As a first step, therefore, we reviewed current knowledge about the role of nutrition on the development of bone tissue and how physical activity affects the nutrient–bone relationship.

**Key words** bone mineral density · nutrients · vitamins · calcium · physical activity

## Introduction

Bone mineral content (BMC) and bone mineral density (BMD) accrual is mainly determined by genotype. Approximately 70% of the variation in bone density is determined by heredity. The remaining 30%, therefore, depends on the phenotype, in which physical activity and/or nutrition can induce physiological responses allowing levels of higher bone mass attainment.

G. Vicente-Rodríguez (✉) · J. Ezquerra · M.I. Mesana · J.M. Fernández-Alvira · J.P. Rey-López · L.A. Moreno
University School of Health Science and Pediatrics Department, HELENA Study Group, University of Zaragoza, Edificio Cervantes, 2nd floor, C/Corona de Aragón, 42 50009 Zaragoza, Spain
Tel. +34 976400338 (ext. 301); Fax +34 976400340
e-mail: gervicen@unizar.es

G. Vicente-Rodríguez · J.A. Casajus
School of Health and Sport Science, University of Zaragoza, Huesca, Spain

G. Vicente-Rodríguez
Unit for Preventive Nutrition, Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden

The crystalline salt deposited on the organic matrix of the bone is composed mainly of calcium and phosphorus, which represents approximately 80%–90% of the BMC [1]. Other important components of bone are proteins: collagen fibers constitute 90%–95% of the organic matrix [2]. Therefore, food intake and the chemical nutrition process are essential to maintain bone structure as they will supply essential substances for the constant process of bone regeneration.

Food intake has to provide the necessary components to develop the normal metabolic functions of the bone. It should principally provide calcium, phosphorus, vitamin D, magnesium, proteins, and fluoride [3], but also other nutrients, such as zinc, copper, manganese, boron, vitamins A, B, C, and K, potassium, and sodium, which are able to intervene in the metabolic process of the bone [4,5]. It is difficult to study the effect of each of these nutrients on bone tissue, because many of them, and quite probably others that have not been examined yet, act in a synergistic way. It is difficult therefore to determine the specific and independent participation of each one. In addition, the degree of participation of these nutrients may vary depending on individual conditions, i.e., physical activity, age, or biological growth. In fact, it is not yet known if the recommended daily intake (RDI) continues to be sufficient for subjects with a high level of sports participation, especially during puberty.

Adolescence is a period of life where major accumulation of bone mass occurs, notably during a short period of time, principally from hormonal development [6]. During this period, the adequate contribution of nutrients involved in bone metabolism is critical [7,8].

It is known that participation in physical activity during puberty may result in greater bone mass accumulation [9–11], and also that physical activity protects against bone fractures later in life [12]. Similarly, some nutritional strategies, such as calcium supplementation, may also benefit skeletal development, although there are controversies in this regard [13–15]. The combined effect or interaction between physical exercise and calcium supplementation has been shown, and it seems to be more efficacious in bone

development than just exercise or calcium [16]. However, the interaction between exercise and food intake or specific diets in bone mass acquisition is not clear [16].

Consequently, the aims of this review were to broaden current knowledge about the role of nutrition on the development of bone tissue and, second, to learn how physical activity affects the nutrient–bone relationship.

## Research strategy

The research strategy for reviewing the studies about the relationship between nutrition, exercise, and bone development was based on the following single terms or combinations of these: bone mass, BMC, BMD, nutrition, calcium, phosphorus, vitamin D, vitamin K, physical activity, exercise, sport, child, and adolescent. The databases used were Medline and PubMed, and the selection process was conducted by at least two independent researchers for each section. Cross-sectional, longitudinal, and intervention studies were included.

## The effect of exercise on bone development

Exercise during growth seems to increase the BMD peak by between 10% and 20% in the loading bones of active adolescents compared with sedentary controls [17]. This effect could be even greater if exercise starts in prepuberty [11,18]. The proportion of BMC attained between age 11 to 13 years in girls and 12 to 14 years in boys is around 25% of the adult BMC [19]. It is also likely that exercise during this period acts in a synergic way, with the growth-related bone development leading to a higher bone mass at the end of the pubertal period [9,19].

Bone seems to adapt to the level of exercise intensity required [20] depending on the mechanical stress generated by exercise [21]. Therefore, the final effects of exercise on bones depend on the type, intensity, and duration of the stimulus. Although the most suitable sporting activities remain unknown, participation in weight-bearing activities generating high ground reaction forces, mainly if they include jumps, sprints, and rapid changes of directions, seem to have the most evident osteogenic effect during growth [22,23].

## Calcium

Calcium is one of the main minerals found in bone, and its supply through diet is crucial. Perhaps for this reason, calcium has been the nutrient most studied in relation to bone mass for many years. Several investigations have demonstrated that calcium supplementation increases bone mass significantly during childhood and adolescence [24,25].

The biggest increase of bone mass, and therefore where calcium intake might be most efficient, is during the pubertal hormonal spurt, because bones grow both in length and in thickness [26,27]. It has been shown that if the consumption of 1200 mg/day of calcium is accompanied with additional estrogen intake, the acquisition of bone mass is higher in other groups of age [28], indicating that a greater contribution of calcium during the stage of increase of estrogen production may produce benefits on bone growth in girls. However, specific studies are needed in this regard.

Nevertheless, most of the information indicates that calcium intake should be constant to maintain bone mass increase [29,30], as the increase can be reversed if the intake is intermittent or interrupted [29,31]. However, there are discrepancies on this matter [32,33], because the biological condition in which the calcium intake occurred, the origin of the calcium, the habit of taking products with calcium, or the level of physical activity may produce different results [34]. New studies in this direction may help to find the most efficient method to make the benefits achieved by calcium intake permanent.

Despite the fact that calcium has always been beneficial for bone mass [35,36], the effects produced by calcium intake are different from the effects observed with intake of dairy products [37]. The latter is suggested in a study in which both milk product intake and the direct intake of calcium had positive effects on BMD, but only dairy products increased bone area ($cm^2$) [37]. These differences may be explained by the greater mineral and protein content of milk and/or the milk drinking habit [37]. In addition to calcium, there are other components of dairy products that are able to act positively on bone metabolism: energetic contribution, hormonal synthesis [such as insulin-like growth factor (IGF-1)], or vitamin D, increasing the effects that calcium has per se.

## Calcium threshold

The relationship between calcium consumption and bone mass is evident. However, how much calcium should be taken for optimal bone growth and how much should be taken to obtain additional benefits? Although discussed, the RDIs (reference dietary intakes) propose minimal quantities required for optimal growth. It seems that a greater contribution of calcium may be transformed in a greater accumulation of bone mass, although when calcium consumption reaches a given level, its beneficial effects cease, suggesting the existence of a calcium consumption threshold after which bone growth does not continue [38–40]. That is, calcium intake could induce changes in the acquisition of bone mass only in subjects with a calcium-poor diet [24]. However, this threshold could vary with age, as Matkovic et al. [41] showed in female adolescents that, at calcium intakes of about 1500 mg/day, urinary calcium started to rise more rapidly, indicating that skeletal saturation with calcium was reached. Although there is little information on this matter in pediatric populations, several studies have found that calcium supplementation is associ-

ated with increments in appendicular BMD and BMC in prepubertal children at dosages ranging between 500 and 2000 mg/day for periods ranging between 12 months and 3 years [42]. In contrast, no changes are produced in supplemented 12- to 15-year-old girls [42]. According to this author, calcium becomes less important, possibly because of the stimulatory effects of estrogen on intestinal absorption and renal reabsorption of this mineral.

Bone benefits are derived not only from calcium, but also from adequate consumption of magnesium, potassium, vitamins C, D, K, A, and B, and other potentially important nutrients that are needed to keep bone metabolism in good working order [40]. The adequate consumption of calcium may play an important role in relation to the correct utilization of other nutrients that participate directly or indirectly on bone metabolism, and these nutrients may be the origin of bone improvements from the calcium threshold [39,43].

## Indirect calcium effects on bone growth in girls

Some studies indicate an interaction between calcium intake and the age of the beginning of menarche. Calcium intake in prepubertal girls may accelerate the initiation of puberty and significantly reduce the age at which menarche begins [34,44,45]. It has been observed that premenarcheal girls with an average calcium consumption of 420 mg/day experienced the menarche at 12.8 years (Tanner maturation stage 4.1), whereas a similar group with a calcium intake of 839 mg/day experienced menarche at 11.9 years of age (Tanner 3.5) [44]. It can be hypothesized, therefore, that low calcium consumption is related to a low adrenal androgen secretion and may affect adrenal steroidal enzymes, thereby delaying the commencement of menarche [34,44].

The delay during female pubertal growth may result in reduced endocortical apposition, resulting in a normal or larger bone with a thinner cortex and larger medullar diameter [46]. However, biomechanical consequences of delayed puberty may be worse in boys than in girls, because boys reduce their bone size [46].

## Joint action of calcium intake and physical activity on bone mass

It has been observed that only those subjects with low calcium consumption are able to benefit from the increase in calcium intake to improve their bone condition [24,47]. Moreover, the effects of calcium intake on bone mass are contradictory, displaying positive [48–50] or negative [51] effects depending on the bone location measured and the habitual consumption of calcium by the subjects.

The effects of physical activity are more evident. Increases in BMC and BMD in the bone areas experiencing tension have been observed, notably in high-performance activities with impacts or a high volume of training [50,52–54]. Therefore, it seems logical, as has been indicated in several studies [48,55–57], that the combination of physical activity and calcium intake may be more effective in increasing bone mass than either calcium intake or physical activity alone [58]. However, a meta-analysis of controlled trials showed that physical activity did not modify the effect of calcium supplementation on BMD [15]; the authors cannot exclude this possibility.

Nevertheless, it seems that a minimum calcium intake of approximately 1000 mg/day is required to make effective these combined inputs [59], as exercise without sufficient calcium supply would not increase the bone mass in adolescents [60,61]. This finding is in agreement with a longitudinal study [62] performed in girls who were between 8 and 13 years old and participated in regular exercise for 7 h/week. It was observed that the group with the higher calcium intake (1800 mg/day) increased total and regional BMC, while the group with low calcium intake did not show significant differences when compared to a nonexercising control group that took the same amount of calcium (950 mg/day) [62].

Therefore, it seems that there is a very important interaction between the mechanic requirement of physical activity and the availability of calcium (and possibly the availability of other nutrients) to reach the greatest bone mass increases. This idea has been emphasized by the results of randomized controlled trial studies in prepubertal children [62–64] and adolescents [65]. Specker and Binkley [63] showed that both exercise and calcium supplementation had an effect on bones, and they found an interaction between calcium intake and exercise, translated into changes in leg BMC by dual-energy X-ray absorptiometry (DXA) and geometry by quantitative computed tomography (QCT). However, while a calcium supplementation effect disappears, exercise effects were still significant 1 year after the intervention [66].

Additionally, when dealing with high mechanical requests, the intestinal absorption of calcium may be higher and the urinary excretion may be lower [67], which would decrease the production of parathyroid hormone (PTH) and would delay bone resorption [68,69]. However, this fact still needs to be confirmed in adolescents.

In any event, additional studies are needed to understand the mechanisms involved in the greater effect on bone mass development when calcium intake is accompanied by physical activity. Other mechanisms by which the physical activity might mediate in cases of high calcium intake, given a global effect [62] and not simply a local one [32] at the areas under mechanical loads, as, for example, through its influence on hormonal secretion [57], should be also investigated.

## Vitamin D

1,25-Dihydroxycholecalciferol is the active form of vitamin D (vitamin $D_3$), and its serum level is the best indicator of vitamin D status. It is involved in bone metabolism in several complex ways [70]. Vitamin D deficit is related to a

decrease in neuromuscular function and with a bone mass decrease that causes a large number of fractures [3]. Vitamin D deficit has also been associated with bone mass decreases during childhood [71–73] and puberty [73–75].

It is difficult to connect vitamin D intake from food with bone mass increase, as the synthesis of vitamin D depends on exposure to sunlight. Therefore, this depends on the geographic area, on the exposure time to sunlight, and so on. Recent recommendations for adequate intake of vitamin $D_3$ have been set at 5 μg/day for children of all ages in the absence of exposure to sun [76]. The ideal healthy blood level of 25-hydroxyvitamin D should be 30–60 ng/ml [77]. Dietary enrichment or supplementation has been suggested for girls with hypovitaminosis D who are at risk of low peak bone mass attainment [75]. However, additional studies are required to demonstrate the positive effects of vitamin D on bone mass without calcium intake.

The combination of vitamin D and calcium, which are the most important nutrients in bone metabolism, has a clear synergistic effect on bone mass in all age groups [78,79]. However, recent literature has opened discussion on the real effect of vitamin D and calcium supplementation on decreased bone fracture risk, which was built on previous literature supporting increased vitamin D and calcium intake as effective methods for decreasing risk of osteoporotic-related fractures [77]. Low levels of vitamin D (and/or calcium) stimulate PTH action and cause defective bone mineralization, therefore increasing the risk of fractures and osteoporosis [73,80].

Because vitamin D and calcium have a synergic effect on bone metabolism, the benefits of combining vitamin D and exercise could be similar to those found for a combination of calcium and exercise. In addition, physical activity and exercise have been related to serum vitamin $D_3$ [81], but evidence of the real effect of exercise on vitamin $D_3$ metabolism remains conflicting [82]. Moreover, there is a lack of information on adolescent populations.

As vitamin D synthesis depends on exposure to sunlight, another possible effect of exercise could be mediated by the fact that some types of physical activities or sports participation take place outdoors, providing the opportunity to be exposed to sunlight. In fact, higher levels of vitamin $D_3$ have been reported in people who exercised outdoors, compared with those who exercised indoors [83].

The direct effect of exercise on vitamin D status has not been specifically studied in adolescents, nor has the relationship between vitamin D and exercise and bone mass. Further studies should be carried out to clarify these issues.

## Phosphorus

The other main component of bone is phosphorus, which together with calcium composes hydroxyapatite, which is the main crystalline salt of bone. Both calcium and phosphorus must be available simultaneously and in sufficient quantities for adequate bone mineralization; therefore, phosphorus is an indispensable micronutrient for bone metabolism [84,85].

From a nutritional point of view, it is more important to quantify the calcium/phosphorus ratio (Ca:P ratio) than solely phosphorus, as their codependence and joint effect on mineral retention are more effective [84,86].

It seems that if phosphorus intake is within normal values (RDI, 700 mg/day) it does not affect bone mass homeostasis, although adequate phosphorus intake is fundamental to reach correct bone mass level [87]. In cases of hypophosphatemia, the formation of new bone could be limited as the osteoblastic function decreases and the osteoclastic resorption increases [87].

There are contradictory data about the effect of excessive phosphorus intake in humans. Some authors propose that excessive intake of phosphorus produces hypocalcemia and reduces the Ca:P ratio, and these effects seem to be harmful for bone mass, especially with low dietary calcium intake, because of its stimulatory effect on PTH action [86,88,89]. These results have been seen in girls (18–25 years) consuming high levels of phosphorus and moderate levels of calcium in diets lasting 4 weeks. The serum levels of PTH increased constantly compared with another group who consumed the recommended levels of P and Ca [86]. However, human studies using calcium kinetic methodology showed no effect on bone turnover by doubling P intake [90].

The Ca/P ratio most efficiently achieving maximum BMC and BMD depends on the influence of other factors, such as different nutrients, high fiber intake, low vitamin D intake, caffeine intake, drug and alcohol intake, age [91], alkaline or acid foods, and so on, which all alter the calcium absorption [92]. For example, the leak of urinary calcium produced by the high consumption of phosphorus is attenuated by the amount of protein consumed [93]. In women between 18 and 31 years old, consumption of 1400 mg/day calcium and 1000 mg/day phosphorus (a relation of 1.4) was established as most effective for achieving the maximal benefits of BMC and BMD, 2800 g and 1.26 g/cm$^2$, respectively, being expected. However, by maintaining the same intake of calcium and increasing phosphorus consumption to 1800 mg/day (a relation of 0.7), a result of 2600 g and 1.16 g/cm$^2$ (10% lower BMC and BMD) was obtained. It is confirmed, then, that if the calcium intake is adequate, the Ca/P ratio is more important than the phosphorus intake alone [94]. These results contradict the recommendations that propose that a Ca/P ratio of 1 is the most effective [94]. More longitudinal studies are necessary to elucidate the best osteogenic Ca/P ratio and the modifications that exercise could introduce into this relationship.

Short-term bouts of exercise increase serum phosphorus concentrations at either low or high exercise intensity in young males, which could result in an increase in serum parathyroid hormone [82]. Phosphorus status has been studied in adolescents athletes involved in different types of sports [95]. Although higher BMD was observed in the impact load sports, no differences were found in males involved in impact load sports (i.e., gymnastics),

compared with loading sports (i.e., pool sports), and controls [95].

Phosphorus intake has been shown to predict BMC at the age of 8 years [96]. In the same study, the interaction between phosphorus and physical activity was suggested but not tested [96]. New studies examining the combined effect of phosphorus and exercise on bone mass during growth are needed.

## Vitamin K

Vitamin K intake is related to BMD and it is used for osteoporosis treatment and prevention of bone fractures. Existing evidence suggests that vitamin K deficiency may contribute to an abnormal bone metabolism [97,98]. The osteoblastogenesis increases and the osteoclastogenesis decreases; that is, the bone formation increases and the resorption decreases [97,98].

Vitamin K status correlates positively with serum concentration of vitamin $K_1$ (phytomenadione) and negatively with 1% decarboxylase osteocalcin (%dcOC) [98]. Osteocalcin is one of the proteins that compose the organic environment of bone, and its levels in blood are used as an indicator of bone composition [99]; both vitamin $K_1$ and %dcOC indicate vitamin K status. Vitamin $K_1$ is an isoform of vitamin K and for this reason they correlate positively. The %dcOC is not able to join adequately to hydroxyapatite; to join it correctly, one of the functions of vitamin K is the gamma-carboxylation of the osteocalcin, which joins the $Ca^{2+}$ ion to the hydroxyapatite molecule [100]. For this reason, this correlation is negative.

In a 4-year longitudinal study carried out in girls (3–16 years), levels of vitamin K were positively associated with the increase in bone formation, the decrease in bone resorption, and the increase of bone mass [98]. More studies are necessary regarding the combined effect of vitamin K with calcium or other nutrients, as these are scarce in children and contradictory in adults [101].

It has been suggested that vitamin K and other nutrients interact with other genetic and environmental factors such as physical activity or sedentary habits [96]. These interactions have been proposed as one of the reasons for inconsistent results on the individual role of nutrients in bone health [96]. No relationship has been found between vitamin K and sedentary behavior [96], but the direct relationship with physical activity has not been studied. Similarly, no studies have been conducted to elucidate if exercise could add additional benefits combined with vitamin K supplementation, so studies on this are also needed.

## Other nutrients

As stated, calcium is a threshold nutrient; therefore, the increase in bone mass from an adequate intake of calcium will give greatest efficiency in bone metabolism when other nutrients are coparticipants.

The contribution of these nutrients may come from fruit and vegetable consumption, as there is a positive correlation between these and bone mass in girls and in boys, at prepubescent and adolescent ages [40,102], and in adults [103,104]. However, much controversy exists on this matter because no relationship has been reported in other studies [105].

Fruits and vegetables supply potassium and magnesium to the organism, and when the diet is acidic, they have a muffling effect on the decrease of bone mass as they contribute to create an alkaline ambient [106,107]. Magnesium also plays an important role in the binomial vitamin D–PTH [3]. Vegetables also supply vitamin K, which is an essential cofactor in osteoclast metabolism [108], natural antioxidants, and phytoestrogens, which may also have a bone protective effect [109].

The effect of exercise on bone mass in combination with other nutrients has not been studied yet. However, it has been suggested that a complex matrix of interactions between nutrients, genes, and lifestyle (i.e., physical activity) could occur [110]. Therefore, to study the effect on bone development avoiding the present inconsistency in the results of individual influences, a combination of potential factors could be the most reasonable approach [96].

Proteins may also affect bone metabolism. Their role is complex and probably depends on the action of other nutrients [111,112]. Both low- and high-protein diets may be detrimental for bone health [111]. High consumption of animal proteins may negatively affect bone mass by their effects on the renal excretion of calcium [113,114], probably because of the increased acid load from metabolism of sulfur-containing amino acids [115]. The consumption of vegetable proteins may attenuate these negative effects on bone mass, being associated with the contribution of other nutrients.

However, a short-term intervention trial showed that protein restriction decreased calcium absorption in young women when daily protein intake was 0.7 and 0.8 g/kg, but not during the 0.9 or 1.0 g/kg intake period. In addition, secondary hyperparathyroidism developed in the low-protein groups [116]. More epidemiological evidence highlights the deleterious effects of a low-protein diet on bone, where the lowest quartile of dietary protein intake is associated with a significantly reduced BMD [117].

Other recent studies suggest that the effect of exercise on bone mass is mediated by diet, not only considering the individual nutrients, but also total energy intake [118]. Thus, sporting activities that are supposed to be osteogenic could result in a decrease in bone mass from a negative energy balance, as has been observed in ballet dancers [119], amenorrheic runners [118], or young anorexic women [120].

It has been suggested that many nutrients are related to bone mass development; therefore, children should consume a varied and nutrient-dense diet [96]. We also suggest that exercise must go hand with hand with diet.

## Conclusion

The first aim of this review was to broaden current knowledge about the role of nutrition on the development of bone tissue. In this regard, an adequate consumption of calcium and phosphorous in the diet is essential in maintaining skeletal health, as these are the two main minerals that compose the structure of bone. Other nutrients such as vitamin D, vitamin K, proteins, or even total energy intake are indispensable as catalysts of the osteogenic process and are also capable of increasing calcium efficacy.

Second, we tried to understand how physical activity affects the nutrient–bone relationship. This study was mainly concerned with calcium. In this line, if exercise is combined with increased calcium intake or supplementation, the benefits on bone mass seem to be greater. The latest evidence coming from randomized controlled trials shows that there is interaction between calcium supplementation and exercise, resulting in important changes not only in BMC but also in the structural properties of bones.

A complete and nutrient-dense diet is recommended, as many nutrients influence bone health as well as exercise participation because of its direct effect on bone development. However, new studies are needed to test the interaction between other specific nutrients or diets and exercise regarding bone development.

**Acknowledgments** This study was supported by the Spanish Ministry of Health (FIS 00/0015), and grants from Panrico S.A., Madaus S.A. and Procter and Gamble S.A and the Fundación Cuenca Villoro. This study was also supported by the DGA (CONSI+D) and CAI (CM 11/07). Special thanks are given to Thaïs Ferguson for her useful comments and English review.

## References

1. Boskey AL (1999) Mineralization, structure, and function of bone. In: Seibel MJ, Robins SP, Bilezikian JP (eds) Dynamics of Bone and Cartilage Metabolism. Academic Press, San Diego, pp 153–164
2. Guyton AC, Hall JE (2003) Tratado de Fisiología Médica. McGraw-Hill. Interamericana de España, Aravaca (Madrid)
3. Prentice A (2004) Diet, nutrition and the prevention of osteoporosis. Public Health Nutr 7:227–243
4. Ilich JZ, Kerstetter JE (2000) Nutrition in bone health revisited: a story beyond calcium. J Am Coll Nutr 19:715–737
5. Ilich JZ, Skugor M, Hangartner T, Baoshe A, Matkovic V (1998) Relation of nutrition, body composition and physical activity to skeletal development: a cross-sectional study in preadolescent females. J Am Coll Nutr 17:136–147
6. Manzoni P, Brambilla P, Pietrobelli A, Beccaria L, Bianchessi A, Mora S, Chiumello G (1996) Influence of body composition on bone mineral content in children and adolescents. Am J Clin Nutr 64:603–607
7. Weaver CM (2000) The growing years and prevention of osteoporosis in later life. Proc Nutr Soc 59:303–306
8. Weaver CM (2000) Calcium requirements of physically active people. Am J Clin Nutr 72:579S–584S
9. Gustavsson A, Thorsen K, Nordstrom P (2003) A 3-year longitudinal study of the effect of physical activity on the accrual of bone mineral density in healthy adolescent males. Calcif Tissue Int 73:108–114
10. Vicente-Rodriguez G, Ara I, Perez-Gomez J, Dorado C, Serrano-Sanchez JA, Calbet JAL (2004) High femoral bone mineral density accretion in prepubertal football players. Med Sci Sports Exerc 33:1789–1795
11. Vicente-Rodriguez G, Jimenez-Ramirez J, Ara I, Serrano-Sanchez JA, Dorado C, Calbet JA (2003) Enhanced bone mass and physical fitness in prepubescent footballers. Bone (NY) 33:853–859
12. Thorpe DL, Knutsen SF, Beeson WL, Fraser GE (2006) The effect of vigorous physical activity and risk of wrist fracture over 25 years in a low-risk survivor cohort. J Bone Miner Metab 24:476–483
13. Slemenda CW, Peacock M, Hui S, Zhou L, Johnston CC (1997) Reduced rates of skeletal remodeling are associated with increased bone mineral density during the development of peak skeletal mass. J Bone Miner Res 12:676–682
14. Wosje KS, Specker BL (2000) Role of calcium in bone health during childhood. Nutr Rev 58:253–268
15. Winzenberg T, Shaw K, Fryer J, Jones G (2006) Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ 333:775
16. Specker B, Vukovich M (2007) Evidence for an interaction between exercise and nutrition for improved bone health during growth. Med Sport Sci 51:50–63
17. Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, Seeman E (1998) Exercise before puberty may confer residual benefits in bone density in adulthood: studies in active prepubertal and retired female gymnasts. J Bone Miner Res 13:500–507
18. Kontulainen S, Sievanen H, Kannus P, Pasanen M, Vuori I (2003) Effect of long-term impact-loading on mass, size, and estimated strength of humerus and radius of female racquet-sports players: a peripheral quantitative computed tomography study between young and old starters and controls. J Bone Miner Res 18: 352–359
19. Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R (2000) Calcium accretion in girls and boys during puberty: a longitudinal analysis. J Bone Miner Res 15:2245–2250
20. Karlsson MK, Magnusson H, Karlsson C, Seeman E (2001) The duration of exercise as a regulator of bone mass. Bone (NY) 28:128–132
21. Heinonen A (2001) Biomechanics. In: Khan K, McKay H, Kannus P, Bailey D, Wark J, Bennell K (eds) Physical Activity and Bone Health. Human Kinetics, Champaign, IL, pp 23–34
22. Vicente-Rodriguez G (2006) How does exercise affect bone development during growth? Sports Med 36:561–569
23. Vicente-Rodriguez G, Ara I, Perez-Gomez J, Serrano-Sanchez JA, Dorado C, Calbet JA (2004) High femoral bone mineral density accretion in prepubertal soccer players. Med Sci Sports Exerc 36:1789–1795
24. Lee WT, Leung SS, Wang SH, Xu YC, Zeng WP, Lau J, Oppenheimer SJ, Cheng JC (1994) Double-blind, controlled calcium supplementation and bone mineral accretion in children accustomed to a low-calcium diet. Am J Clin Nutr 60:744–750
25. Welten DC, Kemper HC, Post GB, van Staveren WA (1995) A meta-analysis of the effect of calcium intake on bone mass in young and middle aged females and males. J Nutr 125:2802–2813
26. Matkovic V (1991) Calcium metabolism and calcium requirements during skeletal modeling and consolidation of bone mass. Am J Clin Nutr 54:245S–260S
27. Matkovic V, Badenhop-Stevens NE, Landoll JD, Goel P, Li B (2002) Long term effect of calcium supplementation and dairy products on bone mass of young females. J Bone Miner Res 17: S172
28. Nieves JW, Komar L, Cosman F, Lindsay R (1998) Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. Am J Clin Nutr 67:18–24
29. Heaney RP (1995) Interpreting trials of bone-active agents. Am J Med 98:329–330
30. Lee WT, Leung SS, Leung DM, Cheng JC (1996) A follow-up study on the effects of calcium-supplement withdrawal and puberty on bone acquisition of children. Am J Clin Nutr 64: 71–77
31. Anderson JJ (2000) The important role of physical activity in skeletal development: how exercise may counter low calcium intake. Am J Clin Nutr 71:1384–1386

32. Bonjour JP, Chevalley T, Ammann P, Slosman D, Rizzoli R (2001) Gain in bone mineral mass in prepubertal girls 3.5 years after discontinuation of calcium supplementation: a follow-up study. Lancet 358:1208–1212
33. Dibba B, Prentice A, Ceesay M, Mendy M, Darboe S, Stirling DM, Cole TJ, Poskitt EM (2002) Bone mineral contents and plasma osteocalcin concentrations of Gambian children 12 and 24 mo after the withdrawal of a calcium supplement. Am J Clin Nutr 76:681–686
34. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP (2005) Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab 90:44–51
35. Merrilees MJ, Smart EJ, Gilchrist NL, Frampton C, Turner JG, Hooke E, March RL, Maguire P (2000) Effects of diary food supplements on bone mineral density in teenage girls. Eur J Nutr 39:256–262
36. Dibba B, Prentice A, Ceesay M, Stirling DM, Cole TJ, Poskitt EM (2000) Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low-calcium diet. Am J Clin Nutr 71:544–549
37. Matkovic V, Landoll JD, Badenhop-Stevens NE, Ha EY, Crncevic-Orlic Z, Li B, Goel P (2004) Nutrition influences skeletal development from childhood to adulthood: a study of hip, spine, and forearm in adolescent females. J Nutr 134:701S–705S
38. Matkovic V, Heaney RP (1992) Calcium balance during human growth: evidence for threshold behavior. Am J Clin Nutr 55: 992–996
39. 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
40. Vatanparast H, Baxter-Jones A, Faulkner RA, Bailey DA, Whiting SJ (2005) Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. Am J Clin Nutr 82:700–706
41. Matkovic V, Ilich JZ, Andon MB, Hsieh LC, Tzagournis MA, Lagger BJ, Goel PK (1995) Urinary calcium, sodium, and bone mass of young females. Am J Clin Nutr 62:417–425
42. Borer KT (2005) Physical activity in the prevention and amelioration of osteoporosis in women: interaction of mechanical, hormonal and dietary factors. Sports Med 35:779–830
43. 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
44. Bonofiglio D, Garofalo C, Catalano S, Marsico S, Aquila S, Ando S (2004) Low calcium intake is associated with decreased adrenal androgens and reduced bone age in premenarcheal girls in the last pubertal stages. J Bone Miner Metab 22:64–70
45. Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, Theintz G, Rizzoli R (1997) Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. J Clin Invest 99:1287–1294
46. Seeman E (2001) Clinical review 137: Sexual dimorphism in skeletal size, density, and strength. J Clin Endocrinol Metab 86: 4576–4584
47. Lee WT, Leung SS, Leung DM, Wang SH, Xu YC, Zeng WP, Cheng JC (1997) Bone mineral acquisition in low calcium intake children following the withdrawal of calcium supplement. Acta Paediatr 86:570–576
48. Lloyd T, Andon MB, Rollings N, Martel JK, Landis JR, Demers LM, Eggli DF, Kieselhorst K, Kulin HE (1993) Calcium supplementation and bone mineral density in adolescent girls. JAMA 270:841–844
49. Tylavsky FA, Anderson JJ, Talmage RV, Taft TN (1992) Are calcium intakes and physical activity patterns during adolescence related to radial bone mass of white college-age females? Osteoporos Int 2:232–240
50. Babaroutsi E, Magkos F, Manios Y, Sidossis LS (2005) Body mass index, calcium intake, and physical activity affect calcaneal ultrasound in healthy Greek males in an age-dependent and parameter-specific manner. J Bone Miner Metab 23:157–166
51. Katzman DK, Bachrach LK, Carter DR, Marcus R (1991) Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. J Clin Endocrinol Metab 73:1332–1339
52. Chilibeck PD, Sale DG, Webber CE (1995) Exercise and bone mineral density. Sports Med 19:103–122
53. Dalsky GP, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birge SJ Jr (1988) Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. Ann Intern Med 108:824–828
54. Suominen H (1993) Bone mineral density and long term exercise. An overview of cross-sectional athlete studies. Sports Med 16:316–330
55. Lau EM, Woo J, Leung PC, Swaminathan R, Leung D (1992) The effects of calcium supplementation and exercise on bone density in elderly Chinese women. Osteoporos Int 2:168–173
56. Prince R, Devine A, Dick I, Criddle A, Kerr D, Kent N, Price R, Randell A (1995) The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. J Bone Miner Res 10:1068–1075
57. Prince RL, Smith M, Dick IM, Price RI, Webb PG, Henderson NK, Harris MM (1991) Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. N Engl J Med 325:1189–1195
58. Welch JM, Weaver CM (2005) Calcium and exercise affect the growing skeleton. Nutr Rev 63:361–373
59. Specker BL (1996) Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. J Bone Miner Res 11:1539–1544
60. Gunnes M, Lehmann EH (1996) Physical activity and dietary constituents as predictors of forearm cortical and trabecular bone gain in healthy children and adolescents: a prospective study. Acta Paediatr 85:19–25
61. Lappe J, Stubby J, Davies K, Recker R (2001) Exercise without sufficient calcium does not increase rate of bone mass accrual in pubertal females. J Bone Miner Res 16:s138
62. Courteix D, Jaffre C, Lespessailles E, Benhamou L (2005) Cumulative effects of calcium supplementation and physical activity on bone accretion in premenarchal children: a double-blind randomised placebo-controlled trial. Int J Sports Med 26: 332–338
63. Specker B, Binkley T (2003) Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res 18:885–892
64. Iuliano-Burns S, Saxon L, Naughton G, Gibbons K, Bass SL (2003) Regional specificity of exercise and calcium during skeletal growth in girls: a randomized controlled trial. J Bone Miner Res 18:156–162
65. Stear SJ, Prentice A, Jones SC, Cole TJ (2003) Effect of a calcium and exercise intervention on the bone mineral status of 16–18-y-old adolescent girls. Am J Clin Nutr 77:985–992
66. Specker B, Binkley T, Fahrenwald N (2004) Increased periosteal circumference remains present 12 months after an exercise intervention in preschool children. Bone (NY) 35:1383–1388
67. Branca F (1999) Physical activity, diet and skeletal health. Public Health Nutr 2:391–396
68. Horowitz M, Morris HA, Hartley TF, Need AG, Wishart J, Ryan P, Nordin BE (1987) The effect of an oral calcium load on plasma ionized calcium and parathyroid hormone concentrations in osteoporotic postmenopausal women. Calcif Tissue Int 40: 133–136
69. Kent GN, Price RI, Gutteridge DH, Allen JR, Blakeman SL, Bhagat CI, St John A, Barnes MP, Smith M, Evans DV (1991) Acute effects of an oral calcium load in pregnancy and lactation: findings on renal calcium conservation and biochemical indices of bone turnover. Miner Electrolyte Metab 17:1–7
70. Carmeliet G, Verstuyf A, Daci E, Bouillon R (1999) The vitamin D hormone and its nuclear receptor: genomic mechanisms involved in bone biology. In: Seibel MJ, Robins SP, Bilezikian JP (eds) Dynamics of Bone and Cartilage Metabolism. Academic Press, San Diego
71. Cooper C, Javaid K, Westlake S, Harvey N, Dennison E (2005) Developmental origins of osteoporotic fracture: the role of maternal vitamin D insufficiency. J Nutr 135:2728S–2734S

72. Zamora SA, Rizzoli R, Belli DC, Slosman DO, Bonjour JP (1999) Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls. J Clin Endocrinol Metab 84:4541–4544.
73. Cheng S, Tylavsky F, Kroger H, Karkkainen M, Lyytikainen A, Koistinen A, Mahonen A, Alen M, Halleen J, Vaananen K, Lamberg-Allardt C (2003) 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 78:485–492
74. Jones G, Dwyer T, Hynes KL, Parameswaran V, Greenaway TM (2005) Vitamin D insufficiency in adolescent males in Southern Tasmania: prevalence, determinants, and relationship to bone turnover markers. Osteoporos Int 16:636–641
75. Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS (2002) Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-year prospective study. Am J Clin Nutr 76:1446–1453
76. Branca F, Vatuena S (2001) Calcium, physical activity and bone health: building bones for a stronger future. Public Health Nutr 4:117–123.
77. Holick MF (2006) The role of vitamin D for bone health and fracture prevention. Curr Osteoporos Rep 4:96–102
78. Moyer-Mileur LJ, Xie B, Ball SD, Pratt T (2003) Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls. J Musculoskelet Neuronal Interact 3:63–70
79. Cumming RG, Nevitt MC (1997) Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 12:1321–1329
80. Khaw KT, Sneyd MJ, Compston J (1992) Bone density parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ 305:273–277
81. Looker AC (2007) Do body fat and exercise modulate vitamin D status? Nutr Rev 65:S124–S126
82. Maimoun L, Manetta J, Couret I, Dupuy AM, Mariano-Goulart D, Micallef JP, Peruchon E, Rossi M (2006) The intensity level of physical exercise and the bone metabolism response. Int J Sports Med 27:105–111
83. Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E (1995) Serum 25-hydroxyvitamin D3 is related to physical activity and ethnicity but not obesity in a multicultural workforce. Aust N Z J Med 25:218–223
84. Shapiro R, Heaney RP (2003) Co-dependence of calcium and phosphorus for growth and bone development under conditions of varying deficiency. Bone (NY) 32:532–540
85. Nordin BE (1988) Phosphorus. J Food Nutr 45:62–75
86. Calvo MS, Kumar R, Heath H (1990) Persistently elevated parathyroid hormone secretion and action in young women after four weeks of ingesting high phosphorus, low calcium diets. J Clin Endocrinol Metab 70:1334–1340
87. Heaney RP, Nordin BE (2002) Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr 21:239–244
88. Calvo MS (1994) The effects of high phosphorus intake on calcium homeostasis. Adv Nutr Res 9:183–207
89. Heaney RP (2004) Phosphorus nutrition and the treatment of osteoporosis. Mayo Clin Proc 79:91–97
90. Heaney RP (1987) The role of nutrition in prevention and management of osteoporosis. Clin Obstet Gynecol 30:833–846
91. Miggiano GA, Gagliardi L (2005) Diet, nutrition and bone health. Clin Ter 156:47–56
92. Buclin T, Cosma M, Appenzeller M, Jacquet AF, Decosterd LA, Biollaz J, Burckhardt P (2001) Diet acids and alkalis influence calcium retention in bone. Osteoporos Int 12:493–499
93. Heaney RP (1993) Protein intake and the calcium economy. J Am Diet Assoc 93:1259–1260
94. Teegarden D, Lyle RM, McCabe GP, McCabe LD, Proulx WR, Michon K, Knight AP, Johnston CC, Weaver CM (1998) Dietary calcium, protein, and phosphorus are related to bone mineral density and content in young women. Am J Clin Nutr 68: 749–754
95. Lima F, De Falco V, Baima J, Carazzato JG, Pereira RM (2001) Effect of impact load and active load on bone metabolism and body composition of adolescent athletes. Med Sci Sports Exerc 33:1318–1323
96. Bounds W, Skinner J, Carruth BR, Ziegler P (2005) The relationship of dietary and lifestyle factors to bone mineral indexes in children. J Am Diet Assoc 105:735–741
97. Booth SL, Broe KE, Gagnon DR, Tucker KL, Hannan MT, McLean RR, Dawson-Hughes B, Wilson PW, Cupples LA, Kiel DP (2003) Vitamin K intake and bone mineral density in women and men. Am J Clin Nutr 77:512–516
98. Kalkwarf HJ, Khoury JC, Bean J, Elliot JG (2004) Vitamin K, bone turnover, and bone mass in girls. Am J Clin Nutr 80: 1075–1080
99. Szulc P, Seeman E, Delmas PD (2000) Biochemical measurements of bone turnover in children and adolescents. Osteoporos Int 11:281–294
100. Vermeer C, Jie KS, Knapen MH (1995) Role of vitamin K in bone metabolism. Annu Rev Nutr 15:1–22
101. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PW, Ordovas J, Schaefer EJ, Dawson-Hughes B, Kiel DP (2000) Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr 71:1201–1208
102. Tylavsky FA, Holliday K, Danish R, Womack C, Norwood J, Carbone L (2004) Fruit and vegetable intakes are an independent predictor of bone size in early pubertal children. Am J Clin Nutr 79:311–317
103. New SA, Robins SP, Campbell MK, Martin JC, Garton MJ, Bolton-Smith C, Grubb DA, Lee SJ, Reid DM (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
104. Wattanapenpaiboon N, Lukito W, Wahlqvist ML, Strauss BJ (2003) Dietary carotenoid intake as a predictor of bone mineral density. Asia Pac J Clin Nutr 12:467–473
105. McGartland CP, Robson PJ, Murray LJ, Cran GW, Savage MJ, Watkins DC, Rooney MM, Boreham CA (2004) Fruit and vegetable consumption and bone mineral density: the Northern Ireland Young Hearts Project. Am J Clin Nutr 80:1019–1023
106. Vescini F, Buffa A, La Manna G, Ciavatti A, Rizzoli E, Bottura A, Stefoni S, Caudarella R (2005) Long-term potassium citrate therapy and bone mineral density in idiopathic calcium stone formers. J Endocrinol Invest 28:218–222
107. Saito N, Tabata N, Saito S, Andou Y, Onaga Y, Iwamitsu A, Sakamoto M, Hori T, Sayama H, Kawakita T (2004) Bone mineral density, serum albumin and serum magnesium. J Am Coll Nutr 23:701S–703S
108. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA (1999) Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 69:74–79
109. Wangen KE, Duncan AM, Merz-Demlow BE, Xu X, Marcus R, Phipps WR, Kurzer MS (2000) Effects of soy isoflavones on markers of bone turnover in premenopausal and postmenopausal women. J Clin Endocrinol Metab 85:3043–3048
110. Bonjour JP, Chevalley T, Rizzoli R, Ferrari S (2007) Gene-environment interactions in the skeletal response to nutrition and exercise during growth. Med Sport Sci 51:64–80
111. 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
112. 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
113. Barzel US, Massey LK (1998) Excess dietary protein can adversely affect bone. J Nutr 128:1051–1053
114. 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
115. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J (2005) Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 81:341–354

116. Kerstetter JE, Svastisalee CM, Caseria DM, Mitnick ME, Insogna KL (2000) A threshold for low-protein-diet-induced elevations in parathyroid hormone. Am J Clin Nutr 72:168–173
117. Kerstetter JE, Looker AC, Insogna KL (2000) Low dietary protein and low bone density. Calcif Tissue Int 66:313
118. Zanker CL, Swaine IL (1998) Relation between bone turnover, oestradiol, and energy balance in women distance runners. Br J Sports Med 32:167–171.
119. Young N, Formica C, Szmukler G, Seeman E (1994) Bone density at weight-bearing and nonweight-bearing sites in ballet dancers: the effects of exercise, hypogonadism, and body weight. J Clin Endocrinol Metab 78:449–454
120. Grinspoon S, Miller K, Coyle C, Krempin J, Armstrong C, Pitts S, Herzog D, Klibanski A (1999) Severity of osteopenia in estrogen-deficient women with anorexia nervosa and hypothalamic amenorrhea. J Clin Endocrinol Metab 84:2049–2055