Prevention of bone fragility: the role of diet

Fragility fractures resulting from osteoporosis are a leading cause of morbidity and even mortality in developed countries. Afflicting both men and women the rates of osteoporosis are increasing in countries with aging populations. Although dietary components, particularly calcium and vitamin D, are widely recognized to be important for overall skeletal health, intakes are often lower than the recommended amount. Such lower than recommended intakes of calcium are of particular concern if diets are rich in protein, sodium and/or caffeine. Dietary components such as omega-3 fatty acids and soy isoflavones may play a positive role in bone health, and this is an active area of study. Combining healthful foods together with current pharmacological agents that preserve bone mass and strength may be an effective and safe strategy for prevention and/or treatment of osteoporosis.

KEYWORDS: bone mineral density ■ calcium ■ fragility fracture ■ nutrition ■ osteoporosis ■ protein ■ vitamin D

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Osteoporosis, characterized by low bone mineral density (BMD), is a silent disease that ultimately results in fragility fractures. Fragility fractures lead to significant morbidity and mortality worldwide. Owing to the rapidly aging population, it is estimated that one in two American adults will be at risk for osteoporosis-related fractures by the year 2020 [101], and bone health will continue to worsen as the population ages. Similar estimates exist for other developed countries [1,2]. It is somewhat ironic that despite the fact that obesity rates in developed countries are at their highest historical level, the quality of an individual's diet is often not favorable for maintaining a healthy skeleton. Moreover, childhood obesity may result in a greater risk of fracture [3,4].

Bone health is classified using criteria established by the WHO, and is based on measurement of BMD using dual energy x-ray absorptiometry and calculating t-scores relative to normal peak values for BMD in young adults. The classification is as follows: normal bone density, t-score above -1.0 standard deviation (SD); osteopenia, t-score between -1.0 and -2.5 SD; osteoporosis, t-score of -2.5 or less; and severe osteoporosis, t-score of -2.5 SD or less with one or more fragility fractures [5]. This classification does not consider bone quality, but rather is strictly based on the quantity of mineral present. Moreover, there is evidence that more than 50% of all incident fractures occur in women with osteopenia [6]. Owing to the natural loss of BMD during aging, most individuals would be classified as having osteopenia during their lifetime. Thus, prevention strategies, as well as strategies for attenuating loss of BMD during aging, warrant attention.

Peak bone mass is the maximum quantity of bone an individual acquires during their lifetime, occurring by approximately 18–25 years of age. While genetics is a major determinant of an individual's peak bone mass, other factors, such as diet, can influence whether an individual's genetic potential for peak bone mass is reached [7–9]. For the best defense against osteopenia, and possibly osteoporosis, an individual should strive to reach a high peak bone mass, as they will have a higher starting point when bone mass starts to decline naturally during the aging process.

The natural decline in bone mass, approximately 1–3% per year, commences during adulthood. The most rapid loss of bone mass in women occurs within 5–10 years after menopause, and therefore, this is a critical time for interventions [2,10–12]. Men also experience a decline in bone mass owing to declining levels of testosterone and estrogen [10–12].

A balanced diet assists the development of a strong skeleton, in addition to a healthy body weight. While diet alone cannot prevent the loss of bone mineral and skeletal weakening that often accompanies the aging process, a diet that provides appropriate levels of nutrients – particularly calcium, vitamin D and protein – is essential to support skeletal health. Moreover, specific pharmacological agents that prevent or slow the

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loss of bone mass, and thus protect against fragility fracture, must be consumed in combination with recommended, or even supplemental, levels of nutrients to achieve an optimal effect on bone health. A classic example, discussed later in this review, is hormone replacement therapy (HRT) taken in combination with supplemental calcium (approximately 1200 mg calcium/day) [13]. Diet has a unique role in both prevention as well as treatment of osteoporosis and the associated fragility fractures.

This article reviews the effects of nutrients known to influence bone health: calcium and vitamin D. The role of vitamin D goes beyond its well-established role in calcium metabolism. In addition, the role of protein, sodium and caffeine, all of which are sometimes perceived to have negative effects on calcium metabolism and thus bone health, are discussed. The potential benefit of diets rich in omega-3 fatty acids and soy isoflavones, which are emerging and active areas of research, is also outlined.

Calcium

In North America, recommended calcium intakes are classified by age [14]. Calcium intakes increase from 1 year of life (500 mg calcium/day, age 1–3 years, 800 mg calcium/day, age 4–8 years), up to 1300 mg calcium/day by 9–18 years of age. Intakes of 1000 mg calcium/day are recommended for the period of 19–50 years of age. From the age of 51 years and older, intakes are increased to 1200 mg/day to attenuate the decline in bone mass during aging. Moreover, there is substantial evidence that the provision of calcium supplements is effective in slowing loss of bone mass and reducing fragility fractures, especially in combination with supplemental vitamin D [2,5,14,15].

It is widely accepted that by simply eating, individuals consume approximately 300 mg, as a wide variety of foods contain small amounts of calcium [16,102]. Foods that contain approximately 300 mg of calcium per serving include the following: milk (regardless of whether it is skim, 1, 2, 3.25%, flavoured milk) or a calcium-fortified beverage, such as orange juice or soy, yogurt, or two slices of cheese. Foods that contain approximately 250 mg of calcium per serving include the following: canned salmon (with bones) and a 1 and a quarter inch cube of firm cheese (e.g., cheddar, swiss or gouda).

For individuals who do not routinely consume dairy products, which may be for a variety of reasons, including lactose intolerance, several beverages are available that provide calcium with or without vitamin D, such as calcium-fortified orange juice and soy beverages with added calcium and vitamin D. Another impediment to achieving appropriate calcium intakes may be soda consumption. Long-term consumption of soda is negatively related to milk intake and protein intake, as well as overall bone remodeling in otherwise healthy children and adolescents [17]. A short-term, 10-day intervention study in young men (aged 22–29 years) suggested that replacement of milk with cola beverages resulted in increased bone resorption [18]. There is also evidence that colas, but not other sodas, are associated with lower bone mass in older women [19].

Calcium supplements

If consumption of recommended levels of calcium by diet alone is problematic, calcium supplements are warranted (**Box 1**). Calcium carbonate – an inexpensive form of calcium – and calcium citrate are common forms of calcium supplements [20]. However, unlike calcium citrate, calcium carbonate should be taken with a meal to aid intestinal absorption. When taking calcium supplements, no more than 500 mg of calcium should be taken at any one time. Calcium citrate is advised for individuals with malabsorptive disorders: achlorohydria, intestinal inflammation or those treated with H_2-receptor agonists or proton pump inhibitors [21]. Calcium supplements should also be taken in combination with vitamin D. The Position Statement of the North America Menopause Society currently recommends vitamin D intakes of 400–600 IU [15], while other organizations including The National Osteoporosis Foundation (Washington DC, USA) [103] and Osteoporosis Canada (Ontario, Canada) [2] recommend higher levels of

Box 1. Practical guidance for calcium supplement use.

- Consume up to 500 mg of calcium at any one time.
- Calcium carbonate should be consumed with a meal to aid absorption.
- Estimate calcium intake from diet to ensure that safe levels of calcium are consumed.
- Take with vitamin D to aid calcium absorption.

Please refer to [20,21] *for additional information.*

vitamin D, 800–1000 IU vitamin D or 800 IU vitamin D, respectively, to achieve desired serum 25(OH)D levels. The combination of calcium and vitamin D is an example of 'food synergy' – defined as the interaction of two or more components within a food or of two or more foods working together such that the potential health benefit is greater than the effect of the single component or food [22]. Vitamin D aids intestinal absorption of calcium. It is therefore important that recommended levels of both calcium and vitamin D are consumed (if not through dietary sources, then through supplementation).

Several organizations recommend use of calcium supplements to maintain bone health during aging. The NIH recommends that women not receiving estrogen therapy consume 1500 mg calcium per day [5]. Osteoporosis Canada recommends that both men and women over the age of 50 years take 1500 mg of calcium per day to help preserve bone health [2]. An individual's calcium intakes are commonly lower than recommended levels [101].

Consumption of too much calcium may have adverse health effects (i.e., kidney stones) and thus an upper intake of 2500 mg has been established [14]. It is prudent that individuals who take calcium supplements estimate their calcium intake from their daily diet to avoid potential adverse health effects.

Vitamin D

Vitamin D is essential for regulating calcium metabolism at its three major sites of regulation: intestine, bone and kidney. At the intestine, vitamin D facilitates the absorption of calcium through the production of a calcium-binding protein. At the bone, vitamin D has a dichotomous effect, promoting resorption of bone when circulating levels of calcium need to be restored, but also stimulating differentiation of preosteoblasts to mature, functional osteoblasts that promote bone formation [23]. Vitamin D also aids the reabsorption of calcium at the kidney [23].

In addition to the well-documented role of vitamin D in calcium metabolism, vitamin D has a positive effect on lower-extremity neuromuscular function and decreases the risk of falls, which often result in fragility fractures, particularly in older individuals who have a higher incidence of falls [24]. Moreover, vitamin D supplementation in older individuals with low vitamin D status results in improved muscle function – reduced body sway, increased walking distance, improved balance and fewer falls [25,26].

As discussed in the next section, many health scientists and health professionals believe that current recommendations for vitamin D intake are too low. As a result, some organizations have suggested higher intakes than are currently recommended by the National Academy of Medicine [14]. Moreover, it is important to recognize that the current recommended intakes of vitamin D were published in 1997 and considerably more data are now available. These data suggest higher intakes are warranted for optimal health. Nonetheless, the current recommended intake of vitamin D in North America is 5 µg/day (or 200 IU/day) from birth through to age 50 years [14]. Owing to the known efficacy of higher levels of vitamin D in preserving bone mass during aging, the recommended intake is higher for age 50–70 years (10 µg/day or 400 IU/day), and even higher for age 70 years and older (15 µg/day or 600 IU/day), to attenuate the loss of BMD [14]. Achieving these levels of vitamin D can be challenging, particularly if fatty fish, or vitamin D-fortified milk or orange juice is not consumed on a regular basis. Indeed, vitamin D intakes are often markedly lower than recommended levels [101] **(Box 2)**. Examples of foods providing the greatest amount of vitamin D per serving include the following: one cup of vitamin D-fortified milk, 2.5 µg (100 IU), regardless of whether it is skim, 1, 2 or 3.25% or flavoured milk; and canned salmon, 8.75 µg (350 IU). Other fatty fish such as tuna, sardines and mackerel have a similar content of vitamin D. Canned salmon, if consumed with bones, provides a good source of both calcium and vitamin D. Other food sources of vitamin D, but at lower levels than milk and fatty fish/salmon, include liver (100 g liver = 0.75 µg or 30 IU), eggs (one egg = 0.75 µg or 30 IU) and margarine (one teaspoon = 0.5 µg or 20 IU).

Vitamin D supplements

The dietary recommendations regarding vitamin D do not account for endogenous synthesis of vitamin D as a result of sun exposure. Endogenous vitamin D synthesis varies by season and geographical location [27]. Indoor activities, use of sunscreen and protective clothing also impedes production of vitamin D by the

Box 2. Challenges of obtaining adequate levels of vitamin D.

- Few foods contain substantial levels of vitamin D.
- Skin production of vitamin D via sun exposure may be limited during specific seasons of the year.
- Prudent use of protective clothing and/or sunscreen to protect against sun damage/skin cancers impedes vitamin D synthesis through sun exposure.

skin (Box 2). As mentioned previously, newer studies, published since 1997 when the dietary reference intakes for vitamin D were developed, are challenging the current recommended intakes of vitamin D. Specifically, studies are demonstrating benefits of markedly higher intakes of vitamin D (25 µg/day or 1000 IU/day) to achieve serum levels of 25-hydroxyvitamin D that are approximately 90 nmol/l. Potential benefits include reduced fracture risk, greater tooth retention, reduced risk of colon cancer and improved lower extremity function [26]. The upper tolerable level for vitamin D is currently set at 2000 IU or 50 µg/day [14]. Potential adverse effects of intakes above this level include hypercalcemia and hypercalciuria, and thus kidney stone formation. However, safety of such levels, as well as higher vitamin D intakes, is an active area of study owing to potential benefits of higher intakes of vitamin D for optimal health [27,28]. In adults, vitamin D intakes of 4000 IU for 2–5 months did not result in hypercalcemia or hypercalciuria [27].

The American Academy of Pediatrics now advises vitamin D intakes of 400 IU for prevention of rickets, in addition to a potential role in reducing risk of diabetes and cancers, and for maintaining innate immunity [104]. For bone health, Osteoporosis Canada recommends 20 µg or 800 IU vitamin D/day (as well as 1500 mg calcium) for adults 50 years of age and older to attenuate the loss of BMD during aging [2]. As discussed earlier, vitamin D can also act to prevent fracture through a reduced risk of falling.

Owing to the link between higher vitamin D intakes and reduced risk of cancer, especially colon cancer, the Canadian Cancer Society recommends 25 µg (1000 IU) vitamin D/day for adults, especially during the fall and winter seasons [105]. Moreover, if an individual is older, has dark skin, is often indoors or wears clothing that covers most of their skin, it is recommended that they consume 25 µg (1000 IU) vitamin D/day throughout the year. In addition to potential health benefits and reduced mortality, a recent published report has shown significant monetary savings for populations with higher serum 25-hydroxyvitamin D levels [29].

Protein, sodium & caffeine

Protein, sodium and caffeine are similar in that each can stimulate the excretion of calcium. However, this potential negative effect is avoided by ensuring that calcium intakes are at recommended or supplemental levels [30,31].

Protein

Consumption of protein, at recommended levels [32], and in combination with recommended [14] or supplemental levels of calcium [2] has a positive effect on bone [30]. The recommended level of protein for adults is 0.8 g protein/kg body weight/day [32] regardless of age, and there is some evidence that higher protein intakes may benefit bone health in older adults. A study in healthy men and women (aged 50 years or older) demonstrated that the amount of urinary calcium excreted did not differ among subjects fed a high (1.55 g/kg body weight/day) versus low protein (0.75 g/kg body weight/day) diet [33]. Moreover, the higher protein intake (1.55 g/kg body weight/day) resulted in higher circulating insulin-like growth factor-1, a positive mediator of both muscle mass and bone metabolism, and also reduced a biochemical marker of bone resorption [33]. Maintenance of muscle mass, particularly during aging, aids coordination and reduces the risk of falling, and ultimately, may reduce the risk of fragility fracture. There is also evidence that provision of protein supplementation results in a better recovery from hip fracture [34].

Sodium

Sodium and calcium compete for reabsorption at the kidney [31]. It is estimated that approximately 20 mg of calcium is excreted per 1 g of sodium [31,35]. Putting this level of sodium in perspective, recommended sodium intakes for healthy adults varies between 1.2–1.5 g/day, depending on age [36]. Less than 30 mg of calcium should be excreted per day, provided an individual is not consuming more sodium than recommended. Given the adverse health effects, including hypertension, prudence is advised with respect to sodium consumption. Moreover, if calcium intake is at recommended or supplemental levels, sodium intake does not have a measurable effect on calcium metabolism, or overall bone health.

Caffeine

Caffeine has a diuretic effect and thereby increases calcium excretion [30]. Caffeine may also result in a small decrease in calcium absorption [30]. As discussed for protein and sodium, caffeine intake per se is not harmful to bone, provided adequate levels of calcium are consumed. Investigators estimate that the addition of 1–2 tablespoons of milk to one cup of coffee compensates for the increase in urinary calcium excretion [30]; however, it is not essential that calcium be consumed simultaneously with a caffeine-containing beverage or food.

Potential role of food components

There is considerable interest in using nutritional supplements and botanicals as preventive strategies as well as complimentary therapies for improved health. With respect to bone health, calcium and vitamin D supplements are the most commonly used nutritional supplements. Other frequently used supplements include omega-3 fatty acids (naturally present in fatty fish, or in fish oil or fish oil capsules) and soy isoflavones (naturally present in soy foods and also available as purified extracts) [37–41].

Omega-3 fatty acids

Fish oil is a rich source of long-chain omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Interest in EPA and DHA and their potential role in bone health stem from the knowledge that these fatty acids are precursors of less inflammatory eicosanoids, thromboxanes, and prostaglandins than those derived from the omega-6 fatty acid pathway [42,43]. Some studies support the use of fish oil for attenuating loss of bone mineral during aging; however, randomized controlled trials are essential to fully determine the efficacy of such a dietary strategy. There is stronger evidence that consumption of fish oil has benefits for heart health. The American Heart Association currently recommends that at least two servings of fatty fish be consumed per week for heart health [44].

Other omega-3 fatty acids of interest, such as α-linolenic acid (ALA), may also have a positive effect on bone health. ALA is increasingly available in the food supply, largely through increased incorporation of flaxseed, which contains very high levels of ALA, into products such as breads, cereals and pastas. The recommended intake for ALA is 1.6 g/day for men and 1.1 g/day for women [32]. This level can be achieved by consuming one tablespoon of flax oil (8 g ALA) or ground flaxseed (1.8 g ALA) or 0.5 ounce of walnuts (1.3 g ALA). There is evidence that men and women who consume higher quantities of ALA rather than linoleic acid (an omega-6 fatty acid) have higher hip BMD [45]. Another study demonstrated that a diet rich in ALA, through consumption of flaxseed and walnut oil, as well as walnuts, resulted in lower amounts of *N*-telopeptide, a collagen crosslink that is routinely used in investigations as a marker of bone resorption [46]. Moreover, the lower *N*-telopeptide was associated with lower TNF-α, a proinflammatory mediator that stimulates bone breakdown [46]. Exact mechanisms by which ALA, as well as longer-chain EPA and DHA, benefit bone strength require further investigation. There is the potential for ALA to be converted to longer chain fatty acids such as EPA and DHA, but the efficiency of conversion is quite low, likely less than 5% in humans. Several human intervention trials demonstrated no effect of feeding ground flaxseed on bone metabolism in postmenopausal women – the lack of effect may be partly due to the fact that the women studied were not observed to have a low BMD [47–49].

Soy & its isoflavones

Soy contains isoflavone (genistein, daidzein), compounds that share a similar chemical structure to 17-β-estradiol and have potential estrogen-like activity [50]. Soy isoflavones can bind to estrogen receptors, resulting in genomic or nongenomic effects in bone tissue. Mechanistic studies report increased osteoblastic activity, decreased osteoclastic activity, as well as favorable modulation of cytokines and growth factors with binding of soy isoflavones [51,52]. Soy isoflavones are sometimes referred to as 'phytoestrogens', 'plant estrogens' or 'dietary estrogens'.

Epidemiological evidence has demonstrated that higher consumption of soy foods (and thus soy isoflavones) results in a lower number of fractures, lower bone resorption (as assessed by biochemical markers of bone turnover), and higher BMD [53–58]. These relationships are strongest in postmenopausal as opposed to premenopausal women. It is speculated that this is because the lower levels of endogenous estrogen provide soy isoflavones with an opportunity to exert their estrogenic effects. Because soy isoflavones have markedly lower binding affinity to the estrogen receptors than endogenous estrogen [59], it is believed that soy isoflavones have measurable biological effects, resulting from interactions with estrogen receptors, only when endogenous estrogen is low. Indeed, soy isoflavone supplementation in premenopausal women has not been shown to benefit BMD [60].

Despite the strong epidemiological evidence supporting a role of soy isoflavones in bone health, human intervention studies have reported mixed results on BMD, including attenuation of loss of BMD at the lumbar spine, or no effect [61–69]. However, data from two recent meta-analyses suggest that intervention studies of 6 or 12 months in duration, providing 80–90 mg of isoflavones per day, levels that can only be achieved through supplements rather than diet, appear to attenuate loss of BMD at the lumbar spine [70,71].

It is important to note that supplementation with isoflavones in postmenopausal women has not been directly compared with clinically approved treatments for osteoporosis, such as bisphosphonates, and thus, isoflavone supplements should not replace clinically approved drug treatments known to maintain BMD and/or reduce risk of fragility fractures. However, soy foods provide a healthy source of protein as well as fiber, micronutrients and essential fatty acids. A typical Asian diet provides 6–11 g soy protein (containing approximately 25–50 mg isoflavones) and thus intakes of soy foods at these levels are believed to be safe [72,73].

Conclusion

What constitutes an ideal dietary strategy to help prevent fragility fracture? Ideally, both men and women should consume the recommended intake levels of calcium, vitamin D and protein [14,32] as part of a general healthy diet, or by supplementation if required. This is essential to ensure that calcium is not unnecessarily lost due to protein, sodium and caffeine in the diet. Evidence to date suggests that diets with a greater proportion of omega-3 fatty acids versus other fatty acids may benefit bone health. Soy isoflavones may play a role in preserving bone health at the lumbar spine, although it appears that any benefit occurs only at supplemental rather than dietary levels.

Executive summary

Diet & bone health

- Fragility fractures often diminish an individual's quality of life and are associated with high rates of mortality.
- A balanced diet can favorably modulate risk of fragility fracture.
- Specific combinations of foods or food components can act together for a greater benefit than each component can provide alone, referred to as 'food synergy'. An example includes calcium and vitamin D.
- Specific combinations of foods or food components with current pharmacological agents that preserve bone mass and strength, termed 'food–drug synergy', may be an effective and safe strategy for preventing fragility fractures. Examples include hormone replacement therapy or bisphosphonate therapy in combination with calcium supplementation.

Calcium

- Ideal sources of calcium include low-fat dairy foods. Calcium-fortified foods, which may include orange juice or soy milk, can also provide substantial levels of calcium.
- Calcium supplements are often required to achieve calcium levels known to attenuate the loss of bone mass during aging.

Vitamin D

- Vitamin D supplementation is often warranted due to challenges in achieving recommended levels of vitamin D through diet alone, and endogenous synthesis by the skin is often insufficient owing to lower exposure to ultraviolet light during specific seasons and/or widespread use of protective clothing and sunscreen.
- Vitamin D requirements for USA and Canada were established in 1997, and studies published since that time suggest that higher intakes of vitamin D may be warranted for certain aspects of health in addition to bone health, such as improved muscle function, reduced risk of specific cancers and prevention and/or treatment of specific autoimmune disorders. The appropriate level of vitamin D is controversial and in need of review.

Protein, sodium & caffeine

- Consumption of protein and sodium, within recommended levels, and in combination with recommended levels of calcium, does not appear to have an adverse effect on bone health.
- Caffeine intake does not adversely affect bone health in the context of recommended levels of dietary calcium. One to two tablespoons of milk per one cup of coffee compensates for loss of calcium in urine.

Potential role of food components

- Use of dietary supplements is widespread for prevention of chronic diseases and as complimentary therapies to pharmacological agents. Common examples include omega-3 fatty acids and soy isoflavones.
- Omega-3 fatty acids are abundant in fish oil (eicosapentaenoic acid, docosahexanoic acid) and flaxseed oil (α-linolenic acid), and may exert positive effects on bone metabolism by reducing osteoclastic activity through anti-inflammatory mechanisms.
- Soy isoflavones share a similar chemical structure to endogenous estrogen and can bind to estrogen receptors, resulting in genomic or nongenomic effects that modulate bone metabolism.

Conclusion & emerging areas

- Both men and women should be vigilant in meeting the recommended intakes of calcium and vitamin D through diet, or supplementation, if required. This is essential for ensuring that calcium is not unnecessarily lost in urine due to protein, sodium and caffeine in the diet.
- Diets with a greater proportion of omega-3 fatty acids versus other fatty acids may benefit bone mineral density.
- Supplemental levels of soy isoflavones may protect against the loss of bone mineral density at the lumbar spine. Further study is required.
- Benefits of combining multiple healthful foods and/or food components alone and in combination with clinically approved drug treatments for osteoporosis require further study.

Future perspective

Diet alone cannot prevent osteoporosis and related fragility fractures in a large proportion of women and men during the aging process and the natural decline in endogenous sex steroid production. Thus, from the viewpoint of a nutritional scientist studying the role of diet in prevention of fragility fracture, the potential synergy that can result when dietary strategies are used in conjunction with current pharmacological agents used to manage osteoporosis is of interest. The term 'food–drug synergy' can be used to describe this area of research, with the following definition: the interaction of a food or food component and a specific drug that confers a greater health benefit than either the food or food component or drug alone [22]. An established example is the combination of HRT and supplemental calcium (approximately 1200 mg calcium/day). Data from a meta-analysis demonstrated that HRT combined with supplemental calcium resulted in higher BMD at the lumbar spine (3.3 vs 1.3% increase per year), hip (2.4 vs 0.9% increase per year) and wrist (2.1 vs 0.4% increase per year) than when HRT alone was provided [13]. Moreover, bisphosphonate drugs and selective estrogen receptor modulators are recommended in combination with supplemental calcium and vitamin D.

Elucidating more combinations of foods and/or food components resulting in food synergy or food–drug synergy that are effective in humans is and should remain an active area of research for prevention of osteoporosis. Potential examples include soy isoflavones in combination with supplemental calcium, soy isoflavones and low-dose HRT (lower doses than traditionally prescribed), and combining fish oil, soy isoflavones and calcium.

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