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Osteoporosis and vitamin K intake[1,2]

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Osteoporosis is a metabolic bone disease characterized by a defect in bone remodeling and the loss of normally mineralized bone. Maximum skeletal mass is achieved in young adults at 18–25 y of age. After age 40 y, the slow phase of bone loss begins in both sexes and continues at a rate of 0.5–1%/y until late in life. In women after menopause, there is an additional rate of bone loss of ≈2–3%/y because of the decreasing estrogen concentrations associated with aging. Osteoporosis is responsible for 1.2 million fractures in the United States annually. The most common fractures are of the vertebrae, distal radius, and hip (1).

The underlying cause of fractures in osteoporosis is bone fragility, which is caused by a reduction in bone density. Fracture risk is determined by absolute mineral bone density (BMD), regardless of age. In the absence of severe trauma, fractures do not occur until BMD has fallen below the fracture threshold of 1 g/cm^2, well below the top peak bone density of 1.4 g/cm^2 in healthy, young adults (2). Further decreases in BMD below the fracture threshold will increase the risk of fracture.

Bone remodeling is the result of the opposing actions of 2 cell types in bone. The process of remodeling begins with the attraction of osteoclasts to an area of microdamage. These osteoclasts remove a finite amount of bone and, after resorption is complete, undergo apoptosis. Osteoblasts are then recruited to the excavation site and synthesize new bone to replace that which was resorbed. Osteoporosis results from an imbalance in the remodeling process that is due to the failure of osteoblasts to repair the bone removed by the osteoclasts (3).

A model for the pathogenesis of osteoporosis has been proposed (2), which is illustrated in **Figure 1**. In this model, the many factors that contribute to low BMD and ultimately to fractures are listed. Inadequate peak BMD in young adulthood is a major contributor to later disease and may be caused by a combination of genetic and nutritional factors. In addition to total energy intake, the nutrients that promote bone synthesis include calcium, vitamin C, vitamin D, and vitamin K. Genes for collagen type 2, 25-hydroxyvitamin D-1α hydroxylase, vitamin D hormone receptor, estrogen receptor, transforming growth factor β, and interleukin 6 are critical for normal bone metabolism (4). Polymorphisms in these genes result in reduced bone density in animals and humans. The sporadic factors that contribute to osteoporosis in individuals include smoking, alcohol intake, physical inactivity, underweight, apolipoprotein (apo) *ϵ4* genotype, and the use of anticonvulsant and anticoagulant drugs. Disorders that exacerbate osteoporosis include Cushing disease, hyperthyroidism, hyperparathyroidism, hypogonadism, and malabsorption.

Vitamin K is required for the γ-carboxylation of glutamate in 2 proteins induced by vitamin D hormone in bone (5). Osteocalcin is a 49-residue protein with 3 carboxyglutamic acid (Gla) residues that is water soluble, adheres to the bone mineral hydroxyapatite, and is secreted by osteoblasts. Matrix Gla protein is a 79-residue protein with 5 Gla residues that is hydrophobic, insoluble in plasma, and associated with the matrix of cartilage and bone.

The level of osteocalcin carboxylation has been proposed as an indicator of the nutritional state of bone with respect to vitamin K (6). In 1989 Knapen et al (7) found that osteocalcin was undercarboxylated by 40% in postmenopausal women when compared with premenopausal women. The postmenopausal women responded to phylloquinone supplementation with an increase in total and carboxylated osteocalcin and a decrease in urinary calcium and hydroxyproline. Szulc et al (8, 9) subsequently found that the incidence of hip fractures in aged women correlated directly with the increase in undercarboxylated osteocalcin and that BMD correlated negatively with the rise in undercarboxylated osteocalcin. In 1997 Shiraki et al (10) found that postmenopausal women with the apo E4 phenotype had a lower BMD than did those with the apo E2 or E3 phenotype. In addition, lower vitamin K concentrations were found in patients with the apo E4 phenotype who had renal failure and were undergoing hemodialysis (11).

In this issue of the Journal, an epidemiologic study of a cohort of elderly men and women from the Framingham Study showed an association of vitamin K intake with the incidence of hip fractures (12). However, no association of vitamin K intake or apo *ϵ* genotype with BMD was found. It was not possible to evaluate the vitamin K status of this cohort accurately from the data obtained from the food-frequency questionnaire because these data clearly overestimated their vitamin K intake (13) and because no plasma concentrations of phylloquinone and undercarboxylated osteocalcin were available. The mean BMD in this study was 0.82 g/cm^2 in men and 0.62 g/cm^2 in women, both well below the fracture threshold. Of the 44 hip fractures observed, 8 occurred in men and 36 in women.

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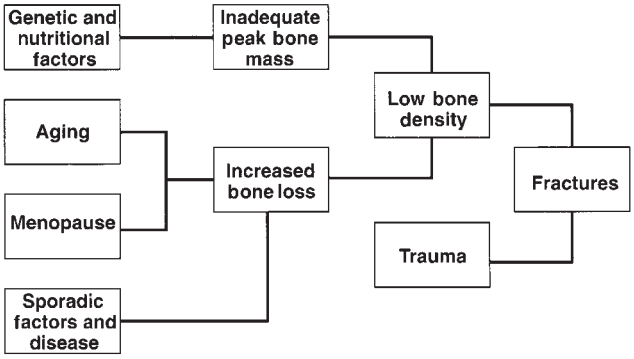

FIGURE 1. Model for pathogenesis of osteoporosis. The major cause of fractures in osteoporosis is a decrease in absolute bone mineral density. Factors contributing to low bone mineral density are inadequate peak bone mass, aging, loss of estrogen at menopause, and a variety of personal factors. Adapted from reference 2.

The lack of a relation of BMD to apo ϵ genotype was not surprising because of conflicting data on the metabolic effects of apo *ϵ2*, *ϵ3*, and *ϵ4* genotypes on the clearance of remnant lipoproteins in humans (14, 15) and the younger age cohort studied by Shiraki et al (10). The suggestion by Booth et al (12) that the effect of vitamin K intake on hip fractures may be independent of BMD is unreasonable, not only because of other reports that indicate a relation of vitamin K to fracture incidence and BMD, but because of their own data. The relative risk (RR) of persons in the 4th quartile of phylloquinone intake corrected for most of the pertinent variables shown in Figure 1 was significantly different from that of persons in the first quartile (RR: 0.35; 95% CI: 0.13, 0.94). However, when this difference was adjusted for femoral neck BMD, it was no longer significant (RR: 0.35; 95% CI: 0.12, 1.02). Feskanich et al (16) also observed a similar relation between vitamin K intake and hip fractures in the Nurses' Health Study. Despite the limitations of these epidemiologic studies, they support a role for vitamin K in the retardation of bone loss in elderly persons.

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