

Everyone knows fat-soluble vitamins are essential, but do you know what they do, or how they work together? Many clinicians encourage women to take vitamin D along with calcium to protect against osteoporosis, but without vitamin K, the calcium is not as effective. Additionally, low levels of vitamin K can lead to calcification in the arteries instead of the bone. Concurrent arterial calcification and osteoporosis has been called the “calcification paradox” and research finds it may be common in postmenopausal women.^{1,2} Besides vitamin D and K, vitamin A is needed for bone remodeling, and supplementation with vitamin E has been shown to improve bone calcium content. Antioxidant intake has also been associated with reduced risk of osteoporotic hip fracture and plays an equally important role in atherogenesis. Vitamin E, beta-carotene, and Coenzyme Q10 (CoQ10) all act as antioxidants. The following article reviews the roles of fat-soluble vitamins in proper calcification and as antioxidants.

Calcification is a process in which calcium builds up in body tissue, causing the calcium to harden. This can be a normal process, as in bone, or abnormal, as in atherosclerosis. Vascular calcification is frequently found in patients with a combination of osteoporosis, atherosclerosis, and chronic kidney disease. Arterial calcification is associated with decreased bone mineral density (BMD).³ The mechanism by which vitamin K may promote mineralization of bone, while inhibiting calcification of vessels, is not entirely clear.⁴ The association of bone pathologies with atherosclerosis has stimulated the search for common mediators linking the skeletal and the vascular system. The fat-soluble vitamins have been found to be essential in this process. Vitamin K has been shown to be a valuable diagnostic as well as therapeutic parameter in osteoporosis and bone fractures.^{5,6} Higher vitamin K status has been associated with lower fracture risks.⁷ The Nurses’ Health Study followed more than 72,000 women for ten years and found that those women with the lowest vitamin K intakes had a 30% higher risk of hip fracture than those with the highest intakes.⁸ In other studies, calcium loss in those with low vitamin K levels was found to be reduced by up to 50% with vitamin K supplementation.^{9,10}

Vitamin K is required for carboxylation, the addition of a carboxyl group (COO-), of glutamate residues on specific proteins. Carboxylation allows the protein to bind calcium

and function properly. If vitamin K is not in adequate supplies these proteins become undercarboxylated. The level of undercarboxylated proteins is correlated to vitamin K levels. In bone, osteocalcin (OC) is synthesized by osteoblasts and must be carboxylated to function. If OC is not completely carboxylated it is said to be undercarboxylated (ucOC), and OC is unable to adequately bind calcium. OC is also called bone Gla-protein (BGP). Undercarboxylation is believed to be a risk factor for poor bone calcification and increased vascular calcification. In atherosclerotic plaque formation, it is believed that calcification involves the participation of arterial osteoblasts and osteoclasts. In the Rotterdam study of some 5000 participants, an adequate intake of vitamin K (menaquinone) was clearly linked to lower rates of cardiovascular disease.^{11,12} A number of reports have correlated decreased bone mineral density or increased fracture rates with a five- to eight-fold increase in undercarboxylated osteocalcin (ucOC). Vascular smooth-muscle cells and arterial intima synthesize a matrix protein that undergoes a vitamin K dependent carboxylation to become matrix Gla protein (MGP). MGP requires vitamin K for optimum function, and is a protein found in numerous body tissues. One of these tissues is bone (together with the related vitamin K-dependent protein osteocalcin), as well as the heart, kidney, and lungs. In bone, MGP production is increased by vitamin D. Fully carboxylated MGP is a potent inhibitor of calcification. Inadequate vitamin K results in undercarboxylation of MGP and is a risk factor for vascular calcification.¹⁰ The carboxylation of MGP is also regulated by several other factors including retinoic acid, vitamin D, and extracellular calcium ions.¹³

Since bone-associated proteins such as osteocalcin and MGP have been detected in calcified vascular tissues, calcification is now considered to be an organized, regulated process similar to mineralization in bone tissue.¹⁴ Vitamin K supplementation has been shown to reverse arterial calcification in animal studies. While early human studies were inconsistent between dietary vitamin K intake and coronary artery calcification, they looked primarily at K1 or phylloquinone. Menaquinone, or vitamin K2, intake has been associated with a lower risk of coronary heart disease mortality.¹⁵⁻¹⁷ Research has found that average vitamin K intakes are not high enough to ensure complete carboxylation of OC or MGP.^{16,18,19} Vitamin K requirements

are currently set to ensure proper coagulation factors, with no consideration for amounts needed for normal carboxylation of OC or MGP.¹⁸

Low 25-hydroxyvitamin D levels have been correlated with the high prevalence of osteoporosis, fractures, cardiovascular disease, cardiovascular mortality and all cause mortality.²⁰⁻²⁶ Many mechanisms are thought to be responsible for vitamin D's protective role in both bone and cardiovascular health and include the:

- inhibition of vascular-smooth muscle proliferation
- suppression of vascular calcification
- down regulation of pro-inflammatory cytokines
- up regulation of anti-inflammatory cytokines
- action of vitamin D as a negative endocrine regulator of the renin-angiotensin system, a regulator of calcium absorption and homeostasis

Vitamin D receptors are also present in osteoblasts.^{27, 28}

Adequate levels of vitamin A (retinol) and vitamin E are also essential in the bone remodeling process. Osteoblasts and osteoclasts have nuclear receptors for retinoic acid. Plasma levels of beta-carotene and retinol were measured in free-living, non-supplemented elderly women with or without severe osteoporosis. Plasma levels of retinol and carotenoids were consistently lower in osteoporotic women than in control women.²⁹ Vitamin E deficiency impairs bone calcification. Supplementation with vitamin E improved bone calcium content, and tocotrienols were specifically found to play an important role.^{30, 31} Antioxidant intake, primarily from vitamin E and beta-carotene, were associated with reduced risk of osteoporotic hip fracture in elderly subjects, an effect strongly modified by smoking status.³²

Lowering oxidative stress and inflammation can also slow the atherosclerotic process. Reactive oxygen species play an important role in heart disease. In studying the oxidative and antioxidant parameters at different stages of atherosclerotic development, high levels of serum lipid peroxide (LPO) products and low retinal contents were found as the most typical sign of unstable plaques. Significant negative correlations were also found between LPO activity and levels of alpha-tocopherol, retinol, and beta-carotene in lipids and proteins at different stages of atherosclerotic focus development.³³ Low plasma concentrations of antioxidants (A, E, beta-carotene,

and CoQ10) have been associated with early carotid atherosclerotic lesions.³⁴⁻³⁶ In a case-control study to assess the association between the atherosclerosis and antioxidant status, cases showed significantly lower plasma levels of retinol, alpha-tocopherol, and all carotenoids compared with controls.³⁴

Independent of its antioxidant effect, CoQ10 is beneficial for cardiovascular disease because it is essential in mitochondrial electron transport.³⁷ The tissue with the largest, most critical energy demand of this function is the heart, which will be the first tissue to show the effects of insufficient CoQ10 levels. Plasma CoQ10 concentrations have been found to independently predict mortality in cardiac patients.³⁸ Interestingly, statin medications given to reduce the chances of cardiovascular disease lower plasma CoQ10 concentrations. CoQ10 may also influence vascular function indirectly via inhibition of oxidative damage to low-density lipoprotein (LDL).

The proper process of calcification in bone formation and related metabolic processes requires an adequate and constant supply of essential nutrients, including vitamin D, A, K, E and beta-carotene, along with calcium, protein, magnesium, phosphorus, potassium, fluoride, manganese, copper, boron, iron, zinc, vitamin C, and the B vitamins. However, you can not assume that just because a patient is supplementing or that if one fat-soluble vitamin level is adequate then all of these nutrient levels are adequate. It's a balance. Research has found a high prevalence of lipid-soluble vitamin values outside their physiological range in normal healthy populations, highlighting the need to evaluate fat-soluble vitamins as a basic tool in clinical practice. Don't let your patients function on their lowest common denominator.

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