# Bone and Nutrition:

# Common Sense Supplementations for Osteoporosis

**Sonoo Advani, MD,**

**Sunil J. Wimalawansa *, MD, Ph.D., FRCP**

Department of Medicine

372 – MED, Division of Endocrinology

UMDNJ-Robert Wood Johnson Medical School

New Brunswick, NJ 08903-0019, USA

(732) 235- 9584-(office)

(732) 235-8892-(fax)

wimalasu@umdnj.edu

* Corresponding Author

## *Abstract*

Osteoporosis is a serious public health concern. In the United States, estimated 250,000 persons suffer a hip fracture each year, with an estimated cost of more than $7 billion [Mossey JM et al, 1990; Cummings SR et al, 1985] [1,2]. Skeletal fragility, leading to spine and hip fractures is a major source of morbidity and mortality. Adequate calcium intake from childhood to the end of the life span is critical for the formation and retention of a healthy skeleton. It is important to prevent bone loss from occurring, to identify potential risk factors and correct them. A variety of genetic and lifestyle factors influence the risk for osteoporosis. Among these, diet is believed to be one of the most important, especially the roles of calcium and vitamin D, and also the importance of other dietary factors, e.g., protein, vitamin K, vitamin A, phytoestrogens, and other nutrients, which may also contribute to the risk for osteoporosis. This article focuses on reviewing the role of diet and nutritional supplementation in preventing, and treating osteoporosis.

## Introduction

Bone is continually being remodeled, old bone is resorbed by osteoclasts, and osteoblasts replace new bone. In general, these two processes are in equilibrium. However this balance is dependent on age, hormones and calcium intake. Adequate calcium and vitamin D intake, exercise, and the appropriate timely exposure to internal hormonal environment are essential for the accretion of peak bone mass at adolescence. After achieving peak bone mass, a gradual decline of the bone mineral density (BMD) starts around the fourth decade of life. Menopause results in a state of high bone turnover due to estrogen deficiency, and increasing calcium intakes during this time helps to slow down this accelerated, early menopausal bone loss. There is no doubt that calcium and vitamin D supplementation potentates the efficacy of anti-resorptive therapies. In the elderly, adequate intake/supplementation of calcium and vitamin has been shown to significantly decrease the rate of bone loss as well as fractures. Hence adequate nutrition is essential at all ages to maintain optimal bone health. This article reviews the importance of essential nutrients on skeletal health, and their effects on maintaining bone mass.

## Dietary Calcium

Calcium is an essential nutrient that is involved in most metabolic processes and provides mechanical rigidity to the bones and teeth. Skeletal status is often equated with calcium nutrition, as 99% of the calcium in the body is stored as the skeleton. Tissue deprivation of calcium caused by insufficient dietary intake, poor absorption, excess excretion or a combination of these, results in a net loss of calcium from bone, thus increasing susceptibility to fractures. There is considerable epidemiological data, showing the positive correlation between calcium intake and bone density. Raising calcium intake to the adequate intake levels recommended by the 1997 Food and Nutrition Board can maximize peak bone mass, attained during adolescence (Table 1). Higher calcium intakes have been related to higher bone mass in children, young adults, and postmenopausal women in 64 out of 86 observational epidemiologic studies [Heaney RP, 2000] [3].

In children, calcium supplementation increases bone density between 1% and 6% per year in the total body and between 1% and 10% at each skeletal region compared with placebo [Johnston CC et al, 1992; Lloyd T et al, 1993; 1996; Lee WT et al, 1995; Nowson CA et al, 1997; Chan GM et al, 1995; Cadogan J et al, 1997] [4-10], with results dependent on pubertal stage. It is becoming increasingly evident that adequate calcium intake is critical during adolescent years. Similarly, a meta-analysis of calcium intake in premenopausal women concluded that calcium supplementation led to an average increase in bone density at the spine and forearm of 1.1% per year compared with women receiving placebo [Welten DC et al, 1995] [11]. These data suggest that adequate calcium intake must be maintained throughout childhood, adolescence, and young adulthood to have a lasting impact on peak bone mass.

Reviews of 20 studies of postmenopausal women have concluded that calcium supplementation (500 to 2000 mg/day) can decrease bone loss by approximately 1% per year [Nordin BE, 1997; Storm D et al, 1998; Baeksgaard L et al, 1998] [12-14]. Therefore, calcium supplementation can be effective in retarding bone loss in postmenopausal women, especially in the years immediately after menopause. Table 1 gives recommended amount of calcium in take for various groups.

**TABLE 1**

| . RECOMMENDED LEVELS OF CALCIUM | |
|---|---|
| Age Group | Adequate Intake Values (mg) |
| Birth to 6 months | 210 |
| 6-12 months | 270 |
| 1-3 years | 500 |
| 4-8 years | 800 |
| 9-13 years | 1,300 |
| 14-18 years | 1,300 |
| Pregnant or lactating teens | 1,300 |
| Recommendations based on the Dietary Reference Intakes for Calcium, National Academy of Sciences; American J. Health System Pharmacy, 1997 [54]. | |

Low-fat milk or low-fat milk products are the best sources of calcium because they contain high amounts of calcium; along with additional nutrients to help the body better absorb calcium. Along with calcium, milk provides other essential nutrients, including vitamin D, potassium and magnesium, all essential for optimal bone health and human development. Green leafy vegetables are healthy sources of calcium too, but it takes at least five servings of collards a day to get the same amount of calcium that is in three glasses of milk.

*Lactose Intolerance:* For children and teens with lactose intolerance, milk is often better tolerated when consumed with a meal. Some dairy foods, such as hard cheeses, or yogurt, contain less lactose than milk and cause fewer symptoms. In addition, lactose-reduced and lactose-free milk products are now available in most supermarkets.

**TABLE 2**

| OTHER SOURCES OF CALCIUM | | |
|---|---|---|
| SERVING SIZE | FOOD ITEM | CALCIUM (mg) |
| 8 fluid oz. | Yogurt, plain, low fat | 415 |
| 1 oz. | Cheese, cheddar | 204 |
| 1 cup | Broccoli, cooked, fresh | 136 |

| | | |
|---|---|---|
| 1/2 cup | Ice cream, soft serve | 118 |
| 1 slice | Bread, white or whole wheat | 20 |
| 1 | Orange, medium | 52 |
| 1/2 cup | Macaroni and cheese* | 180 |
| 1 slice | Pizza, cheese* | 220 |
| 8 fluid oz. | Calcium fortified orange juice | 300 |
| *Calcium content varies depending on ingredients | | |

Sources: American Dietetic Association, USDA Handbook 8, and National Dairy Council [55].

## Calcium Supplements

Ingesting a large amount of calcium at one time is not beneficial, as all of it is not absorbed. Thus, taking calcium supplements in several smaller doses (less than 500 mg) during the day rather than all at once will increase the proportion of the calcium that is absorbed. The preferred time to take most supplements is with meals, because calcium is better absorbed in an acid environment (with the exception of calcium citrate). Calcium carbonate has more calcium per tablet (40%) than some of the other forms of calcium such as calcium citrate (23%). Some studies indicate that calcium citrate may be more readily absorbed. Calcium citrate may be preferred source for patients with achlorhydria or those on acid blockers.

## Safety of Calcium Supplements

In most healthy individuals, total calcium intakes up to 1500-2000 mg/day are safe. However, in patients who have a history of kidney stones, 24-hour urine calcium should be measured before increasing calcium intakes because hypercalciuria may be exacerbated at higher intakes, especially in patients with hyperparathyroidism. In general, adequate dietary calcium does not increase the risk of calcium oxalate kidney stone formation (the most common); rather, calcium may prevent stones by binding to oxalate in the intestine [Curhan GC et al, 1993; Wimalawansa SJ, 2003; Borghi L et al, 2002] [15-17].

## Vitamin D

Vitamin D has a major role in calcium absorption. Vitamin D is obtained by two mechanisms: 1) sunlight activation of 7-dehydrocholesterol in the skin, and 2) intestinal absorption of vitamin D from dietary sources. Although vitamin D deficiency is relatively rare in healthy younger populations, it is more common in the elderly population, especially among those who are institutionalized or living in climates in which exposure to sunlight is limited. Vitamin D deficiency is associated with osteomalacia in adults and rickets in children, osteoporosis, muscle weakness, and decreased immune function [Wimalawansa SJ, 2003; Holick MF, 1998] [16,18]. Elevations in serum parathyroid hormone and greater bone loss are often associated with lower levels of 25(OH) D. Vitamin D insufficiency is believed to play a strong role in osteoporosis. The current U.S. recommendation for vitamin D intake in people aged 51 to 70 years is 10 μg/day (400 IU/day); the recommendation for people over age 70 is 15 μg/day (600 IU/day). However, higher doses of vitamin D (800 IU/day) in the elderly (65 years and over) may actually be required and would be beneficial for optimal bone health.

## Calcium, Vitamin D and Fractures

Several randomized, controlled clinical trials have shown modest benefits to calcium supplementation in the prevention of bone loss and fractures, some in combination with vitamin D [Chapuy MC et al, 1992; Dawson-Hughes B et al, 1997; 1990; Reid IR et al, 1995] [19-22]. A review of 16 observational studies assessing hip fracture and calcium intake found that an increase in usual calcium intake of 1 g/day was associated with a 24% reduction in the risk of hip fracture [Chapuy MC et al, 1992] [19]. Two randomized, clinical trials, which evaluated calcium supplementation alone, found vertebral fractures reduced by 28% and symptomatic fractures reduced by 70% in the calcium-supplemented group (Table 3). Significant reductions in fracture have also been seen in those randomized clinical trials in which calcium was given in conjunction with vitamin D (26% to 54% reduction in hip and non-spine fracture rates, respectively) [Chapuy MC et al, 1992; Dawson-Hughes B et al, 1997; Cumming RG et al, 1997] [19,20,23].

**Table 3**

| Table 3 Clinical Trials: Calcium, Vitamin D, and Fractures | | | | | | | |
|---|---|---|---|---|---|---|---|
| Author & [Reference] | Date | Number | Age (Yr) | Subject Characteristic | Intervention | Duration of Follow-Up | Results and Comments |
| Reid [22] | 1995 | 78 | 58 | Healthy volunteers; baseline calcium = 734 mg/day | 1000 mg calcium vs. placebo | 4 years | Symptomatic Fractures reduced 70% in the calcium group |
| Recker [24] | 1996 | 197 | 73 | Healthy volunteers; baseline calcium = | 1200 mg calcium vs. placebo | 4.3 years | Vertebral fractures Incidence reduced by 28%; |
| Lips [25] | 1996 | 2578 | 75 | 2570 elderly males; calcium = 868 mg/day | 400 IU vit D vs. placebo | 4 years | Vit D alone led to no reduction in hip or nonvertebral fractures |
| | | | | | | | |
| Komulainen [26] | 1998 | 464 | 53 | Recently postmenopausal calcium = 800 mg/day | 300 IU/d (vit D) vs. placebo | 5 years | 53% reduction in nonvertebral fractures |
| Chevalley [27] | 1994 | 93 | 72 | 82 female, 11 male; baseline calcium = | 800 mg calcium vs. placebo (vit D | 18 months | 31% reduction in vertebral fractures |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | 619 mg/day | repleted by 300,000 IU single dose) | | |
| | | | | | | | |
| Chapuy [19] | 1992 | 2303 | 84 | Nursing home Elderly females; no serious medical conditions | 1200 mg calcium 800 IU vit D vs. double placebo | 3 years | 27% reduction in hip fractures; 26% reduction in nonvertebral fractures |
| Dawson-Hughes [20] | 1997 | 389 | 71 | 176 men, 213 women | 500 mg calcium and 700 IU vit D vs. placebo | 3 years | 54% reduction in nonvertebral fractures |

Reproduced by permission: [Nieves J et al, 1999] [28].

## Vitamin K

Vitamin K is important for bone building and repair. Some literature suggests that vitamin K has an important role in bone metabolism [Wimalawansa SJ, 2003; Binkley NC et al, 1995] [16,29]. Vitamin K is a cofactor in the [gamma]-carboxylation of many proteins, including osteocalcin. Osteocalcin or bone–gla protein is the most bone-specific protein. Several cross-sectional and retrospective epidemiologic studies have found lower dietary vitamin K1 intakes among those with lower BMD or those who have suffered fractures, and one prospective study by [Szulc P et al, 1994] [30] found a threefold increase in the risk for hip fracture among elderly women with increased baseline levels of undercarboxylated osteocalcin. Luckily, it is abundant in vegetables especially lettuce, broccoli and spinach.

## Vitamin A

It has been postulated that the high incidence of hip fractures observed in northern European populations, particularly in Norway and Sweden (where milk is fortified with vitamin A), may be because of Vitamin A. Therapy with etretinate, a synthetic retinoid, has been shown to increase the risk for osteoporosis [Okada N et al, 1994; DiGiovanna JJ et al, 1995] [31,32]. Furthermore, animal studies have shown hypervitaminosis A to be associated with more rapid bone resorption and an increased risk for fractures [Melhus H et al, 1998; Feskanich D et al, 2002] [33,34]. Excess vitamin A seems to stimulate osteoclasts, scavenger cells that break down bone, while suppressing osteoblasts cells that build up bone. High levels of vitamin A also interfere with vitamin D, which is crucial for calcium absorption. In a case control study in Swedish women aged 40-76 years, [Melhus et al, 1998] [33], found a negative association between retinol intake and BMD. Women with higher retinol intakes in excess of 1.5 mg /day (compared with those whose intakes were less than 0.5 mg /day) had a two-fold increased risk for hip fracture. In a recent report from the Nurses Health Study [Feskanich D et al, 2002] [34], researchers analyzed the relationship between intake of vitamin A and hip fracture rates in 72,337 postmenopausal women followed for 18 years. They separated the women into five equal groups from lowest intake of vitamin A to highest intake. The group who had the highest intake (i.e., the top 20 percent) of vitamin A had a 48 percent increased risk of hip fracture, compared to women with the lowest intake. It's also interesting to note that in this study population, the average age for hip fractures was only 64 years.

***Vitamin A comes from two sources:*** Retinol is the form of Vitamin A that comes from animal sources-primarily milk, butter, and liver; it is also added to many foods including margarine, breakfast cereals, skim milk, cheese, and vitamin supplements. Beta-carotene comes predominantly from plant sources (e.g., carrots) and is converted into vitamin A in the body. When comparing the two sources, only retinol was significantly associated with hip fracture risk. [Feskanich D et al, 2002] [34]. Intake of retinol over 500 micrograms (1650 IU) per day is unadvisable; as it seems to increase the rates of hip fractures. On the other hand, the vitamin A generated through dietary beta-carotene (via brightly colored fruits and vegetables) has many protective health benefits and doesn't increase the risk of hip fractures.

## Vitamin C

Vitamin C influences collagen development and may have a role in bone matrix formation [Spindler KP et al, 1989] [35]. Leveille et al have found that the long-term use of vitamin C supplements was associated with higher BMD in women aged 55 to 64 years in comparison with those who had never used estrogen [Leveille SG et al, 1997] [36]. In another study conducted among women aged 45 to 64 years who were participants in the postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a significant positive correlation was found between dietary vitamin C and hip BMD. [Hall SL et al, 1998] [37].

Magnesium also contributes to bone development. Most physicians agree that you should get between 600 mg and 1,200 mg each day – this is not hard to do if one eats a balanced diet [Wimalawansa SJ, 1993] [38]. There are several dietary components, which affect the dietary calcium absorption from the gut, and influence urinary calcium losses. Summary of these are illustrates in the Figure 1.

## Dietary Protein

The influence of dietary protein on rates of bone loss and fracture risk in the elderly population is controversial. The typical US diet consists of high dietary intake of animal protein, together with a low intake of vegetables and has been associated with chronic, low-grade metabolic acidosis [Sebastian A et al, 1994] [39]. This occurs as sulfur-containing amino acids in meats are oxidized, leading to high acid loads relative to base products obtained from the consumption of vegetables. High-protein dies generate a high acid load, resulting in sub-Clinical metabolic acidosis, which promotes calcium mobilization from the bone, thus leading to an increased rate of bone loss, and an increased risk for fracture [Denke M, 2001] [40]. High-protein diets increase calcium excretion, raise parathyroid levels, and raise the urinary N-telopeptide concentrations [Breslau NA et al, 1988; Kerstetter JE et al, 1999] [41,42]. Markers of bone formation remain steady, suggesting that high protein diets increase bone resorption without increasing bone formation. Overall, the results of epidemiologic studies of the association between dietary protein intake and BMD,

rates of change in BMD, and risk for hip fracture have been inconclusive [Wimalawansa SJ, 2003; Cooper C et al, 1996; Feskanich D et al, 1996] [16,43,44].

## Phytoestrogens

Phytoestrogens are naturally occurring compounds abundant in certain plants, e.g., sprouts, beans, and soybeans, which contain estrogen-like effects in the body. These compounds have both estrogenic and anti-estrogenic activity, and seem to achieve these properties by binding to estrogen receptors [Martin PM et al, 1978; Verdeal K et al, 1980] [45,46]. However, the quantities need to be ingested to achieve these estrogenic effects are considerably higher than that contained in the normal diet.

They are diphenolic in structure [Rees M et al, 1999] [47]. A number of classes have been identified, such as lignans, isoflavones, coumestans, and resorcylic acid lactones [Knight DC et al, 1996] [48]. The most extensively investigated are the isoflavones and lignans [Wimalawansa SJ et al, 2003; Knight DC et al, 1996] [16,48]. Isoflavones are found in high concentrations in legumes, such as soybeans, soy products, chickpeas, and red clover as well as sweet potatoes, carrots, garlic, and green beans. The major isoflavones are genistein and daidzein. Whereas, the soya plant contains only genistein and daidzein, other legumes such as chickpeas and lentils contain formononetin and biochanin, but the red clover plant contains all four. Oilseeds, especially linseed (which is also called flaxseed), contain the highest concentrations of lignans, which are also found in berries, cereal bran, whole cereals, vegetables, legumes, and fruits. The major lignans are enterolactone and enterodiol [Wilcox G et al, 1990] [49].

Phytoestrogens are attenuated estrogens. The estrogenic effect of phytoestrogens in postmenopausal women was established with the maturation of vaginal epithelium after dietary supplementation with isoflavones and lignans [Wilcox G et al, 1990] [49]. The isoflavones have the most potent estrogenic activity in comparison to other phytoestrogens [Jones KP, 2000] [50].

## Phytoestrogens and Bone

Studies of the effects of isoflavones on bone health have also produced mixed results. According to two multi-center studies, the synthetic isoflavone, ipriflavone, prevents bone loss in postmenopausal women with low bone mass [Wimalawansa SJ, 2003] [16]. Four hundred fifty-three women were given either 200 mg of oral ipriflavone three times a day or a placebo for 2 years. All of the women were also given 1 gm of calcium daily. In both studies, the ipriflavone group maintained bone mass, whereas the placebo group experienced a decrease in bone mineral density [Gennari C et al, 1997] [51]. Overall, there was a bone-sparing effect of 1.6% in one study and 3.5% in the other. Ipriflavone prevented both axial and peripheral bone loss and was well tolerated. Recently data have been presented regarding a year-long double-blind, placebo-controlled study involving 107 women showing that 40 mg of red clover isoflavones decreased the rate of loss of bone mineral density (BMD) and bone mineral content (BMC) in lumbar spine of pre- and perimenopausal women. However, no differences were seen between treatment groups in hip BMD, BMC, or urinary bone markers. Another study has shown that bone density increases in postmenopausal women consuming soy-enriched bread, compared with a control group eating wheat bread [Dalais FS et al, 1998] [52].

## Summary

Adequate calcium and vitamin D intake needs to be maintained throughout childhood, adolescence, and young adulthood, and are critical for the accretion of maximal bone mass. Enhanced intake of calcium and vitamin D is essential for preventing bone loss, which occurs throughout life. The recommended daily calcium intake probably maximizes the efficacy of other osteoporosis therapies. Adequate doses of vitamin D given in conjunction with calcium have been shown to reduce fracture risks particularly in patients aged 65 years and older with osteoporosis. Different nutrients play a role in calcium homeostasis; diets rich in high protein and salt, increase urinary calcium loss, same is the effect with carbonated beverages. Oxalates, phytates, iron in diet decrease calcium absorption (Figure 1). With reference to supplementation, moderation is the best, and anything ingested excessively could be harmful. Other nutrients, e.g., vitamins C and A, and phytoestrogens may also be determinants of the risk of osteoporosis [Stone KL et al, 1999; National Academy of Sciences, 1997; American Dietetic Association, 2002] [53-55], but

researchers must carefully consider the correlations among the various nutrients and also the combinations of various nutrients in optimal doses maybe be important, however further epidemiological studies are needed to confirm this.

## References:

Papers of particular interest, published recently, have been highlighted as:
- ● Of importance
- ●● Of major importance

1. Mossey JM, Knott K, Craik R: The effects of persistent depressive symptoms on hip fracture recovery. J Gerontol 45:M163-M168, 1990.
2. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ: Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 7:178-208, 1985.
3. Heaney RP: Calcium, dairy products and osteoporosis. J Am Coll Nutr. 19:83S-99S, 2000.

● Very relevant to the current review, which gives additional information on calcium supplementation via dairy products.

4. Johnston CC, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, Peacock M. Calcium supplementation and increases in bone mineral density in children. N Engl J Med. 327:923-987, 1992.
5. Lloyd T, Andon MB, Rollings N, Martel JK, Demers LM, Eggli DF, Kieselhorst K, Kulin HE. Calcium supplementation and bone mineral density in adolescent girls. JAMA. 270:841-844, 1993.
6. Lloyd T, Martel JK, Rollings N, Andon MB, Kulin H, Demers LM, Eggli DF, Kieselhorst K, Chinchilli VM. The effect of calcium supplementation and Tanner stage on bone density, content and area in teenage women. Osteoporos Int. 6:276-283,1996.
7. Lee WT, Leung SS, Leung DM, Tsang HS, Lau J, Cheng JC. A randomized double-blind controlled calcium supplementation trial, and bone and height acquisition in children. Br J Nutr. 74:125-139, 1995.

8. Nowson CA, Green RM, Hopper JL, Sherwin AJ, Young D, Kaymakci B, Guest CS, Smid M, Larkins RG, Wark JD . A co-twin study of the effect of calcium supple-mentation on bone density durng adolescence. Osteoporos Int. 7:219-225, 1997.
9. Chan GM, Hoffman K, McMurry M. Effects of dairy products on bone and body composition in pubertal girls. J Pediatr. 126:551-556, 1995.
10. Cadogan J, Eastell R, Jones N, Barker ME. Milk intake and bone mineral acquisition in adolescent girls. A randomized, controlled intervention trial. Br Med J. 315:1255-1260, 1997.
11. Welten DC, Kemper HCG, Post GB, Van Staveren WA. A meta-analysis of the effect of calcium intake on bone mass in young and middle-aged females and males. J Nutr. 125:2802, 1995.
12. Nordin BE. Calcium and osteoporosis. Review Article. Nutrition. 13:664-686, 1997.
13. Storm D, Eslin R, Porter ES, Musgrave K, Vereault D, Patton C, Kessenich C, Mohan S, Chen T, Holick MF, Rosen CJ. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women. A randomized placebo-controlled trial. J Clin Endocrinol Metab. 83L3817-3825, 1998.
14. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy postmenopausal women. Osteoporos Int. 8:255-260,1998.
15. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 328:833-838, 1993.
16. Wimalawasna SJ. Osteoporosis: Time to Act. Manual for Primary Care Physicians (in press) Hot Topic Press, Ohio, USA.

●● This book gives a good overview of osteoporosis including etiology, diet, supplementation and treatment, written for both physicians and patients.

17. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A. Comparison of Two Diets for the Prevention of Recurrent Stones in Indiopathic Hypercalciuria. N Engl J Med 346:77-84, 2002.

18. Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. Osteoporos Int. 8(Suppl):S24-S29, 1998.
19. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 327:1637-1642, 1992.
20. Dawson-Hughes B, Harris SS, Krall EA, Gerard ED: Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age and older. N Engl J Med 1997, 337:670-676, 1997.
21. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S: A placebo-controlled trial of calcium supplementation in postmenopausal women. N Engl J Med. 323:878-883, 1990.

- These two articles (References 20 and 21) highlight the importance of calcium supplementation in preventing fractures.

22. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ: Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. Am J Med 98:331-335, 1995.
23. Cumming RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res. 12:1321-1329, 1997.
24. Recker RR, Hinders S, Davis KM, Heaney RP, Stegman MR, Lappee JM, Kimmel DB. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. Bone Miner Res. 11:1961-1962, 1996.
25. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 124:400-406, 1996.
26. Komulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, Saarikoski S. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Mauritas. 31:45-54,1998.
27. Chavelley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, Vasey H,

Bonjour JP. Effects of calcium supplements on femoral bone mineral density and Vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporosis Int. 4:245-252, 1994.

28. Nieves JW, Nutrition. 1999, Chap 4, Table 4-7.Osteoporosis: An Evidence-Based Guide to Prevention and Treatment. American College of Physicians--American Society of Internal Medicine (Women's Health Series) 2002. Edited by Cummings, S.R.; Cosman, F; Jamal,S. Nutrition. 1999, Chap 4, Table 4-7.

●● This chapter is very informative and a concise review on nutritional aspects of osteoporosis.

29. Binkley NC, Suttie JW: Vitamin K nutrition and osteoporosis. J Nutr 125:1812- 1821, 1995.
30. Szulc P, Arlot M, Chapuy MC, Duboeuf F, Meunier PJ, Delmas PD: Serum undercarboxylated osteocalcin correlates with hip bone mineral density in elderly women. J Bone Miner Res. 9:1591-1595, 1994.
31. Okada N, Nomura M, Morimoto S, Ogihara T, Yoshikawa K: Bone mineral density of the lumbar spine in psoriatic patients with long term etretinate therapy. J Dermatol 21:308-311, 1994.
32. DiGiovanna JJ, Sollitto RB, Abangan DL, Steinberg SM, Reynold JC: Osteoporosis is a toxic effect of long-term etretinate therapy. Arch Dermatol 131:1263-1267, 1995.
33. Melhus H, Michaelsson K, Kindmark A, Bergstrom R, Holmberg L, Mallmin H, Wolk A Ljunghall S. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med 129:770-778, 1998.
34. Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women, JAMA 287:47-54, Jan. 2, 2002.
35. Spindler KP, Shapiro DB, Gross SB, Brighton CT, Clark CC: The effect of ascorbic acid on the metabolism of rat calvarial bone cells in vitro. J Orthop Res 1989, 7:696 Res 7:696-701, 1989.

36. Leveille SG, LaCroix AZ, Koepsell TD, Beresford SA, Van Belle G, Buchner DM: Dietary vitamin C and bone mineral density in postmenopausal women in Washington State, USA. J Epidemiol Community Health 51:479-485, 1997.
37. Hall SL, Greendale GA. The relation of dietary vitamin C intake to bone mineral density: results from the PEPI study. Calcif Tissue Int 63:183-189, 1998.
38. Wimalawansa S.J. Therapeutic options in prevention and treatment of osteoporosis (Review) Exp. Clin. Endocrine. (Life Science Advances), 12:1-27,1993.
39. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris Jr, RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med 330:1776-1781, 1994.
40. Denke, M. Metabolic effects of high-protein, low-carbohydrate diets. The American Journal of Cardiology. 88 :59-61, 2001.
41. Breslau NA, Brinkley L, Hill K, Pak CYC: Relationship of animal-protein rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab 66:924-929, 1988.
42. Kerstetter JE, Mitnick ME, Gundberg CM, Caseria DM, Ellison AF, Carpenter TO, Insogna KL. Changes in bone turnover in young women consuming different levels of dietary protein. JCEM 84:1052-1055, 1999.
43. Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL, Melton LJ: Dietary protein intake and bone mass in women. Calcif Tissue Int 58:320-325, 1996.
44. Feskanich D, Willett WC, Stampfer MJ, Colditz GA: Protein consumption and bone fractures in women. Am J Epidemiol 143:472-479, 1996.
45. Martin PM, Horowitz KB, Ryan DS, McGuire WL: Phytoestrogen interaction with estrogen receptors in human breast cancer cells. Endocrinology 103:1860-1867, 1978.
46. Verdeal K, Brown RR, Richardson DS: Affinity of phytoestrogens for estradiol-binding proteins and effect of cumestrol on growth of 7,12-dimethylbenz(α)anthracene-induced mammary tumors. J Natl Cancer Inst 64:285-290, 1980.
47. Rees M, Purdie D. Non-hormone replacement therapy options and alternative therapies. Management of the Menopause: The Handbook of the British Menopause Society, 2nd Ed. Marlow: BMS Publications Ltd, 42-49, 1999.

- This book gives some insight in to non-hormonal approaches to the management of menopause, and useful information on phytoestrogens.

48. Knight DC, Eden JA. A review of the clinical effects of phytoestrogens. Obstet Gynecol 87 (Pt 2): 897-904, 1996.
49. Wilcox G, Wahlqvist ML, Burger HG Medley G. Oestrogenic effects of plant foods in postmenopausal women. BMJ 301:905-906, 1990.
50. Jones KP. Menopause and cognitive function: estrogens and alternative therapies. Clin Obstet Gynecol 43:198-206, 2000.
51. Gennari C, Adami S, Agnusdei D Bufalino L, Cervetti R, Crepaldi G, Di Marco C, Di Munno O, Fantasia L, Isaia GC, Mazzuoli GF, Ortolani S, Passeri M, Serni U, Vecchiet L. Effect of chronic treatment with ipriflavone in postmenopausal women with low bone mass. Calcif Tissue Int. 61 (Suppl 1): S19-S22, 1997.
52. Dalais FS, Rice GE, Wahlqvist ML. Effects of dietary phytoestrogens in postmenopausal women. Climacteric 1:124-129, 1998.
53. Stone KL, Wolfe RL. Diet, bone loss and fracture risk: a review of the recent literature. Curr Opin Ortho 10:334-338, 1999.
54. National Academy of Sciences. Report unveils new approach to nutrient recommendations. Higher calcium intakes backed for many. Am J Health Syst Pharm. 54:2438-2439, 1997.
55. American Dietetic Association and the Canadian Dietetic Association: Women's health and nutrition. J Am Diet Assoc. 6:668-671, 1994.

- Good review on the effects of nutrition on fracture prevention.