

Osteoporosis: Beyond Bone Mineral Density (Part II)

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Background

Primary osteoporosis occurs with bone loss as people age, while secondary osteoporosis is caused by other factors such as medications and medical conditions. Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis and can lead to further disability and early mortality. Osteoporosis is generally viewed as a disease of low bone mineral density (BMD) as defined by a T-score. However, T-scores and, hence, BMD criteria may not accurately reflect fracture risk. Thus, if clinicians are too reliant on the idea that BMD/T-scores are the major concern in fracture risk, they may fail to recognize other danger signs and prevent painful, costly,

and life-shortening fractures in patients. Early detection and treatment of risk factors for osteoporosis and osteoporotic fractures are essential for practicing clinicians.

Family physicians will frequently be the doctors who recommend screening for osteoporosis and who are uniquely positioned to ensure both detection and appropriate treatment. Understanding bone histology, the physiology of bone turnover, and current research on the prevention and treatment of osteoporotic fractures including pharmaceutical and nutritional interventions can contribute towards the development of an integrative approach to treating this condition.

Editor's note: This is the second of a 2-part article. Part 1 was published in the Oct/Nov 2008 issue of IMCJ (IMCJ 7.5:34-38).

After reading Part I of this article, you are now aware of the complex issues surrounding osteoporosis and the risk factors for osteoporotic fractures. In this second article, we will discuss pharmacological and nutritional therapies for treating the disease.

Integrative Approaches for Prescriptions and Supplements

Once the need for intervention has been decided, what should a physician recommend?

Pharmacological Therapies

Pharmacological therapy is the standard of care for conventional approaches to osteoporosis treatment. Antiresorptive pharmacological medications, such as alendronate (Fosamax), risedronate (Actonel), raloxifene (Evista), and parathyroid hormone minimally improve bone mineral density (BMD). They also have been shown to effectively decrease vertebral fracture risk by 47% for alendronate,⁵⁰ 49% for risedronate,⁵¹ 30% for raloxifene,⁵² and 65% for parathyroid hormone⁵³ (see Table 5 in the conclusion of this article). However, some studies have concluded that, with antiresorptive drug therapies, BMD accounts for only 4% to 28% of the reduction in vertebral fracture risk.⁵⁴⁻⁵⁷ Thus, focusing solely on therapies that increase BMD does not maximize potential clinical benefits.

Additionally, new evidence is suggesting that treatment with bisphosphonate medications may actually increase fracture risk after approximately 7 years of use. A recent retrospective review of patients admitted to a Level 1 trauma center over a

5-year period was published in the *Journal of Orthopaedic Trauma*.⁵⁸ During that time period, 70 patients (59 women, 11 men; mean age 74.7 years) were evaluated. Twenty-five of these patients had been taking alendronate, and, of those 25, there were 19 (76%) who experienced a "transverse fracture with a unicortical break in an area of cortical hypertrophy." In contrast, only 1 patient (2%) not being treated with alendronate suffered this fracture pattern. The odds ratio of a fracture for people taking alendronate was 139.33 ($P < .0001$). The average duration of alendronate treatment was significantly greater in those with the fracture pattern compared to those without this pattern: 6.9 years versus 2.5 years, respectively ($P = .002$).

At least 2 additional retrospective analyses have come to similar conclusions. One study published in *The Journal of Bone and Joint Surgery* identified 13 women who suffered subtrochanteric fractures with minimal or no trauma over a 10-month period from May 2005 to February 2006 in 2 hospitals in Singapore.⁵⁹ Of those women, 9 had been taking alendronate for an average of 4.2 years (2.5 to 5.0 years; mean age 66.9 years), and 4 had not been taking alendronate. Interestingly, of these 13, 4 reported a BMD score that put them in the category of osteopenia rather than osteoporosis. Three others reported BMD scores that placed them in the osteoporosis category, and the rest did not report a score.

Another report of US cases is particularly condemning: The report identified 9 patients who experienced traumatic nonspinal fractures after 3 to 8 years of alendronate therapy "while performing normal daily activities such as walking, standing, or turning around."⁶⁰ These patients continued taking alendronate after their fracture, and 6 of those patients exhibited delayed fracture healing for 3 months to 2 years after the fracture.

While preliminary, these reports are alarming. There is evidence that alendronate therapy may suppress bone remodeling

to the point of increasing fracture risk in some patients. This risk may be extremely small, but no long-term prospective study has been carried out to quantify this risk. In the meantime, clinicians may consider other medication and/or a more integrative approach than monotherapy with alendronate to help decrease fracture risk in their patients.

Nutritional Therapies

One of the conceptual problems with many clinical trials of dietary supplements for BMD or fracture prevention is that they tend to study effects of only 1 or maybe 2 added nutrients. However, bone is a complex mixture of different minerals, and even minerals that are not found in the bone matrix are still required as cofactors in bone remodeling. The importance of vitamin and mineral supplements in maintaining bone health was demonstrated in a study of postmenopausal women ages 50 to 60.⁶¹ Those women who took a complex supplement containing calcium, magnesium, zinc, and vitamins D and K lost significantly less BMD than those who did not take the supplement.

Calcium and Vitamin D

Calcium and vitamin D are currently recommended for the primary prevention of osteoporosis and the primary and secondary prevention of osteoporotic fractures.

Secondary prevention of osteoporotic fracture was assessed in a trial of 5292 people aged 70 years or older (mean age, 77 years).⁶² Volunteers (85% female) were randomized to receive 1 of 4 protocols: 800 IU vitamin D₃, 1000 mg calcium carbonate, 800 IU vitamin D₃ plus 1000 mg calcium carbonate, or placebo daily for up to 62 months (median duration, 45 months). In this trial no significant difference in fracture risk was detected among the groups.

However, another study noted a 16% reduction in fracture risk ($P < .025$) over 3 years in 2532 community-dwelling residents (median age, 73 years; 59.8% female) who supplemented with 400 IU vitamin D₃ and 1000 mg calcium as calcium carbonate daily.⁶³ As well, in a randomized, open-label, 2-year sequential follow-up study of 43 healthy adult volunteers (14 men, mean age 60.6 years; 29 postmenopausal women, mean age 54.1 years), participants followed their usual diet for the first year and then were randomized to receive 500 IU vitamin D₃ and 500 mg calcium (form of calcium not reported), or no supplementation, from October to March.⁶⁴ During these winter months in which volunteers took vitamin D₃ and calcium, their lumbar BMD was 0.8% greater than in controls ($P = .04$), while no significant differences between the groups were noted for femoral-neck BMD.

Vitamin K₂

Vitamin K is a group of structurally similar, lipid-soluble, 2-methyl-1,4-naphthoquinones, which include phyloquinone (K₁), menaquinones (K₂), and menadione (K₃).⁶⁵ Plants synthesize vitamin K₁ while bacteria can produce a range of vitamin K₂ forms, including the conversion of K₁ to K₂ by bacteria in the small intestines. Vitamin K₃ is synthetic and, because of its toxicity, has been banned in by the US Food and Drug Administration for human uses. In contrast to vitamin K₃, no known toxicity exists for the vitamin K₁ and K₂ forms.

Clinicians should understand that there are primarily 2 forms of vitamin K₂, MK4 and MK7, commercially available. MK4 is a synthetic form of vitamin K₂ and the agent used in the clinical trials mentioned below. MK7 is produced by bacterial fermentation of soy, appears to have a longer half life than MK4, and can also decrease serum undercarboxylated osteocalcin (ucOC).⁶⁶ However, only MK4 has demonstrated the ability to decrease fracture risk, the clinically relevant end point in randomized, controlled clinical trials on bone health.

Taking broad-spectrum antibiotics can reduce vitamin K production in the gut by nearly 74% in people compared to those not taking these antibiotics.⁶⁷ Diets low in vitamin K also decrease the body's vitamin K concentration.⁶⁸ Additionally, in the elderly, there is a reduction in vitamin K₂ production.⁶⁹ Natto (fermented soybean) is the richest dietary source of vitamin K₂. Dairy products (milk, butter, cottage cheese, cheese) and egg yolk also provide small amounts.

It's important to note that vitamin K₁ is preferentially used by the liver as a clotting factor. Vitamin K₂ on the other hand is used preferentially in other organs, such as the brain, vasculature, breasts, and kidneys. Coagulation studies in humans using 45 mg per day of vitamin K₂ (as MK4)⁷⁰ and even up to 135 mg/day (45 mg tid) of K₂ (as MK4),⁷¹ showed no significant increase in pathologic coagulation risk. In fact, doses in rats as high as 250 mg/kg body weight did not alter the tendency for blood clot formation to occur.⁷²

Vitamin K₂ exerts a powerful influence on bone building, especially in osteoporosis, and in Japan has been accepted as an osteoporosis treatment.⁷³ It is a fat-soluble vitamin that is a coenzyme for a vitamin K-dependent carboxylase enzyme that catalyzes carboxylation of the amino acid glutamic acid, resulting in its conversion to gamma-carboxyglutamic acid (Gla). This carboxylation reaction is essential for formation of bone collagen, which allows bone to deform upon impact, for example during a fall, without fracturing. Although vitamin K-dependent gamma-carboxylation occurs only on specific glutamic acid residues in a small number of proteins, it is critical to the calcium-binding function of those proteins.

Three vitamin K-dependent proteins have been isolated in bone—osteocalcin, matrix Gla protein, and protein S. Of these, osteocalcin is a protein that is synthesized by osteoblasts and regulated by the active form of vitamin D, 1,25-(OH)₂D₃, also called calcitriol. The mineral-binding capacity of osteocalcin requires vitamin K-dependent gamma-carboxylation of 3 glutamic acid residues. Multiple randomized, double-blind, placebo-controlled clinical trials have shown significant decreases in ucOC in volunteers supplemented with 45 mg of vitamin K₂ with and without the addition of calcium and vitamin D₃ compared to controls.^{69,74-76}

A 2006 meta-analysis published in the *Archives of Internal Medicine* by Sarah Cockayne, MSc; Joy Adams, PhD; Susan Lanham-New, PhD; and colleagues, at the University of York in England, evaluated clinical trials on vitamin K₂ and fracture risk.⁷⁷ They identified 13 randomized, controlled trials of the effect of vitamin K₂ on osteoporosis. Of those, 7 had fracture risk as an end point and so were included in their meta-analysis.

They concluded that 45 mg of vitamin K₂ as menaquinone-4 (MK-4) could decrease vertebral fracture by 60%, hip fracture by 73%, and all nonvertebral fractures by 81%.

An excellent review of vitamin K₂ by Stephen Plaza, ND, and Davis Lamson, ND, was published in 2005 in the journal *Alternative Medicine Review*.⁶⁵ In this article they reviewed clinical trials using vitamin K₂ that showed increases in BMD and/or reduction in fracture risk in volunteers who had bone loss from anorexia nervosa, Parkinson's disease, biliary cirrhosis, and stroke and also in volunteers who were taking prednisone and leuprolide; in other volunteers, it increased the efficacy of bisphosphonate medications.

IMCJ also published a thorough vitamin K review, written by Lara Pizzorno and Joseph Pizzorno, ND, in the April-May 2008 issue (*IMCJ* 7.2:24-30) where they explain how vitamin K aids bone health in a number of ways, including completing the bone-building effects of vitamin D₃'s upregulation of osteoblasts' expression of osteocalcin and inhibiting the differentiation of osteoclasts.

Antioxidants

In healthy bone, free radicals are used by osteoclasts to "chisel away at older bone,"⁷⁸ which creates small holes in bone that are filled by osteoblasts with new bone. As long as this is kept in check, all is well. When the balance becomes skewed with too many free radicals (ie, an inadequate intake of antioxidants), however, osteoporosis may result. An Italian study compared the antioxidant status of 75 post-menopausal, osteoporotic women to 75 women without osteoporosis, ages 62 to 79 years, for 12 months. Compared to controls, postmenopausal women with osteoporosis had significantly lower levels of plasma vitamin A (2.37 ± 0.22 vs 2.14 ± 0.22 $\mu\text{mol/L}$, respectively), plasma vitamin C (55.5 ± 13.1 vs 30 ± 3.7 $\mu\text{mol/L}$, respectively), plasma vitamin E (62.8 ± 8.76 vs 46.7 ± 5 $\mu\text{mol/L}$, respectively), plasma uric acid (383.5 ± 63.7 vs 227.8 ± 34.6 $\mu\text{mol/L}$, respectively), plasma glutathione peroxidase (0.11 ± 0.01 vs 0.09 ± 0.01 mmol NADPH/min/ml, respectively), plasma superoxide dismutase (31.34 ± 3.1 vs 24.22 ± 3.8 U/ml, respectively), and erythrocyte superoxide dismutase (3402 ± 505.8 vs 2265 ± 314.7 U/g hemoglobin, respectively).⁴⁶ All antioxidant concentrations correlated with femoral BMD; however, significant positive correlations were noted only for vitamin A ($P < .01$), vitamin C ($P < .05$), and plasma glutathione peroxidase ($P < .05$).

Previous human studies have shown that vitamin C supplementation, especially in conjunction with calcium supplementation, and vitamin E protect against bone loss.⁷⁹⁻⁸¹ In an animal study, supplementation with N-acetylcysteine increased levels of the antioxidant glutathione.⁸² Although no randomized, controlled trial has been conducted that analyzed the effects of multi-antioxidant supplementation on bone health, it is logical to conclude that increasing the body's antioxidants may help decrease the rate of loss of BMD.

Other Micronutrients

Osteoporosis risk is increased by low intakes of calcium,^{83,84} potassium,⁸⁵ magnesium,⁸⁵ and vitamin K⁸⁶ and by low concen-

trations of vitamin D.⁸⁴ Additionally, people with low BMD have lower zinc concentrations in their bones.⁸⁷ Copper and zinc are important for bone health. Zinc is found in the bone matrix incorporated into hydroxyapatite crystal. It is also involved in stimulating osteoblastic activity while suppressing osteoclastic activity.⁸⁸ Copper, also required for bone formation, is a cofactor for the lysyl-oxidase enzyme.⁸⁸ This enzyme forms collagen and elastin cross-links from the essential amino acid lysine.⁸⁸

Strontium

Strontium, an alkaline earth metal, has been studied for its ability to increase BMD and reduce fracture risk. Strontium ranelate (SR) is a form of strontium salt from ranelic acid patented by a French company. SR is well studied and currently approved for the treatment of osteoporosis in most of Europe but is not yet approved in the United States. Animal studies have shown it to have an affinity for bone, decreasing bone resorption and increasing bone formation in rats.⁸⁹ A recent in vitro study determined that SR affects bone through induction of osteoblastogenesis.⁹⁰ Several studies have evaluated the efficacy of SR in preventing and reversing osteoporosis in experimental animals and humans.

In 2002, results were published from a phase II, 2-year, randomized, multicenter, double-blind, placebo-controlled, dose-response trial of SR for the treatment of osteoporosis (STRATOS).⁹¹ Participants in the study were 353 nonobese, post-menopausal, osteoporotic women between 45 and 78 years of age who were randomized to 1 of 4 groups (placebo, SR 0.5 g/d, SR 1.0 g/d, and SR 2.0 g/d). In addition to supplemental strontium or placebo, all patients received supplemental calcium (500 mg/d) and vitamin D (vitamin D₃, 800 IU/d) "to ensure," as the researchers said, "that patients affected by severe osteoporosis received a minimum level of active treatment." All women had at least 1 previous vertebral fracture (T4 to L5) and a lumbar T-score of -2.4 or less. The primary endpoint was lumbar BMD, and the secondary outcomes included femoral neck BMD (FN-BMD), incidence of new vertebral deformities, and biochemical markers of bone metabolism. Bone measurements were tested using dual-energy x-ray absorptiometry (DEXA) and were verified by iliac crest bone biopsies taken at months 12 and 24.

By 12 months an increase in BMD was observed in all treatment groups, with further increases at 24 months. FN-BMD also increased in the treatment groups but decreased in the placebo group. By the end of the second year of the study, the incidence of new vertebral deformities, while having increased in the placebo group, decreased in the treatment groups. However, during the second year, women receiving 0.5 g SR/day had a 0.51 (95% CI 0.31; 0.84) relative risk of experiencing a new deformity, while women taking 2 g SR/day had a higher relative risk of 0.56 (95% CI 0.35; 0.89). The overall relative risk of a new deformity over the entire 2-year period, compared to placebo, was 0.71 (95% CI 0.49; 1.02) and 0.77 (95% CI 0.54; 1.09) in the SR 0.5 g/d and SR 2.0 g/d groups, respectively. Urinary excretion of bone-resorption markers was decreased in all treatment groups, while alkaline phosphatase (an indicator of osteoblast activity) was increased. Although the fracture risk was greater in the higher treatment group (2 g SR/d) versus the lower (0.5 g SR/day), the higher SR

group experienced the greatest increases in BMD, about 3% per year. Adverse effects were mild to moderate, and the treatment was well tolerated in all treatment groups.

A second study evaluated the reduction in fracture risk in a phase III, randomized, double-blind, 3-year clinical trial utilizing 2 g SR/d or placebo in 1442 postmenopausal women (mean age approximately 69 years) with osteoporosis.⁹² All volunteers also received at lunchtime, dependent on dietary calcium intake, up to 1000 mg elemental calcium to ensure an intake of more than 1500 mg calcium daily, plus 400 to 800 IU vitamin D (form of vitamin D not specified), depending on their baseline vitamin D₂ (25-hydroxyvitamin D) status.

After 12 months, total vertebral-fracture risk decreased by 49% in the SR group compared to placebo ($P<.001$), and the SR group also had a 52% reduction of symptomatic fractures ($P=.003$). By the end of the 3-year study, BMD in the SR group increased over baseline by 12.7% at the lumbar spine, 7.2% at the femoral neck, and 8.6% at the total hip ($P<.001$ for all 3 sites). Also by study end, volunteers taking SR had a 41% lower risk of a new vertebral fracture than those in the placebo group ($P<.001$). The researchers concluded that to prevent 1 patient from suffering a vertebral fracture, 9 patients would need to be treated for 3 years with SR.

A cautionary note should be inserted about SR. Strontium has an atomic mass greater than calcium. As such it attenuates the X-rays from a DEXA scan to a greater extent than does calcium.⁹¹ Unless the radiologist corrects for this, the DEXA scan will not provide an accurate measure of BMD.⁹¹ Additionally, the form of strontium used in clinical trials (strontium ranelate) is not available in the United States. The form available in dietary supplements in the US is strontium citrate. Although the strontium citrate form may be effective at improving BMD and decreasing fracture risk, clinical trials have not been performed on strontium citrate to demonstrate its safety and efficacy.

Conclusion

Osteoporosis is a major and growing health risk. To identify and minimize risk for fragility fractures, clinicians need to move beyond simply evaluating BMD. A more holistic approach to evaluating risk is an important adjunct to BMD and may lead to earlier treatment and improved clinical outcomes. Lifestyle and dietary counseling are important aspects in any treatment plan to mitigate modifiable risk factors. Medications and dietary supplements may be helpful in preventing fractures (see Table 5).

Table 5. Reduction in Risk of Fracture

Drug/dietary supplement	Percent risk reduction and site
Alendronate (Fosamax) 10 mg ⁵⁰	47%, all vertebrae
Risedronate (Actonel) 5 mg ⁵¹	49%, all vertebrae
Raloxifene (Evista) 60 mg ⁵²	30%, all vertebrae
Parathyroid hormone 20-40 µg ⁵³	65-69%, respectively, all vertebrae
Strontium ranelate 500-2000 mg ⁹²	41-49%, respectively, all vertebrae
Vitamin K2 (as MK4) 45 mg ⁷⁷	60%, all vertebrae, 73%, hip, 81% all nonvertebral fractures

As baby boomers age, the healthcare system will likely be overwhelmed by the financial and medical burden of treating osteoporotic fractures and the disability they create. Aggressive treatment approaches that distinguish BMD from fracture risk and so identify and prevent fractures before they occur should be considered and implemented in clinics, by insurance companies, and as a matter of public policy.

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