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Review article

Pleiotropic actions of vitamin K: protector of bone health and beyond?

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Abstract Vitamin K is a nutrient that was originally identified as an essential factor for blood coagulation. Recently, vitamin K has emerged as a potential protector against osteoporosis, atherosclerosis, and hepatocarcinoma. Accumulated evidence indicates that subclinical non-hemostatic vitamin K deficiency in extrahepatic tissues, particularly in bone and possibly in vasculature, exists widely in the otherwise healthy adult population. Vitamins K1 and K2 have been shown to exert protective effects against osteoporosis, although it is important that the beneficial effects will be further confirmed by large-scale, randomized, clinical trials. Increasing evidence implicates a role for vitamin K in calcification of arteries and atherogenesis. Moreover, the therapeutic potential of vitamin K2 as an antihepatoma drug has recently been highlighted. Most of the new biological functions of vitamin K in bone, vasculature, and hepatoma cells are considered attributable to promotion of γ-carboxylation of glutamic acid residues in vitamin K–dependent proteins, which is shared by vitamins K1 and K2. In contrast, vitamin K2–specific, γ-carboxylation–unrelated functions have also been demonstrated. Thus, biological differences between vitamins K1 and K2 and potential involvement of γ-carboxylation–independent actions in the new roles of vitamin K remain open issues. Molecular bases of coagulation-unrelated pleiotropic actions of vitamin K and its implications in human health deserve further investigations.

Keywords: Menaquinone; Phylloquinone; Subclinical vitamin K deficiency; Undercarboxylated osteocalcin; Osteoporosis; Hepatocellular carcinoma; Atherosclerosis

Introduction

Vitamin K was originally identified as a fat-soluble nutrient required for coagulation and then discovered to be an essential cofactor for post-translational modification of glutamic acid (Glu) residues to γ-carboxyglutamic acid (Gla) residues of vitamin K–dependent hepatic blood-coagulating proteins including prothrombin and factors II, VII, IX, and X [1]. Hence, vitamin K deficiency results in a bleeding tendency due to malfunction of vitamin K–dependent clotting factors. In particular, neonates are susceptible to vitamin K–deficiency bleeding, and therefore prophylactic vitamin K supplementation has been successfully employed in neonates [2,3]. Recommended dietary intake of vitamin K has been determined based on γ-carboxylation status of coagulation factors.

Recently, however, coagulation-unrelated functions of vitamin K have attracted scientific attention [4–6]. These pleiotropic actions of vitamin K include potential protective effects against osteoporosis, hepatocarcinoma, and atherosclerosis. In contrast to newborn babies, in the absence of aggravating factors such as chronic gastrointestinal disorders or parental feeding in critically ill patients, vitamin K deficiency in terms of blood coagulation, referred to as "classic (clinical)" vitamin K deficiency, is rare. Nonetheless, a growing body of evidence indicates that "subclinical" vitamin K deficiency in extrahepatic tissues, particularly in

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Table 1
Vitamin K Deficiency

	Classic (clinical)	Subclinical
γ-Carboxylation of coagulation factors	Impaired	Normal
Bleeding tendency	(+)	(−)
Marker	Blood clotting factors (e.g., prothrombin time)	Undercarboxylated osteocalcin
Infants	Relatively common	Unknown
Adults	Rare	Relatively common
Vitamin K target tissue	Liver	Bone (possibly vasculature, hepatoma cells)
Actions (roles) of K_1 versus K_2	Quite similar	Different (?)
Mechanisms of vitamin K action	γ-Carboxylation dependent	γ-Carboxylation dependent and independent (?)
Category of vitamin K function	Classic	Pleiotropic actions

bone, is not uncommon in the adult population. Classic (clinical) vitamin K deficiency causes hemorrhage. In contrast, subclinical vitamin K deficiency is related to pleiotropic actions in bone, possibly in the vasculature, and locally in hepatoma cells. It has been proposed to contribute to osteoporosis, aortic calcification, atherosclerosis, and hepatoma development (Table 1).

Vitamin K exists in two forms in nature: vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). Vitamin K1 is produced by plants and algae and is widely distributed in green and leafy vegetables; vitamin K2 is of microbial origin and is contained in meats, eggs, curd, cheese, and fermented soybeans. Menaquinones comprise a family of molecules distinguished from phylloquinone by unsaturated side chains of isoprenoid units varying in length from 1 to 14 repeats (Fig. 1). With regard to hemostasis, actions of vitamins K1 and K2 have been considered quite similar or essentially the same. In contrast, several lines of evidence suggest that vitamins K1 and K2 may also have distinct roles in the pleiotropic actions. Vitamin K2 may also have γ-carboxylation–independent functions. In this review, we provide an overview of recent studies on the emerging new roles for vitamin K in bone, vasculature, and hepatoma cells and attempt to clarify questions to be answered for future research.

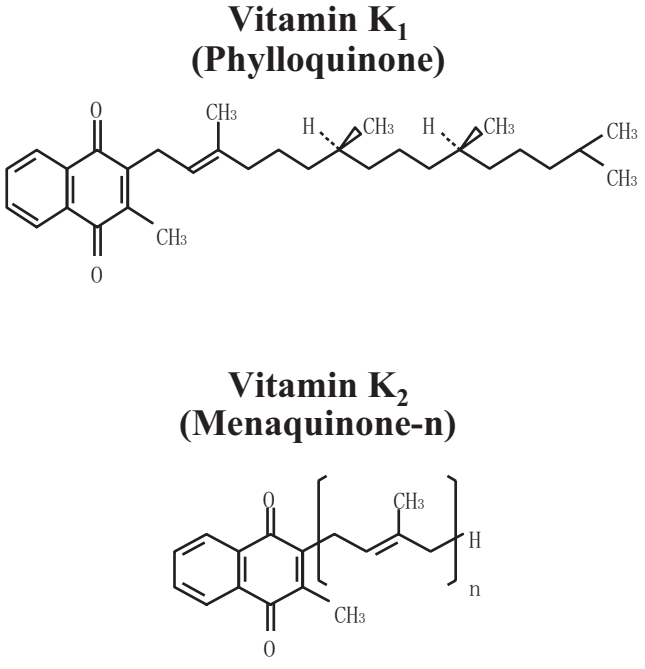

Fig. 1. Chemical structure of vitamins K1 and K2.

Subclinical vitamin K deficiency in bone

Among vitamin K–dependent proteins in bone, osteocalcin (OC, also termed bone Gla protein), matrix Gla protein (MGP), and protein S, γ-carboxylation of OC has been extensively studied. In healthy adults, a very small portion of blood clotting factors is undercarboxylated. In contrast, a substantial portion of circulating OC is undercarboxylated [7,8]. Thus, circulating undercarboxylated OC (ucOC) is a more sensitive measurement of vitamin K status than are the conventional blood coagulation tests [9].

The cutoff value of ucOC for subclinical vitamin K deficiency has not been established, although Shiraki et al. [10] proposed an ucOC level of 4.0 ng/mL. They found that postmenopausal women with a serum ucOC level ≥4.0 ng/mL displayed lower serum vitamin K concentrations, higher bone resorption markers, deoxypyridinoline, and increased vertebral fracture incidence. To facilitate the discussion on the guideline of subclinical vitamin K deficiency, however, ucOC values measured by distinct assay systems will need to be standardized, because there are substantial variations in ucOC values among immunoassays.

A pathogenic role for ucOC in osteoporosis is poorly understood. OC knockout mice exhibited increased bone formation and resistance to ovariectomy-induced bone loss [11], suggesting that, although OC seems to be a regulator of bone formation, decreased function of OC due to impaired γ-carboxylation may not be necessarily associated with osteopenia. In contrast, MGP knockout mice displayed short stature, osteopenia and fractures, and accelerated calcification of arteries and cartilage [12]. These findings sug-