Vitamin K

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Vitamin K has been recognized as a key factor for the synthesis of blood clotting factors in the liver, and is currently known to be involved in a wide range of biological processes and is associated with many pathological conditions.The most well-known function of vitamin K is as a cofactor for the γ-glutamyl carboxylase (GGCX) enzyme responsible for the post-translational modification of vitamin K-dependent proteins (VKDPs) through the conversion of specific glutamic acid (Glu) into calcium binding γ-carboxyglutamic acid (Gla) residues. Vitamin K deficiency has been linked to several pathological conditions such as cardiovascular diseases (CVD), chronic kidney disease (CKD), osteoarthritis (OA) , rheumatoid arthritis (RA), osteoporosis, cancer, dementia, certain skin pathologies, functional decline, and disability. A new concept on the involvement of vitamin K in *inflammation* is growing. In fact, novel roles have been disclosed for vitamin K independent of its activity as a cofactor for GGCX, such as an antioxidant, anti-inflammatory, promoter of cognition, inhibition of tumor progression, and transcriptional regulator of osteoblastic genes. A growing number of studies has raised an increasing interest on the use of vitamin K as a health promoting supplement. Aging societies represent a major economic challenge for health care systems, and diet supplements promoting healthy aging and improving the prognosis of age-related diseases, are required to be implemented in clinical practice.This work thoroughly reviews available data regarding differences between vitamin K1 and K2, contextualized with clinical aspects of vitamin K deficiency, including their sources, functions, target activity, and involvement in age-related diseases. Processes for the chemical and biological production of vitamin K1 and K2 will be briefly addressed. Additionally, novel sources with potential biotechnological application, and new formulations to improve vitamin K absorption and bioavailability are presented.

vitamin K | diet supplement | age-related diseases | vitamin K-dependent proteins | pathological calcification | inflammation

1. Introduction

Vitamin K health benefits have been recently widely shown to extend beyond blood homeostasis and implicated in chronic low-grade inflammatory diseases such as cardiovascular disease (CVD), osteoarthritis, dementia, cognitive impairment, mobility disability, and frailty [1]. Novel and more efficient nutritional and therapeutic options are urgently needed to lower the burden and the associated health care costs of these age-related diseases. Naturally occurring vitamin K comprise the phylloquinone (vitamin K1), and a series of menaquinones broadly designated as vitamin K2 that differ in source, absorption rates, tissue distribution, bioavailability, and target activity [2][3][4]. Both forms share a 2-methyl-1,4-naphtoquinone double ring structure in their chemical backbone but differ in their

lipophilic side chain. While vitamin K1 has a phytyl substituted chain, vitamin K2 contains unsaturated isoprenyl side chains, designated as MK-4 through to MK-13, depending on its length[3] [4]. Although vitamin K1 and K2 sources are mainly dietary, consumer preference for diet supplements is growing, especially when derived from marine resources. The aim of this review is to update the reader regarding the specific contribution and effect of each K1 and K2 vitamers in human health, identify potential methods for its sustainable and cost-efficient production, and novel natural sources of vitamin K and formulations to improve absorption and bioavailability. This new information will contribute to foster the use of vitamin K as a health-promoting supplement, which meets the increasing consumer demand. Simultaneously, relevant information on the clinical context and direct health consequences of vitamin K deficiency focusing in aging and age-related diseases will be discussed.

2. Role of Vitamin K

Overall, the concept of multifunctional vitamins associated with vitamin K has been growing in recent decades with evidence showing its involvement in a wide range of biological functions with a pivotal role in several highly prevalent low-grade inflammatory diseases. Several age-related diseases such as skeletal and CVD, Alzheimer's disease, and dementia are becoming a major social and economic burden in our aging society. Compelling clinical evidence combined with a strong scientific biological rational clearly support a beneficial health effect of vitamin K and has led to an increased procurement of vitamin K as a health promoting supplement [1]. Interestingly, some scientific evidence from in vitro and in vivo models, as well as from clinical studies, suggests a synergistic effect of vitamin K combined with vitamin D, with beneficial effects of joint supplementation at optimal concentrations of both vitamins, particularly for bone health [5][6]. However, although the benefits of vitamin D in bone health are well established, high levels of vitamin D might promote hypercalcemia and soft tissue calcification with consequent detrimental effects on the cardiovascular system[7]. While additional studies are required to establish the optimal concentration of a combined supplementation with vitamins K and D, high levels of K1, MK4, or MK7 have no documented toxicity or adverse health effect. No hypercoagulable state was observed in individuals consuming doses above the recommended daily allowance of 75 micrograms vitamin K (Commission Directive 2008/100/EC) [8]. Additional specific cases of extremely high levels of vitamin K intake have also been reported without adverse effects [9][10]. However, the current and increasing knowledge on the different types of vitamin K vitamers and their specific biological activity imply a clearer differentiation between the potential health effect and target specificity for each vitamer. It is well accepted that both K1 and K2 can play an important role in the pathogenesis and progression of many diseases. Nevertheless, the K2 vitamer (MK-7) has been shown to have advantages given its superior bioavailability and higher half-life in circulation when compared with other K vitamers [11][12][13]. In addition, the vast majority of available clinical studies are still related to the effects of vitamin K1 in health, while K2 has been shown to have a prevalent function in extra-hepatic tissues with a protective role in the vascular system reducing the risk of CVD, mitigating cognitive diseases, and suppressing inflammation [1]. Although both vitamin K1 and K2 are commercially available, optimized production methods and more efficient formulations for each vitamer are needed to meet the increasing customer requirements at affordable prices. Additionally, marine diet supplements and functional products are already well represented in the global market and the exploitation of new

aquatic-derived sources for vitamin K should represent a benefit for human health with a potential economic and environmental interest.

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