NUTRICEUTICALS: OVER-THE-COUNTER PRODUCTS
AND OSTEOPOROSIS

Osteoporosis is a complex multifactorial condition affected by a spectrum of biochemical and biomechanical factors, including age, diet, heredity, hormonal status, and dozens of medical conditions and their therapies. The bulk of these factors are beyond patients’ control; however, nutrition is one they can change. Marketers have taken advantage of the public’s desire for good health by promoting a plethora of nutritional supplements and food derivatives, generically called “nutriceuticals,” for their purported health benefits.

Nutriceutical products include isolated nutrients, dietary supplements, herbal preparations, and what are called “medical foods.” The use of nutriceuticals has exploded in the past decade. Today, it is estimated that two-thirds of Americans use some sort of nutriceutical product.

In this issue of “Osteoporosis: Clinical Updates,” we will look at a variety of nutriceuticals available over the counter that are promoted for the “treatment” and “prevention” of osteoporosis and review the evidence for (and against) their effectiveness.

Editor-in-Chief, Angelo Licata, MD, PhD.

Contents

Nutriceuticals: Implications for Patient Care ................................................................. 2
Nutriceuticals with Known Skeletal Benefits ................................................................. 2
Calcium and Bone ............................................................................................................... 2
Calcium Safety .................................................................................................................. 4
Vitamin D and Bone ......................................................................................................... 5
Nutriceuticals with Potential Skeletal Benefit or Harm ................................................ 6
Vitamin A ........................................................................................................................... 6
B Vitamins ....................................................................................................................... 7
Boron .................................................................................................................................. 8
Vitamin C ............................................................................................................................ 9
Vitamin K ........................................................................................................................... 9
Magnesium ........................................................................................................................ 10
Manganese, Copper, Zinc ............................................................................................... 11
Phosphorus ....................................................................................................................... 11
Strontium .......................................................................................................................... 11
Phytoestrogens ................................................................................................................. 12
Protein ............................................................................................................................... 13
Tea ..................................................................................................................................... 13
DHEA ................................................................................................................................... 14
Over-the-Counter Products and Osteoporosis Case Discussions .................................. 14
Case 1: 55-Year-Old Postmenopausal Woman ................................................................. 14
Case 2: 45-Year-Old Perimenopausal Woman ................................................................ 16
Case 3: 75-Year-Old Woman with Low Bone Mass ....................................................... 16
Summary ............................................................................................................................ 17
References ......................................................................................................................... 17

National Osteoporosis Foundation

National Osteoporosis Foundation

1150 17th Street, NW • Washington, DC 20036 • 202/223-2226 • www.nof.org

© National Osteoporosis Foundation. All rights reserved

Production of this activity was made possible by an unrestricted educational grant by Merck.
Nutraceuticals: Implications for Patient Care

There are hundreds, if not thousands, of products on the market advertising bone health benefits. Some contain ingredients that have been studied in high-quality placebo-controlled clinical trials, but most have not. Sorting through the claims made by manufacturers of these products can be difficult for health care professionals. For patients and the general public, it can be almost impossible to determine which claims are reliable.

Increasingly, specific diets and foods are being promoted to prevent or manage particular medical conditions and diseases. When it comes to bone health, data support the benefit of a diet rich in calcium, fruits, nuts, and vegetables, as well as adequate protein. We will review a sampling of the many ingredients and products purported to improve or maintain bone health that are available through online and conventional pharmacies, grocery stores, and specialty shops.

Healthcare providers need to be aware of the many vitamins, minerals, dietary supplements, and herbal products that their patients may be taking. Most patients must be prompted to discuss the supplements and nutraceutical products they use. Many don’t realize that these products can have complex health impacts and may interact with prescribed medications.

It is critical that healthcare providers elicit a complete reporting of their patients’ intake of all nutraceutical products. To aid in this process, clinicians can ask focused questions, such as, “What dietary supplements and over-the-counter health products do you use?” or “What kinds of foods do you typically eat in a day?”

Open-ended questions such as these lead patients to provide more detailed information on their nutritional intake, aiding the clinician in providing optimal patient care.

The recommended daily allowances, adequate intakes, and tolerable upper limits cited in this newsletter are those established by the Food and Nutrition Board of the Institute of Medicine.¹ When insufficient data exist for establishing a recommended daily intake level, adequate intake levels are indicated, representing the median intakes reported from the Food and Drug Administration Total Diet Study. Nutrient information on specific foods reported in this article is from the U.S. Department of Agriculture’s National Nutrient Database.²

Nutraceuticals with Known Skeletal Benefits

There are two nutrients with undisputed benefit to bone: calcium and vitamin D. Research has amply demonstrated the importance of these nutrients in building and maintaining healthy bone tissue and in preventing osteoporosis and related fractures.

Calcium and Bone

Calcium is essential for blood clotting, nerve function, and countless other metabolic processes. It is also essential for building and maintaining a healthy skeleton. Ninety-nine percent of the body’s calcium reserve is stored in bone. Serum calcium balance is tightly regulated by parathyroid hormone (PTH) and calcitriol. Because the body cannot produce calcium, calcium normally lost through the gastrointestinal tract, kidneys, and skin must be replaced through the diet. When
serum calcium levels are too low, and adequate calcium is not provided by the diet, calcium is taken from bone.

Long-term dietary calcium deficiency is a known risk factor for osteoporosis. The recommended daily calcium intake from diet and supplements combined is 1000 mg/day for people aged 19 to 50 and 1200 mg/day for people older than 50. For all ages, the tolerable upper limit is 2500 mg calcium per day.

Adequate calcium intake is necessary for attaining peak bone mass in early life (until about age 30) and for slowing the rate of bone loss in later life. Although calcium alone (or with vitamin D) has not been shown to prevent estrogen-related bone loss, multiple studies have found calcium consumption between 650 mg and over 1400 mg/day reduces bone loss and increases lumbar spine BMD.

How to take calcium supplements:
- Take calcium supplements with food.
- If unable to take calcium with food or if taking acid-blocking medication, calcium citrate is recommended.
- Spread calcium out
- 600 mg or less is absorbed best at one time
- Best to take supplement at a relatively low-calcium meal
- Chew chewables, swallow tablets
- Take with full glass of water and food

Dietary sources of calcium include:
- Dairy products: milk (300 mg/cup), yogurt (300-400 mg/cup) and cheeses (138 mg/cup skim cottage cheese)
- Fortified orange juices (300 mg/8 oz), breads (150-200 mg/slice), and cereals (Total® brand Raisin Bran 1038 mg/cup);
- Nuts (almonds 75 mg/1 oz, about 25 nuts) and seeds (sesame seed butter, tahini, 64 mg/tbsp)
- Fish eaten with bones (sardines 325 mg/3oz, canned salmon 183 mg/3oz)
- Soy milk (61 mg/cup)
- Tofu processed with calcium salts (164 mg/quarter cup)
- Green vegetables, such as collards (357 mg/cup)
- Beans, such as navy beans (126 mg/cup) and soy beans (261 mg/cup)

Calcium supplements are available in several forms: calcium carbonate (most common), calcium citrate,
and calcium phosphate. Compounds contain different amounts of elemental calcium. Calcium intake should be estimated on the basis of elemental calcium in the supplement taken (shown on the nutrition supplement label).

Calcium in over-the-counter supplements is generally well absorbed in the various compounds available. Individual users may find that one compound works better for them because it causes fewer side effects, such as gas or constipation. Because the body doesn’t readily absorb more than about 600 mg of elemental calcium at a time, it is best to take calcium supplements with a low-calcium meal and to spread out supplements, perhaps taking one in the morning and one at night. Calcium carbonate is absorbed best when taken with food. Calcium citrate can be taken anytime.

Achieving bone-building and bone-preserving effects of pharmacologic therapies for osteoporosis requires adequate calcium intake.

<table>
<thead>
<tr>
<th>Per Day</th>
<th>(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 oz.)</td>
<td>X 300</td>
</tr>
<tr>
<td>Yogurt (6 oz.)</td>
<td>X 300</td>
</tr>
<tr>
<td>Cheese (1 oz. or 1 cubic inch)</td>
<td>X 200</td>
</tr>
<tr>
<td>Fortified Foods &amp; Juices</td>
<td>X 80 - 1,000</td>
</tr>
</tbody>
</table>

Estimated total from other foods
Note: Increase this amount if you get more than 250 mg of calcium from other foods.

Total Daily Calcium Intake, in mg = 250

Calcium Safety

Concern has been raised about a possible connection between calcium supplementation and cardiovascular risks. Associations have been observed between calcium supplementation without vitamin D and increased risk of myocardial infarction (MI). Using a more powerful tool of combining effects seen in individual studies by meta-analysis of randomized trials of calcium supplementation (minus vitamin D), the same association was demonstrated: roughly a 30% increase in MI, but not stroke or mortality.7,8 A similar, although smaller increase in MI was observed in meta-analysis of data from the Women’s Health Initiative.9

Data on calcium taken in conjunction with vitamin D and pharmacotherapy for osteoporosis, however, have demonstrated no increase in overall mortality and cardiovascular events.10-12 There is still much that is unknown about the risk of high calcium intake on the cardiovascular system.

The current consensus is that calcium consumed through food intake is the best means to meet daily intake recommendations and is unlikely to have a negative impact. Therefore, individuals should consume as much calcium as possible from foods. Supplements should be used only to bring all-source intake to recommended levels of 1000-1200 mg/day. In general, more calcium than the recommended amount will not provide added benefit and may, indeed, pose a risk.

In years past, the main concern about calcium supplements was lead contamination in calcium-carbonate based supplements derived from dolomite, bone meal, or unrefined oyster shell. Like other nutritional supplements, calcium supplements are not FDA tested for lead content. It is up to the manufacturer to ensure that a supplement meets FDA standards. The FDA Provisional Total Tolerable Intake level for lead is 75 mcg for adults. Several studies have found detectible lead in commercial calcium supplements.13,14 In 2008, the FDA tested lead content in 324 multivitamins sold in the U.S. Small amounts of lead were found in most of them (320 of 324), but none came close to the harmful threshold (highest daily exposure was <5 mcg/day).15

If the supplement has a USP label, the lead content has been tested and determined to be within acceptable levels. Most major brands of calcium supplements voluntarily meet the USP standards for purity and safe

---

Figure 1. This calcium calculator is available on the NOF website. Patients can use it to estimate their calcium intake and need for supplementation to reach intake goals.

Available at: http://www.nof.org/aboutosteoporosis/prevention/calciumcalculator
lead levels.

Calcium is known to offset the effects of lead by blocking its absorption (both in the supplement and in other dietary contributors of lead). Research has shown that blood lead levels are lower in people who take calcium supplements than in those who do not. Data available to date support the view that patients are safe taking calcium-plus-vitamin-D supplements from respected manufacturers. Patients should, however, avoid supplements derived from dolomite, bone meal, or unrefined oyster shell. Be advised that calcium carbonate preparations are currently the least expensive and the most widely available. Alternatives to calcium carbonate include calcium citrate, calcium phosphate, and (by prescription) calcium acetate.

**Vitamin D and Bone**

Vitamin D regulates intestinal calcium absorption and helps mineralize bone. The most readily available source of vitamin D is direct sunlight, which some people avoid because of skin cancer risk and concern about wrinkles and photo damage. Additionally, the skin’s ability to metabolize vitamin D declines with age. Other sources of vitamin D are needed such as fish liver oils, fatty fish, eggs, liver, and fortified foods such as milk and cereal.

Vitamin D deficiency can be a problem among individuals who avoid sunlight, do not drink vitamin D fortified milk, or do not take a multivitamin containing vitamin D. It is also common in people who are homebound or institutionalized, are on dialysis or anticonvulsive medication, or who suffer from diabetes, hypertension, chronic neurological disorders, or gastrointestinal diseases. In addition, research on hospital inpatients found a significant degree of vitamin D deficiency (42%) in patients with no known risk factors.

For a more in-depth coverage of the critical role of vitamin D in calcium metabolism and maintenance of bone health, please see the issue of *Osteoporosis: Clinical Updates* entitled, “Vitamin D and Bone Health.”

US RDI for vitamin D is 600 IU for men and women ages 50 to 70 and 800 IU for all people over age 70. The safe upper limit is 4000 IU. Dietary sources of vitamin D include:

- Salmon 815 IU/half fillet
health, including isolated vitamin A (carotene form), soy proteins, vitamin K, omega-3 fatty acids, and B vitamins. Other commonly used supplements may harm bone if taken at high doses, such as vitamin A (retinol form) and strontium.

Vitamin A

There are two basic categories of vitamin A in the diet: retinol and the provitamin carotenones (which are converted into retinol in the human body). The chart below shows the rough equivalence of retinol to the carotenones in terms of retinol equivalents, as defined by a joint commission of the Food and Agricultural Organization of the United Nations and the World Health Organization (FAO:WHO) in 2001.

\[
1 \mu g \text{ Retinol Equivalent} = 1 \mu g \text{ of all-trans retinol} = 6 \mu g \text{ all-trans } \beta \text{-carotene} = 12 \mu g \text{ of } a \text{-carotene, } \beta \text{-cryptoxanthin and other provitamin A carotenoids}
\]

1 IU Retinol = 0.3 \mu g Retinol Equivalents

Excessive vitamin A (over tolerable upper limits) can lead to many serious problems, including birth defects, liver toxicity, central nervous system disorders, and reduced bone mineral density. It has long been observed in animal studies that excessive levels of vitamin A causes disruption of normal bone remodeling processes and increased risk of fracture.

Research in humans has been inconclusive. Several studies have shown that too much vitamin A is harmful to bones, leading to decreased bone density and increased hip fracture risk.\textsuperscript{20-23} Other studies, including analysis of the large-scale Women’s Health Initiative Observational Study (WHIOS), found no link between high vitamin A intakes, blood retinol levels, and increased risk of fracture.\textsuperscript{24-27}

Researchers have suggested reasons for these divergent findings, including the vitamin D and hormonal status of WHI participants. In the WHIOS analysis, women with the highest intake of both vitamin A and retinol plus the lowest vitamin D intake had a small increased risk of fracture.\textsuperscript{24}

The carotenones, (alpha-, beta-, and gamma-carotene), have also been studied for their impact on bone. The carotenoids are vegetable sources of vitamin A. Unlike

- Milkshake, thick vanilla, 150 IU/11 fluid oz
- Malted milk drink mix made with whole milk 326 IU/cup
- Sardines with bone in oil 164 IU/3 oz
- Milk fortified with 100 IU

Nutriceuticals with Potential Skeletal Benefit or Harm

Clearly, calcium and vitamin D are essential to bone health and, in cases of low intake, supplementation may be needed. Other nutrients contribute to bone metabolism and may be beneficial in supplemental form. Many nutriceutical products may promote skeletal
retinol, the carotenoids have shown promise in studies to increase bone density and/or reduce fractures.\textsuperscript{26-30} In the Framingham study, the highest intake levels of total carotenoids were associated with reduced 15-year fracture incidence (46\% in women and 34\% in men).\textsuperscript{28} The recommended intake of vitamin A is 900 mcg/day (3000 IU) for men and 700 mcg/day (2300 IU) for women with a limit of 3000 mcg/day (10,000 IU).\textsuperscript{29} Dietary sources of vitamin A or its precursor carotene include:

- Skim or fat-free milk 500 IU/cup as retinol
- Beef liver 22175 IU/cup as retinol
- Carrot juice 45133 IU/cup as carotene
- Sweet potato 28058 IU/potato as carotene
- Spinach 22916 IU/cup as carotene
- Beet greens 11022 IU/cup as carotene

Because of the possible detrimental effects of retinol on bone, it is advisable to select supplements that contain no more than 2000–3000 IU retinol. Alternatively you can choose supplements that provide vitamin A as carotene.

**B Vitamins**

Inadequate intake and/or compromised metabolism of folic acid/folate (B\textsubscript{9}), pyridoxine (B\textsubscript{6}), riboflavin (B\textsubscript{2}), or cobalamin (B\textsubscript{12}) have been shown to lead to high homocysteine levels.\textsuperscript{30} Emerging data point to a dose-response association between elevated serum homocysteine and a modest increased risk of fracture.\textsuperscript{31-34}

Large studies in the Netherlands observed high homocysteine combined with low vitamin B\textsubscript{12} was associated with high markers of bone turnover, increased fracture risk, and low ultrasound measurement of bone density.\textsuperscript{33,34} In the Rotterdam study, a dose response was seen between low B\textsubscript{6} intake, high homocysteine levels, and increased risk of hip fracture independent of BMD.\textsuperscript{33} The same study also observed a positive independent relation between dietary intake of riboflavin (B\textsubscript{2}) and pyridoxine (B\textsubscript{6}) and BMD.\textsuperscript{33}

Studies of B vitamin effects on bone have shown divergent effects in men and women. In a large Norwegian observational study, elevated homocysteine and low folate were associated with reduced BMD in women but not in men.\textsuperscript{35,36} No specific action on bone has been identified either for B vitamins or homocysteine.

It has been speculated that, rather than a direct bone support NOF ............... Join us in the fight against osteoporosis

NOF depends on the generosity of individuals who recognize our important work educating the public and health professionals alike on how to prevent, diagnose and treat osteoporosis.

There are many ways to support NOF in its mission to defeat osteoporosis:

**Individual Giving**

Your gift will help us provide better care and support for the most vulnerable – those who have suffered a fracture – and to protect future generations from this debilitating disease.

**Recurring Gift**

By giving a little each month to sustain NOF throughout the year, you can make a big impact in our efforts to start conversations about bone health and family health history in order to elevate osteoporosis to an issue of national concern. Your support will help us reach our goals of better treating and ultimately preventing osteoporosis.

**Memorial and Tribute Gifts**

Give a tribute or memorial gift honoring the memory of friends and loved ones. For all gifts made, NOF will send appropriate notification to the honoree or to the family of the deceased on your behalf and you will receive acknowledgment of your gift either online or through the mail.

**Planned Giving**

NOF offers a variety of planned giving options. Planned giving allows supporters to leave gifts to NOF at death or to invest gifts during their lifetime. Investing during your lifetime allows you to receive the benefits while you are alive and bequest the remaining funds to NOF at the time of your death.

**Visit www.nof.org today to make your tax-deductible donation.**

The National Osteoporosis Foundation is a qualified 501(c)(3) tax-exempt organization and all donations to the organization are tax deductible.
to characterize the role of B vitamins in bone metabolism and the potential for therapeutic supplementation to prevent fracture. It is clear that a diet rich in foods that are good sources of B vitamins, such as whole grains, fruits, and vegetables, should be recommended to all patients.

US RDI for B₂ (riboflavin) is 1.3 mg/day for adult men and 1.1 mg/day for adult women. Dietary sources of B₂ include:
- Beef liver 2.9 mg/3 oz
- Turkey giblets 2.2 mg/cup
- Duck meat 1 mg/half duck
- Malted milk drink mix made with whole milk 1 mg/cup

US RDI for B₆ (pyridoxine) is 1.3 mg/day for adults under age 50, male and female. Over age 50, the RDI for women is 1.5 mg/day and for men is 1.7 mg/day. Dietary sources of vitamin B₆ include:
- Cereal, raisin bran 2.1 mg/cup
- Fish, salmon 1.1 mg/half fillet
- Chickpeas 1.1 mg/cup
- Malted milk drink mix made with whole milk 1.015 mg/cup

US RDI for folate (B₉) is 4 mg/day for adults, male and female. Foods are fortified with folic acid in order to raise folate intake. Dietary sources of B₉ include fortified sources such as bread, cereal, and rice and natural sources such as beans:
- Rice, white long grain 797 mg/cup
- Cereal, malt-o-meal 756 mg/cup
- Wheat flour, white, bread 358 mg/cup
- Beans, pinto 294 mg/cup

US RDI for B₁₂ is 2.4 µg/day for adults, male and female. Dietary sources of vitamin B₁₂ include:
- Beef 70.7 µg/3 ounces
- Mollusks, clam 15.8 µg/3 ounces
- Chicken 13.7 µg/cup
- Soup, New England clam chowder 12 µg/cup

(Because 10% to 30% of older people may malabsorb food-bound B₁₂, the Institute of Medicine advises those older than 50 years to meet their RDA mainly by consuming foods fortified with B₁₂ or a supplement containing B₁₂.)³⁸

**Boron**

Currently no recommended daily intake or average...
intake levels are established for the trace element boron. The boron content in most diets is estimated to be about 1.5-3 mg/day, and supplements contain up to 9 mg/day. A tolerable upper limit for boron has been established at 20 mg/day. Studies in rats have shown increased bone mass with unchanged bone brittleness following exposure to boron. In addition, a study in humans found a positive impact on calcium metabolism in postmenopausal women receiving supplemental boron of 3 mg/day.

Common sources of boron are nuts, fruits, milk, eggs, potatoes, vegetables, legumes, and pulses (e.g., peas, beans, lentils). Given that there is no requirement for boron, it is recommended that people get boron from eating a well-rounded diet rather than from supplements.

**Vitamin C**

Intakes of vitamin C that are just above the recommended levels (~100 mg to 125 mg/day) have been linked in some studies of postmenopausal women to small increases in BMD and reduction in fractures. This effect was found to be stronger in women with high calcium intakes and estrogen therapy. However, research into the effect of vitamin C on BMD is not conclusive, and contrary results have been found.

U.S. RDI for vitamin C is 90 mg/day for men and 75 mg/day for women. The tolerable upper limit is 2000 mg/day. Dietary sources of vitamin C include:

- Orange juice, fresh 124 mg/cup
- Fruit, peaches, frozen 235 mg/cup
- Peppers, red, sweet, raw 190 mg/cup
- Broccoli 101 mg/cup

**Vitamin K**

Vitamin K is made by bacteria in the intestinal tract and stored in the liver. Besides being essential to blood clotting, vitamin K is necessary for making osteocalcin, a protein involved in bone formation. Vitamin K supplements are contraindicated in women taking warfarin or similar agents.

Food sources of vitamin K include fermented soy and dairy products, fish, meat, liver, eggs, leafy greens, brussel sprouts, cabbage, and plant oils. Phylloquinone (vitamin K₁) is found in plants (green leafy vegetables), and menaquinone (vitamin K₂) is found in meat, eggs, dairy, and natto. Patients with malabsorption syndromes or in whom intestinal bacteria have been destroyed by antibiotic therapy should be monitored for vitamin K deficiency. The role of vitamin K supplementation in osteoporosis therapy is as yet unclear. Several forms of vitamin K—are currently under study for their potential effect on bone mass and fracture rates.

Studies looking at the impact of K₁ alone and in combination with calcium and vitamin D have demonstrated no significant impact on BMD, while showing some protection against fractures in postmenopausal women with osteoporosis. For example, an analysis of the large Framingham observational study found a link between vitamin K₁ intake and decreased risk of hip fracture but no effect on BMD. The double-blinded
placebo-controlled Canadian ECKO trial compared 5 mg vitamin K, per day with placebo in about 325 women with osteopenia but without osteoporosis for two years and observed a statistically significant lower risk of clinical fractures (RR 0.46, 95% CI 0.22 to 0.99) with no significant change in BMD. Morphometric vertebral fractures were not reported, and this finding is based on a small number of fractures. (All participants in the ECKO trial were assessed for dietary intake and supplemented to bring them to 1500 mg calcium and 800 IU vitamin D.34)

Several small studies on vitamin K, conducted in Japan have published observations of over 20% reduction in vertebral fracture with K, versus without.55,57 These trials were insufficiently powered to reach statistical significance. However, one of the larger of these studies, the Osteoporotic Fracture (OF) Study, observed no statistically significant difference in treatment groups.58 Due to differences in study design, population, dose and end-point measurement/definition, comparing these studies is difficult.

Researchers concur that all forms of vitamin K play a role in regulating bone metabolism. However, exactly how to make best use of it in protecting bone health will require more research in the form of large-scale and long-term controlled clinical trials. In the meantime, rather than supplements, patients should be encouraged to consume diets rich in vitamin K.

The US RDI for vitamin K is 120 μg/day for men and 90 μg/day for women, with no established upper limit.

Dietary source of vitamin K include:
- Kale, frozen, cooked 1147 μg/cup
- Spinach, frozen, cooked 1027 μg/cup
- Brussel sprouts, frozen, cooked 300 μg/cup
- Noodles, egg or spinach, boiled 162 μg/cup

Magnesium

Magnesium is required for many enzyme reactions, as well as synthesis of proteins and nucleic acids. Magnesium supports the secretion and action of parathyroid hormone, an important regulator of calcium balance.

The recommended daily magnesium intake for men is 420 mg and for women is 320 mg. The safe upper limit for magnesium is established at 350 mg/day from supplement and/or pharmaceutical sources (not including

Alkaline vs. Acidic Foods

Patients may have read or heard that they should pursue an alkaline diet, while avoiding so-called acidic foods, such as dairy products, meats, and grains. These foods contain phosphates.

According to the acid-ash or acid-base hypothesis, phosphates increase acidic ion excretion, thus increasing urinary calcium excretion, demineralization of bone, and fractures. To test this hypothesis, researchers have undertaken systematic review and meta-analysis of dozens of published randomized intervention trials, prospective cohort studies, and meta-analyses. No evidence was found that phosphate (or dietary acid) intake is associated with change in calcium balance or in increased calcium loss from bone.1,2

In fact, the opposite was observed in a meta-analysis of studies that increased phosphate levels through use of supplements. In this analysis, higher phosphate intakes were associated with decreased urine calcium and increased calcium retention.10


Food and water), if kidney function is normal. Sources include chlorophyll-containing (dark green) vegetables, whole grains, meats, milk, bananas, nuts, and seeds. Because magnesium is found in many foods, magnesium deficiency is uncommon. It can, however, be seen in patients with malabsorption conditions or diabetes, as well as in people on a restricted diet or those taking certain medications (such as proton pump inhibitors, diuretics, and calcineurin-inhibitor immunosuppressive medications, among others).

Magnesium appears to affect bone remodeling, strength, and preservation. Greater magnesium intake was associated with higher BMD in Caucasian but not African American adults in the Health ABC study.59 However, no association was observed between magnesium intake and fracture risk in the Women's Health Initiative outcomes.59,60 In small supplementation trials, magnesium appears beneficial against bone loss in magnesium-deplete individuals.61 However, to date, the few well-designed studies looking at magnesium intake and BMD have yielded inconclusive results. Patients
with chronic kidney disease should be warned not to take magnesium supplements without first consulting their physician.

The RDI for magnesium is 420 mg for men and 320 mg for women. Dietary sources of magnesium include:
- Trail mix with chocolate chips, salted nuts, seeds 235 mg/cup
- Semisweet chocolate 193 mg/cup
- Spinach, canned, drained 163 mg/cup
- Beans, black, cooked, boiled, no salt, 120 mg/cup

**Manganese, Copper, Zinc**

The dietary minerals manganese, copper, and zinc are cofactors for enzymes required for healthy bone metabolism.62

There is currently no recommended daily intake for manganese. Adequate intake for men is 2.3 mg/day and for women is 1.8 mg/day, with a tolerable upper limit of 11 mg/day. Dietary sources of manganese include nuts, legumes, tea, and whole grains. Research in animal models has suggested a potential role for manganese supplementation in maintenance of bone health; however, more research is needed.63,64

The recommended intake of copper for adults is 900 mcg/day with an upper limit of 10000 mcg/day. Dietary sources of copper include organ meats, seafood, nuts, seeds, cereals, whole grains, and cocoa.

The recommended intake of zinc for adults is 11 mg/day for men and 8 mg/day for women with an upper limit of 40 mg/day, assuming that the person has normal kidney function. Dietary sources of zinc include fortified cereals, eggs, dairy products, nuts, red meat, peas, and certain seafoods. Patients with chronic kidney disease should not take zinc supplements.

**Phosphorus**

The recommended intake for phosphorus is 700 mg/day for men and women, with an upper limit of 4000 mg/day until age 70, after which the safe limit drops to 3000 mg/day. Dietary sources of phosphorus include dairy products, meat, peas, eggs, and some cereals. Phosphorous is also widely used as a preservative (phosphoric acid) in carbonated beverages and processed foods. As is the case with many nutrients, too much or too little phosphorus leads to problems.

It has long been known that excess phosphorus intake increases the need for calcium by interfering with calcium absorption through increased secretion of parathyroid hormone. Studies have also observed that phosphorous deficiency may reduce the absorption of calcium and thereby lead to bone loss.55 The key is to maintain a balance between intake of calcium and intake of phosphorus (roughly 2:1). The common Western diet is characterized by low calcium-to-phosphorus ratios (less calcium than phosphorus). Research has demonstrated that habitually low calcium-to-phosphorus diets negatively impact calcium metabolism.66 It seems clear that adding dietary calcium and reducing non-nutritive phosphorus intake (i.e. soda drinks and foods high in phosphorus preservatives) can be beneficial to bone health.

The RDI for phosphorus is 700 mg/day for men and women. Dietary sources of phosphorus include:
- Cornmeal, self-rising enriched 860 mg/cup
- Milk, canned sweetened, condensed 774 mg/cup
- Fast foods biscuit with egg and sausage 562 mg/biscuit
- Fish, salmon, cooked, dry heat 491 mg/half fillet

**Strontium**

Strontium is a trace element found in seawater. Its primary source in the diet is seafood. Other strontium-containing foods include whole milk, wheat bran, meat, poultry, and root vegetables. There are no recommended daily or adequate intakes established for strontium. However, average daily intakes have been estimated to be about 1–3 mg.

Research on humans and animals over the past thirty odd years has shown pharmacologic doses of strontium to be associated with increased bone strength and reduced fracture rates.67-71

Several large, randomized placebo-controlled studies of postmenopausal women with osteoporosis taking 1 to 2 grams/day of strontium in the form of the drug strontium ranelate observed reductions in rates of fractures over 4 to 5 years: roughly 30% to 50% for vertebral fractures, 15% to 20% for nonvertebral fractures, 20% to 30% for major fragility fractures, and 20% for hip fractures.72-74

**Strontium Ranelate:**
- ↓ 50% Vertebral Fractures
- ↓ 15-20% Nonvertebral Fractures
20-30% Major Fragility Fractures

20% Hip Fractures

The drug strontium ranelate at 1 to 2 grams/day has been demonstrated in trials to reduce vertebral, non-vertebral, major fragility, and hip fractures in studies postmenopausal women. Similar positive effects were seen in early postmenopausal women without osteoporosis in studies looking at bone loss prevention using strontium ranelate doses between 120 mg and 1 g/day. Strontium ranelate is a drug currently approved for use in Europe and the UK but not FDA approved in the US. The effects of dietary strontium or strontium formulations in over-the-counter supplements (usually strontium citrate) have not been evaluated in clinical trials and should not be confused with pharmacologic strontium ranelate. Strontium supplements are available in doses from 100 mg to around 700 mg. Frequently these supplements come in combination with calcium, vitamin D and other vitamins, minerals, and nutrients, such as the flavonoids quercetin and hesperidin.

Too much strontium from supplements (over the studied doses of strontium ranelate 2000 mg/day), may lead to a range of side-effects, from diarrhea to blood clots. In addition, long-term excessive strontium can lead to disorders such as rickets and bone fragility as a result of over-recruitment of strontium to bone, where it takes the place of calcium.

Phytoestrogens

Phytoestrogens are naturally occurring compounds found in plants, which have mild estrogenic or anti-estrogenic effects on specific tissues in the body, depending on factors such as gender, age, and hormonal status. There are three forms of phytoestrogens:

- Isoflavones (genistein, daidzein, glycitein, and equol) are primarily found in soybeans and soy products, chickpeas, and other legumes.
- Coumestans (coumestrol) can be found in alfalfa and clover.
- Lignans (enterolactone and enterodiol) are found in oilseeds (primarily flaxseed), cereal bran, legumes, and alcohol.

Isoflavones have been promoted to consumers as beneficial to bone and therapeutic for menopausal symptoms, such as hot flashes. Two of the primary soy isoflavones, genistein and daidzein, are found both in foods and concentrated as ingredients in dietary supplements.

Soy isoflavones have been widely researched. In animal studies, soy isoflavones have been shown to prevent but not reverse bone loss in a dose-dependent fashion. In human studies, results have been less straightforward. While several clinical studies in the late 1990s and early 2000s observed soy intake to benefit bone in postmenopausal women, most more-recent studies show no bone preservation or fracture prevention.

Because there are so many different compounds categorized as phytoestrogens, teasing out the effects and potential applications of each compound has been difficult. It has become apparent that any beneficial impact on bone, menopausal symptoms, or cardiovascular health depends on the compound in question.

One isoflavone in particular, genistein, has been used in concentrated form to develop a medical food. According to the US Food and Drug Administration, the term medical food, is a food which is formulated...
In clinical trials, a medical food containing 27 mg genistein aglycone, 20 mg citrated zinc bisglycinate, and 200 IU cholecalciferol (trade name FOSTEUM\textsuperscript{89}) was demonstrated to decrease markers of bone turnover and increase markers of bone formation. While this trial did not report fracture outcomes and the magnitude of change observed is very small in real terms, the preliminary data are suggestive of bone density maintenance.\textsuperscript{90} Additional information is needed on fracture outcomes and long-term impacts in order to establish if this intervention is a practicable adjunct and/or addition to current osteoporosis therapies.

Another isoflavone under study is the coumestan-rich red clover. Clover has been researched in recent years in both animal and human studies.\textsuperscript{91,92} Typical of these studies is the one-year double-blind trial reported by Atkinson, et. al., that randomized postmenopausal women to placebo or a red-clover-derived isoflavone supplement. Results showed significantly less spine bone loss in the red-clover group along with higher markers of bone formation. No change was seen in bone loss at the hip or markers of bone resorption.\textsuperscript{93}

Dietary sources of isoflavones include soybeans, chickpeas, red clover, and legumes. Long-term clinical trials are needed to assess the effectiveness of isoflavones on fracture rates and BMD at various skeletal sites.

Omega-3, or n-3, polyunsaturated fatty acids come from plant sources (lignans) or animal sources (fish oil). Omega-3 fatty acids have been shown in animal and cell research to have a beneficial effect on bone mass.\textsuperscript{94} However, these results have not been replicated to date in human studies. The effects of omega-3 fatty acids on BMD have been variable, with either positive or no effect on BMD.\textsuperscript{95,96}

Plant sources of omega-3 fatty acids (lignans) include soybeans, flaxseed, and walnuts. Animal sources of omega-3 fatty acids include fatty fish (e.g., salmon, mackerel, and sardines).\textsuperscript{97} Vegetable sources may be preferable to avoid any detrimental effects of retinol, found in high concentrations in fish oil. (See above discussion on vitamin A.) Supplements are widely available.

**Protein**

There have been a large number of observational studies and clinical trials looking at the impact of protein on bone.\textsuperscript{98–100} Although outcomes have varied, research data support the view that adequate protein intake is needed to achieve peak bone mass in childhood and maintain healthy bone in adulthood. In the elderly, nutrition is often inadequate, and protein intake may be suboptimal for skeletal health.

A recent meta-analysis of hundreds of double-blind placebo-controlled clinical studies conducted over the past 30 years found no association, negative or positive, between fracture rates and dietary protein (animal or vegetable) in healthy adults. The meta-analysis found a small but significant positive correlation between dietary protein intake and BMD, BMC (bone mineral content), and markers of bone turnover at all skeletal sites. However, no reduction in fracture risk was observed.\textsuperscript{101} Because the studies under review did not include long-term interventional trials, the possibility of positive effects on fracture rates over time could not be assessed.

Further investigation is needed to determine if changes to current protein intake recommendations are warranted for any specific age group. At present, daily intake at recommended levels from animal and/or vegetable sources is sound policy for patients of all ages. Recommended intake of protein is 56 grams/day for adult men and 46 grams/day for adult women (roughly 1 g to 1.5 g/day per kg). Dietary sources of protein include:

- Duck 51.89 g/half-duck
- Chicken meat 42.59 g/cup
- Fish salmon, cooked dry heat 39.37 g/half-fillet
- Fast food hamburger, double large patty 34.28 g/burger

**Tea**

Multiple population and retrospective studies have investigated tea drinking and any effect it may have on bone and fracture risk. Observations have trended in a slightly positive direction concerning BMD and fracture reduction.\textsuperscript{102–104} However, there have been no
Progestrone Creams

Clinical studies have reported that progesterone applied topically as a cream is absorbed into the body.\textsuperscript{18} One study compared the serum progesterone levels in women taking prescription oral progesterone with women using over-the-counter transdermal progesterone cream and found them to be roughly equivalent at 12 days (median AUC[0-24] 12.5 ng x h/mL vs 10.5 ng x h/mL, respectively, \( P = .81 \)).\textsuperscript{11}

For many years, progesterone creams have been promoted over the counter as remedies for menopausal symptoms and prevention of postmenopausal bone loss. None of the placebo-controlled randomized studies of transdermal progesterone to date have observed bone-protective effects using doses of progesterone cream ranging from 5 mg to 60 mg/day\textsuperscript{10-11}

\footnotesize{\textsuperscript{1} O’Leary P, Federman P, Chan K, Taranto M, Smith M, Evans B. Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women. \textit{Clin Endocrinol (Oxf)}. 2000;53(6):615-20.


controlled clinical trials investigating the question to date. Green tea, as opposed to black or oolong, is being studied for its specific characteristics.\textsuperscript{105} But, while a cup or two of tea a day may be good for bones, gallons are not. Multiple cases of skeletal fluorosis have been reported in the medical literature documenting cases of women who consumed 1 to 2 gallons of instant or brewed tea per day throughout adult life (20 to 30 years).\textsuperscript{106-108}

\section*{DHEA}

The adrenal hormone dehydroepiandrosterone (DHEA) is a normal endogenous precursor to estrogens and androgens. It has been promoted by vendors of nutraceuticals as a hormonal fountain of youth, promising cures to age-related concerns from cognitive decline and hot flashes, to osteoporosis.

Small increases in BMD have been observed in studies of DHEA supplementation (50 mg to 100 mg/day).\textsuperscript{109,110} For example, a small randomized placebo-controlled trial of 50 mg/day DHEA reported by von Mühlen, et. al., demonstrated a 3% BMD increase at the lumbar spine, but not at other sites, in women but not men.\textsuperscript{111}

DHEA supplements are widely sold in drugstores and vitamin stores in 15 mg to 100 mg capsules with a recommended dose of one per day. The long-term safety of DHEA supplementation is uncertain, with some analyses linking it to breast and/or ovarian cancer.\textsuperscript{112,113} The data are preliminary, but suggest recommending caution when it comes to the use of DHEA dietary supplements until large-scale trials have demonstrated potential bone benefits and ruled out cancer concerns over the long term.

\section*{Over-the-Counter Products and Osteoporosis: Case Discussions}

Patients are bombarded with sales pitches from manufacturers of nutraceuticals on every visit to the pharmacy. Many do not realize that their healthcare providers need to know what vitamins and supplements they take. In the following case discussions, we will consider typical cases of nutraceutical use common in primary care. We will demonstrate techniques clinicians can use to reinforce the take-home message that, rather than relying on supplements, patients would benefit most from good general nutrition coupled with sufficient calcium and vitamin D, preferably in dietary rather than supplement form.

\subsection*{Case 1: 55-Year-Old Postmenopausal Woman}

The first patient we will discuss is a 55-year-old woman who is three years postmenopausal with no history of fracture. The patient presents for her yearly physical exam. She reports that her 75-year-old mother recently broke a hip after slipping on ice and is worried that she, herself, may be at risk. The patient has never had a bone density test.

\textit{Given her family history, is this patient at risk for osteoporosis?}

Yes. History of fragility fracture in a first-degree relative is an established risk factor for osteoporosis.
As part of taking the patient’s medical history, the clinician asks if she is using any over-the-counter supplements or preparations for her health. The patient reports that she has been taking a multivitamin and using topical progesterone cream and oral soy supplements for prevention of bone loss. She asks if she should be doing anything else.

**What is the effectiveness of topical progesterone cream and soy supplements for preventing osteoporosis?**

There has been very little clinical research on the effectiveness of many over-the-counter products on the market that promote themselves as treatments or preventatives for osteoporosis.

Neither of the products the patient is using has been shown in clinical trials to prevent osteoporosis or osteoporotic fracture.

The patient’s intake of soy supplements may have some health benefit but is unlikely to improve her risk for osteoporosis. Clinical trials have shown progesterone creams to have no beneficial effect on bone.

**Should this patient be cautioned about her nutriceutical use?**

Not in so many words. However, this is a good opportunity to discuss the evidence (or lack thereof) to support the claims made by manufacturers of these products.

While neither product the patient is using has been proven to prevent osteoporosis, neither has been shown to cause harm in recommended doses. However, there is solid scientific evidence that adequate calcium and vitamin D intake can slow the rate of bone loss.

**How can this patient’s calcium intake be estimated?**

The patient’s calcium intake can be quickly estimated by multiplying the number of dairy servings in the patient’s daily diet by 300, adding 250 mg for nondairy dietary calcium sources, and then adding the calcium in any multivitamin or supplement taken.

After estimating the patient’s dietary calcium intake to be 700 mg, the physician recommends the patient continue her daily multivitamin, which contains 500 mg calcium. This gives her a combined total calcium intake of 1200 mg/day.

**How can the patient’s vitamin D status be estimated?**

The patient’s vitamin D status is dependent on many factors, including diet, sun exposure, and age. The clinician can ask about sun exposure and intake of vitamin D fortified dairy products, but may still not have an accurate assessment of her vitamin D status. A blood test to measure her serum vitamin D level would be needed.

**Should this patient have serum vitamin D measured?**

It is probably not necessary. Because the patient’s daily

---

**Buyer Beware**

Patients seeking health advice online can quickly become inundated with unreliable information. A systematic review of websites claiming to provide information on natural products for the prevention and/or treatment of osteoporosis found unsupported claims for products that had not been studied and exaggerated claims for those that had. Roughly half did not cite sources for their claims, and even those that did were written in language too technical for the average reader’s understanding.  

The Food and Drug Administration has limited regulatory control of the over-the-counter nutriceutical industry. Oversight, such as it is, is restricted to voluntary organizations that charge a fee for their review and certification of a product. United States Pharmacopeia (USP), Good Housekeeping Institute, and Consumerlab.com are three such organizations. There are efforts on the part of these groups and others to tighten and standardize their testing and certification procedures. However, the bottom line is still “buyer beware.”

multivitamin contains vitamin D (600 IU), she participates regularly in outdoor activities, and is not elderly, she is at low risk for low vitamin D. However, vitamin D deficiency is very common in American adults, especially African Americans. The only way to rule it out is to perform serum measurement.

What should be done to assess the patient’s bone health?
Because she is postmenopausal with a family history of fragility fracture, a baseline bone density scan is appropriate. The clinician prescribes a bone density test by DXA and schedules a follow-up appointment to discuss results, future fracture risk (using the FRAX® tool) and, if warranted, possible pharmacologic options and tracking of biochemical markers of bone turnover.

Case 2: 45-Year-Old Perimenopausal Woman
The second patient we will discuss is a 45-year-old woman with no family history of osteoporosis. She is perimenopausal and concerned about maintaining her bone health. The clinician finds no indicators of elevated osteoporosis risk in her history. Neither she nor her parents has experienced bone fractures.

She has always been in good health, has never smoked or consumed alcohol, and has never taken medications that cause bone loss. The clinician asks if the patient takes any supplements or herbal products, she reports that she takes multiple nutritional supplements, including multivitamins, flax seed oil, magnesium, zinc, and six fish oil capsules twice a day for their cardiovascular benefits.

Does anything in the patient’s reported history raise concern about her bone health?
Perhaps. Observational studies suggest that ingestion of high doses of supplemental retinol, found in high concentrations in fish oil, may increase a woman’s risk of hip fracture. This patient’s daily fish oil intake may reach the level of concern.

Should the patient be advised to curtail her use of fish oil supplements?
It may be a good idea. The potential cardiovascular benefit of fish oil supplements (for their omega-3 fatty acid content) may be offset by skeletal harm. The clinician recommends that the patient discontinue intake of fish oil supplements and that she limit her intake of vitamin A in multivitamins to the beta-carotene form.

Animal and epidemiological studies have indicated that omega-3 fatty acids from nonretinol sources such as flax seed oil may have a positive impact on bone and cardiovascular health, so the physician recommends this as an alternative source of omega-3 fatty acid.

Should the physician discourage continued use of supplemental magnesium, zinc, and soy?
Not if they are kept within safe limits (350 mg/day for magnesium and 40 mg/day for zinc). Because zinc and magnesium are involved in healthy bone metabolism, it is possible that intake of these minerals may be beneficial to bone. However, research is lacking to support this hypothesis.

The clinician recommends a varied diet that includes leafy greens, fruits, and vegetables. In addition, the clinician recommends that the patient engage in weight-bearing exercise and a bone density test at age 60.

Case 3: 75-Year-Old Woman with Low Bone Mass
The third patient we will discuss is a housebound elderly woman, 75 years old, who lives alone. She is in good general health. Her recent DXA scan is diagnostic of osteopenia (hip BMD –2.0).

What dietary supplements or nutriceutical products, if any, could be of benefit to this patient’s bone health?
Adequate calcium, vitamin D, and protein intake have all been shown to significantly benefit bone health in elderly women. Although these alone will not prevent osteoporosis, they are necessary components of an overall prevention or treatment plan.

Because of her age and lack of sun exposure, it is probably safe to assume that this patient is vitamin D deficient. Vitamin D deficiency contributes significantly to bone loss. To establish serum calcium and 25-hydroxyvitamin D levels, the physician orders appropriate blood panels.

The patient is asked about her diet. She reports that she eats mostly canned soup, tea, and toast: foods she can easily prepare.

Can the patient’s diet be modified to improve her bone status?
Her diet is high in sodium and low in calcium and protein. It is advisable for her to take a daily supplement that contains adequate vitamin D (800 IU) and calcium (1000 mg). The clinician explains the importance of adequate protein, calcium, and vitamins and recommends adding nuts, dairy foods, fresh fruits, and vegetables to her diet. To help the patient make these dietary changes, the clinician makes an appointment with a dietician who can help her develop a healthy eating plan she can manage on her own.

**Are there any other measures that can be taken to help this patient preserve her bone mass?**

Inactivity is an established risk factor for bone loss and osteoporosis. The patient is referred to a physical therapist to develop a safe movement/exercise plan to ease the patient into bone-preserving weight-bearing exercises that she may perform at home.

The clinician discusses drugs approved for osteoporosis prevention and recommends that the patient consider beginning drug therapy to prevent further bone loss.

**Summary**

There are multiple effective FDA-approved therapeutics for preventing and treating osteoporosis. Unfortunately, there are also hundreds of non-FDA-approved nutriceuticals on the market that claim to do the same things. Healthcare providers can educate patients about which products’ claims can be supported by data, which products may potentially benefit bones, and which provide no benefit and may indeed cause harm. Through this process, patients become better able to make more-informed choices regarding their healthcare options.

**References**


65. Knappen MH, Hamulyak K, Vermeer C. The effect of vitamin K supplementation on circulating osteocalcin (bone Gla protein) and urinary cal-


74 Seeman E, Bosman S, Borgström F. Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age. Bone. 2010 Apr;46(4):1038–42.


Osteoporosis International

Osteoporosis International is the leading scientific journal for clinical research in osteoporosis and related bone diseases. Published monthly, the journal is an international, multi-disciplinary joint initiative of NOF and the International Osteoporosis Foundation.

Free Subscription for NOF Professional Members

NOF STORE: Order Education Materials for Your Patients

Member Discount on All Purchases

How Strong Are Your Bones?

This brochure helps people understand osteoporosis, their risk factors for the disease and the importance of bone healthy behaviors. It explains bone density testing and includes information on when to have a bone density test, what the results mean and when to consider treatment.

A Guide to Osteoporosis Medicines

This brochure will help you better understand your osteoporosis treatment options. It provides information on the osteoporosis medicines approved by the U.S. Food and Drug Administration (FDA), discusses factors to consider when making a treatment decision and the issues you may face in staying with a treatment plan.

Boning up on Osteoporosis: A Guide to Prevention and Treatment

This 100+ page patient care handbook offers up-to-date information on the prevention, diagnosis and treatment of osteoporosis.

Free printable downloads and discounts on print patient education publications for NOF Professional Members