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To Prevent Fractures, Consider Bone Flexibility Not Just Mineral Density

By John Neustadt, ND / Contributing Writer - Vol. 12, No. 1. Spring, 2011

Bone mineral density is just one part of the physiological equation that adds up to bone health. Bone flexibility, a reflection of the collagen content in a person's bone, is equally important but usually overlooked.

Fracture prevention efforts have been focused almost exclusively on BMD, and on drugs and/or supplements that increase it. But physiology is seldom as simplistic as our medical thinking, and the myopic focus on mineral density leaves out other important factors that--were they included--would greatly improve our ability to prevent fractures.

It's akin to the single-minded focus on cholesterol reduction for heart disease prevention. It took decades for the medical community to acknowledge that elevated lipids were only part of a pathologic picture that also includes chronic inflammation, calcification and abnormal glucose metabolism.

The key point is that dense bones are not necessarily more fracture-proof than less dense bones. Think of a piece of chalk: it has very high calcium density, but that won't prevent breakage when you drop it on the floor!

Mineral density is certainly important but only if the mineral content is well-supported by a strong, supple collagen matrix. The collagen in bone is what gives it the springiness to absorb shock and stress, and prevent fracture. Like BMD, collagen quality and quantity also decline with age. Our prevention interventions will be more effective if they also include nutrients like vitamin K that improve bone flexibility.

Beyond BMD

BMD may be convenient and easy to measure, but it is not particularly predictive of fractures, which is the outcome our patients care about.

Half of all hip fractures occur in women who are not osteoporotic based on BMD (Robbins JA, et al. Osteoporos Int. 2005;16(2):149-154). This corroborates a metanalysis published back in 1996 showing that BMD accounts for less than half the total cumulative risk of hip fractures (Marshall D, et al. BMJ. 1996;312(7041):1254-1259).

In a systematic review sponsored by the American College of Physicians in 2008, the authors estimated that lumbar and hip BMD only predict, at best, 44% of fractures in elderly women, and 21% of fractures in men (Liu H, et al. Ann Intern Med. 2008;148(9):685-701; Schuit SC, et al. Bone. 2004;34:195-202)).

The North American Menopause Society concluded in a 2006 position paper that fracture risk, "depends largely on factors other than BMD (Menopause. May-Jun 2006;13(3):340-367). Yet most physicians seldom look beyond BMD. It's high time we shift our focus and start looking seriously at the other

physiological factors that determine bone quality and fracture susceptibility.

Homocysteine Predicts Risk

There's evidence that homocysteine, a marker of systemic inflammation and a predictor of heart disease, is also an independent risk factor for hip fractures. In 2004, McLean published data from 825 men and 1,174 women, aged 59-91 years. Age-adjusted incidence of hip fractures was much higher among people in the highest versus lowest homocysteine quartiles.

Those in the lowest quartile (mean serum level of 7.6 µmol/L) had an incidence of 1.96 fractures per 1,000; those in the highest quartile (18.6 µmol/L) had 16.6 fractures per 1,000. There was a progressive rise across intermediate quartiles.

The authors also found a distinct gender difference, with males at particularly high risk. Odds of hip fracture were almost four times higher in the highest versus lowest homocysteine quartiles among men; for women, the risk differential was a factor of 1.9 from lowest to highest homocysteine levels(McLean RR, et al. N Engl J Med. 2004 May 13; 350(20): 2042-9).

Homocysteine elevations are easy to correct via nutritional interventions to raise B vitamin levels. McLean's group showed that bone loss and fracture risk were both inversely associated with serum B6 levels. They note however that the associations were attenuated after controlling for baseline BMD, serum vitamin D, and homocysteine.

People with high homocysteine (over 14 µmol/lL) had a 70% higher hip fracture risk after adjusting for folate and vitamin B6, but this association was also attenuated after controlling for vitamin B12 (McLean RR, et al. J Clin Endocrinol Metab. 2008 Jun;93(6):2206-12). The relationship between B vitamins, vitamin D, minerals and bone metabolism are complex, but worth careful assessment.
Osteocalcin: A Useful Marker?

Osteocalcin is a bone-specific protein synthesized by osteoblasts that plays an important role in binding hydroxyapatite in bone matrix. Osteocalcin contains three glutamic acid components, which must be carboxylated for the protein to function properly. Vitamin K is necessary for this process, and under-carboxylation of osteocalcin is an independent risk factor for fractures.

Elevated levels of under-carboxylated osteocalcin (uOC) correlate with increased prevalence of osteoporosis and hip fracture risk (Vergnaud P, et al. The EPIDOS Study. J Clin Endocrinol Metab. 1997;82(3):719-724). The correlation between uOC and hip fracture was independent of femoral neck BMD.

Several studies show that high serum uOC can be corrected by giving vitamin K2 at a dose of 45 mg/d (Yasui T, et al. Gynecol Endocrinol. 2006; 22(8): 455-59; Takahashi M, et al. Clin Endocrinol. 2001;54(2):219–224). The uOC assay is a simple blood test, well worth considering for at-risk patients.

Vitamin K: A Key to Bone Health

Vitamin K is one of the most potentially valuable but underutilized tools to improve bone health and reduce fracture risk.

The term "vitamin K" is a catch-all for several structurally related, lipid soluble compounds that includes phylloquinone (vitamin K1), the menaquinones (K2), and menadione (K3). For clinical purposes, only the first two are important; menadione is toxic and banned for human use. Vitamins K1 and K2 (which actually comes in two forms, MK4 and MK7) are naturally occurring, completely non-toxic and quite important for bone health.

Phylloquinone (K1) is present in leafy green vegetables, some fruits and grains, and dairy (see Food Sources of Vitamin K). In humans, gut bacteria produce vitamin K2 and also convert some dietary K1 into

K2 forms. K2 is also found in certain foods, most particularly natto, a sticky Japanese staple made from fermented soy. K2 has more impact on bone, while K1 is preferentially used by the liver as a coagulation factor.

Vitamin K intake correlates inversely with osteoporosis (Vermeer C, et al. Ann Rev Nutr. 1995; 15:1-22). Endogenous vitamin K production and dietary consumption tend to decline with age, and production of both K1 and K2 can be compromised by commonly used drugs, including broad-spectrum antibiotics (see Are We Inducing Osteoporosis?).

An observational study of 888 elderly people (335 men, 553 women) from the Framingham Heart Study showed an inverse correlation between phylloquinone (K1) consumption and fracture risk over a 7-year period. There was a 65% reduction in hip fracture risk among people in the highest (254 mcg/d) quartile versus the lowest (56 mcg/d) vitamin K quartiles. This risk reduction was independent of BMD (Booth SL, et al. Am J Clin Nutr. 2000; 71(5):1201-1208).

Bearing in mind the limitations of any observational study, this one underscores the importance of dietary vitamin K1 on overall bone strength. But because amounts of K found in food sources will vary significantly, diet alone is unlikely to provide sufficient quantities to stabilize bone in at-risk elderly people.

Clinical Trials of Vitamin K2

Menaquinone (K2) is particularly important in collagen formation; it is the main cofactor in carboxylation of osteocalcin. The menaquinone-4 (MK4) form of vitamin K2 has been the subject of numerous studies. A 2006 metanalysis of 13 trials showed robust risk reduction. At a dose of 45 mg per day, MK4 reduced vertebral fracture risk by 60%, hip fracture risk by 73%, and non-vertebral fractures by 81% (Cockayne S, et al. Arch Intern Med. 2006; 166(12):1256-61).

Japanese physicians have been ahead of the curve on clinical use of MK4. In one trial, 241 older women (mean age 67 years) who already had osteoporosis were randomized to 150 mg calcium per day alone, or calcium plus 45 mg of MK4. After two years, 30.3% of the women in the calcium monotherapy group had vertebral fractures versus only 11% of those who also got MK4 (Shiraki M, et al. J Bone Min Res. 2000; 15(3): 515-522).

Another study involved 200 ambulatory elderly Japanese women (mean age 78 years), randomized to no treatment or to a combination of 45 mg/d MK4, 1,000 IU/d ergocalciferol (vitamin D), and 600 mg/d calcium. After 2 years, 22% of the untreated women had fractures (15 hip, 2 distal forearm, 2 proximal femur, 1 each at proximal humerous, ribs and pelvis). In contrast, only 3% of those receiving the supplements had fractures (2 hip, 1 proximal femur). Interestingly, there were no significant difference in number of falls (Sato Y, et al. Bone. 2005; 36(1):61-68).

MK4 at a dose of 45 mg has been approved for treatment of osteoporosis by the Ministry of Health in Japan since 1995.

Vitamin K1 and K2 are both very safe. There is no established Tolerable Upper Limit, and human coagulation studies using up to 135 mg/day MK4 showed no increase in pathologic coagulation risk. The only caveat is that people on warfarin need to be careful, as vitamin K can block the action of this drug.

Many vitamin K supplements in the US market contain only the MK7 form of the vitamin. It is important to keep in mind that this form has never been shown to decrease fracture incidence in any clinical trial, and one cannot assume that the positive findings for MK4 can be generalized to MK7.

Strontium Gives Strength

Widely used in Europe but much less so in the US, strontium reduce fracture risk. Strontium ranelate (SR), the most studied form, induces osteoblastogenesis, and has been shown to prevent and to reverse osteoporosis.

In a 3-year, phase III trial, 1,442 post-menopausal women with osteoporosis were randomized to placebo or SR at a dose of 2.0 g/d. All were also taking up to 1,000 mg/d calcium, and 400-800 IU/d vitamin D, depending on baseline levels.

After 12 months, total vertebral fracture risk was reduced by 49% among the SR-treated women, who also had a 52% reduction in symptomatic factures. By the end of the 3rd year, vertebral fracture risk was reduced by 41%, and there were significant BMD increases at lumbar, femoral neck and hip sites (Meunier PJ, et al. N Engl J Med. 2004; 350(5): 459-468). To prevent one vertebral fracture, 9 patients would need to take SR for 9 years.

There are no major safety issues with SR, but because strontium has a higher atomic mass than calcium, it can alter DEXA scans. Radiologists can correct for this if they know someone is taking strontium, but it is essential to inform the radiologist about this.

SR is a standard osteoporosis treatment in most of Europe. Unfortunately, it is not widely available in the US. Strontium citrate is the most common form on the American market. It might be effective in improving bone health, but it has not been studied sufficiently to state confidently that it is equivalent to SR.

The bottom line is, we need to do a better job of preventing osteoporotic fractures. Unless we start doing things differently, our health care system will have to manage an estimated 3 million fractures each year by 2025, at a cost of $25.3 billion (Burge R, et al. J Bone Miner Res. 2007;22(3):465-75).

By applying what we know about strengthening collagen and utilizing all safe, and scientifically sound nutritional interventions, I believe we can significantly reduce the burden of suffering and the economic costs of osteoporotic fractures.

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