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Vitamins D and K as pleiotropic nutrients: clinical importance to the skeletal and cardiovascular systems and preliminary evidence for synergy

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Abstract

Vitamins D and K are lipid-phase nutrients that are pleiotropic - endowed with versatile homeostatic capacities at the organ, tissue, and cellular levels. Their metabolic and physiologic roles overlap considerably, as evidenced in the bone and cardiovascular systems. Vitamin D_3 (cholecalciferol, D_3) is the prehormone for the vitamin D endocrine system. Vitamin D_3 undergoes initial enzymatic conversion to 25-hydroxyvitamin D (25D, calcidiol), then to the seco-steroid hormone 1alpha, 25-dihydroxyvitamin D (1,25D, calcitriol). Beyond its endocrine roles in calcium homeostasis, 1,25D likely has autocrine, paracrine, and intracrine effects. At least 17 tissues likely synthesize 1,25D, and 35 carry the vitamin D receptor (VDR). Vitamin D functional deficiency is widespread in human populations. Vitamin K_1 (phylloquinone) is more abundant in foods but less bioactive than the vitamin K_2 menaquinones (especially MK-4, menatetrenone). Menadione (vitamin K_3) has minimal K activity. Vitamin K compounds undergo oxidation-reduction cycling within the endoplasmic reticulum membrane, donating electrons to activate specific proteins via enzymatic gamma-carboxylation of glutamate groups before being enzymatically re-reduced. Warfarin inhibits this vitamin K reduction, necessitating K supplementation during anticoagulation therapy. Along with coagulation factors (II, VII, IX, X, and prothrombin), protein C and protein S, osteocalcin (OC), matrix Gla protein (MGP), periostin, Gas6, and other vitamin K-dependent (VKD) proteins support calcium homeostasis, facilitate bone mineralization, inhibit vessel wall calcification, support endothelial integrity, are involved in cell growth control and tissue renewal, and have numerous other effects. This review updates vitamin D and K skeletal and cardiovascular benefits and evidence for their synergy of action.

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