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Chapter

Physiological and Cellular Functions of Vitamin K on Cardiovascular Function

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Abstract

This chapter reviews the physiological and cellular functions of vitamin K in the cardiovascular system based on the latest pre-clinical and clinical evidence. Vitamin K belongs to a family of structurally similar fat-soluble vitamins, actively required by the body for the synthesis of essential proteins as well as regulate blood clotting, bone metabolism and calcium level. The authors emphasize the quintessential association between dietary vitamin K2 and cardiovascular diseases shown in various studies. The association, through the vitamin K - dependent hormones, plays a primary role in regulating calcification of different cell types, especially their role in calcification of the vascular endothelial cells. The consequences of vitamin K deficiency in the vascular system are unfavorable, shown in various clinical studies on statins - well-known inhibitors of vitamin K production in the body. New clinical insights suggest that vitamin K levels in the body and its dietary supplementation play a crucial role in cardiovascular disease prevention. There is negative influence of these antagonist's pate in vascular composition and functions. Therefore, there is a need for prospective studies to make more in-depth exploration and increase the current understanding of this critical relationship to confidently apply such knowledge to prevent cardiovascular diseases and improve their outcomes.

Keywords: Vitamin K, hormone, heart, cardiac disease, vascular system, gene expression, statin

1. Introduction

Vitamin K applies to fat-soluble vitamins, which are similar in structure and essential in the blood coagulation process and to control the calcium mineral binding in bones and other tissues. The discovery of vitamin K can be attributed to the observations of a high incidence of bleeding in chickens on a low-lipid diet during the 1930s [1]. Until the 1970s, it was believed that vitamin K was essential exclusively for homeostasis, maintaining an adequate blood supply, and preserving vascular

integrity in animals and humans. Today, we know that vitamin K is involved in gamma-carboxylation as a co-factor in several essential proteins located within the bone, heart, and blood vessels. Moreover, only in the presence of vitamin K, specific essential proteins called vitamin K-dependent proteins (VKDPs) are able to switch from inactive uncarboxylated forms to active carboxylated forms. Vitamin K allows switching VKDPs to their active states by the carboxylation of VKDPs glutamic acid (Glu) residues in specific tissues and organs [2]. VKDPs include seven proteins involved in blood coagulation (coagulation factor II, VII, IX, and X, and anticoagulant proteins C, S, and Z); proteins responsible for bone mineralization (osteocalcin (OC) and matrix gamma-carboxyglutamic acid (Gla)-protein (MGP)); and recently discovered proteins, including growth arrest-specific gene 6 (Gas-6), the transmembrane Gla proteins (TMG3 and TMG4), the proline-rich Gla proteins (PRGP1 and PRGP2), the Gla-rich protein (GRP), periostin and transthyretin [3–7]. In nature, there are two main variants of vitamin K: phyloquinone (or vitamin K1) can be found in some green vegetables, and menaquinone (or vitamin K2) can be found in some meat, fermented milk, and fermented soybean products. Structurally, vitamins differ in their degree of saturation and side-chain lengths; vitamin K2 is more biologically active than vitamin K1 and circulates longer in the body [8]. Cardiovascular diseases (CVDs) comprise a group of disorders affecting the heart and blood vessels that cause conditions such as coronary heart disease (CHD) and cerebrovascular disease, which affect the blood vessels that supply the brain [9]. In recent years, numerous physiological studies have pointed out the critical role of vitamin K as an anti-vascular calcification (VC) factor. VC is recognized as an autonomous and prominent risk factor for CVDs, and several human observational studies have shown a positive correlation between low vitamin K supplementation and VC [10, 11]. Meta-analysis studies showed that patients with regular dietary of vitamin K showed significantly less VC while maintaining vascular stiffness compared with patients with no vitamin K supplementation [12]. In this chapter, we will cover the following topics: the importance of dietary vitamin K; physiological functions of vitamin K beyond blood coagulation; vitamin K-dependent hormones; physiological and protective roles of vitamin K on cardiovascular (CV) processes; cellular and molecular mechanisms of vitamin K in the vascular cells and whether vitamin K promotes or encounters statins.

2. The importance of dietary vitamin K in CVD

Vitamin K is vital for healthy bones and the heart and increases blood clotting. Although a deficiency of vitamin K is not common, its deficiency may affect the body over time. Bleeding and weak bones, as well as higher CV risks, are some consequences of vitamin K deficiency [13, 14]. Hence, vitamin K intake must not be ignored. Usually, the daily value (DV) of 120 mcg of vitamin K is sufficient in adult males and less than this in females and children (**Table 1**) [17, 18]. Vitamin K can be in both forms in our diets, where phyloquinone can be sourced from leafy green vegetables, and menaquinone can be sourced from animal-based food that includes meats, fermented dairy, fermented soybeans, and dietary supplements [19]. Vitamin K2 is also available on the market in the form of synthetic menaquinone-4 (MK-4) and menaquinone-7 (MK-7) in natural or synthesized form. Naturally, in animals, MK-4 is more commonly produced, while MK-7 (as well as MK-5 to MK-14) is made by bacteria. Many animals can convert vitamin K1 to vitamin K2 (MK-4).

Type of product	Amount of Vitamin K2 (mcg/100 g)	% of daily value (120mcg)	Ref.
Ground beef	9.4	8	[15]
Beef liver	106	88	[15]
Beef kidney	5.7	5	[15]
Chicken	60	50	[15]
Chicken liver	13	11	[15]
Duck breast	5.5	5	[15]
Goose liver	369	308	[15]
Pork chops	69	57	[2]
Pork liver	7.8	7	[2]
Bacon	35	29	[2]
Eggs	≤1	≤1	[16]
Whole milk	9	8	[3]
Fish	≤1	≤1	[3]

Table 1.
Amount (% of daily value) of vitamin K2 in 100 g of animal products that prevent insufficiency in man.

Vascular health can be improved by ensuring the consumption of sufficient amounts of vitamin K2. Vitamin K2 stimulates MGP, which prevents calcium from depositing inside the vessel walls. When calcium is not deposited in the arteries, it offers dual benefits of clear arteries as well as the availability of calcium for various functions in the human body [20]. Presently, MGP is found to be highly effective for the modulation of arterial calcification. Although MGP binds calcium to protect calcification within blood vessels, it needs to be first activated via an adequate dose of vitamin K2 [20]. A total of 4807 healthy individuals from both genders with ages above 55 were involved in a population-based study conducted in Rotterdam. The study aimed to investigate the impact of dietary intake of vitamin K on calcification within the aorta, CVDs, and all-cause mortality [21]. It was found that the risk of calcification within the arteries and CVDs were reduced by half, while the all-cause mortality risk was reduced by one-quarter as a result of a higher dietary intake of vitamin K2 (minimum daily intake of 32 µg) instead of vitamin K1 [22]. Another population-based study that involved 16,000 healthy females with ages between 49 and 70 was conducted; this study showed corresponding results. The study participants were selected from the cohort population of the European Prospective Investigation into Cancer and Nutrition (EPIC) study [23]. The data obtained from the study depicted that vitamin K2 instead of vitamin K1 had to be consumed in high quantities to prevent CV disorders. The data revealed that there was a 9% reduction in the risk of CHDs with every dose of 10 µg of vitamin K2 (taken as MK-7, MK-8, and MK-9). In the Netherlands, ultrasound and pulse wave velocity methods were utilized by the researchers working at the research and development (R&D) Group Vita K of Maastricht University to study 244 healthy postmenopausal females [23]. The subjects were observed for three years. Some of the subjects were administered a dose of vitamin K2 (180 µg) in the form of MK-7 (as MenaQ7 from NattoPharma), while some of the participants were given a placebo capsule every day for three years [22].

This was conducted on a random basis. At the end of the treatment, the group given vitamin K2 supplementation demonstrated a steady decline in stiffness index than the placebo group that showed a slight rise in the index. The study outcomes showed the positive impact of MenaQ7 on vascular health by enhancing vascular elasticity in females with stiff arteries and by suppressing age-related artery-wall stiffening. The researchers also found that the CV conditions improved as the subjects were administered a nutritional dose of vitamin K2 in the form of MK-7 (as MenaQ7). Moreover, if vitamin K2 is taken on a daily basis, there is a high chance of preventing the hardening of arteries [23, 24].

3. Vitamin K-dependent hormones

The growing clinical evidence suggests that regular vitamin K supplementation may improve bone structure, prevent VC, improve the body's sensitivity to the insulin hormone, which increases the life expectancy and treatment outcome in patients [25]. In the past ten years, more evidence has been published supporting the hypothesis that vitamin K2 should be considered a hormone. Vitamin K2 was found to activate many genes directly and indirectly by binding to the intranuclear receptor SXR, activating sirtuins and/or histone deacetylases (HDACs) responsible for cell-type determination and specific cell functions [26]. A study by Lanham et al. on rats and their offspring explored the effect of a high-fat diet on bone development and vascular development, particularly the role of VKDPs, including Gas-6, MGP) and OC [27]. The study also shows the importance of proper nutrition during pregnancy. During the study, the team observed increased levels of Gas-6 proteins, increased expression of the gene responsible for vitamin K-dependent gamma-glutamyl carboxylase (GGCX) in the cardiovascular tissues, while decreased levels of MGP in the femoral bones of female offsprings of high-fat dietary fed mothers [27]. The osteoblastic synthesis gives rise to OC production, deposited into bone or released into circulation, giving the histological measures of bone formation. OC's structure is greatly affected by vitamin K-dependent Gla residues, resulting in bone mineral maturation. The circulating uncarboxylated OC (unOC) levels have been applied as biomarkers for vitamin K deficiency and correlated with age-related bone loss. In animals, in-vivo and in-vitro tests have revealed unOC as an active hormone affecting glucose metabolism; however, the results are inconclusive on human levels and need to be investigated further [28]. Post-translational GGCX enzymes detected both hepatically and extrahepatically are critical for the functionality of Gla residues in VKDPs. OC (bone-derived protein) has been associated with energy metabolism as the skeleton system has been considered an endocrine organ [29]. Via molecular mechanisms, OC mediates vitamin K positive effects, improves insulin resistance, lipid, and glucose profiles. OC is also detected by insulin to regulate bone mineralization. It has been hypothesized that normal VKDP carboxylation is an essential step in the prevention of vascular endothelial calcification [30]. Vitamin K2 has been found to affect bone and CV health. A study of the vitamin K2 homolog MK-7 found that serum levels increased, as evidenced by healthy Japanese women, who supplemented their diet with MK-7, which can be particularly important for extrahepatic tissue health [31]. In a study of the murine model, the importance of the vitamin K-dependent MGP on the inhibition of extraskeletal calcification was suggested. With a high dose dietary supplementation of MK-7, the induced VC was inhibited, and the aortic alkaline phosphatase tissue concentration was reduced [32].

4. Molecular mechanism of vitamin K-dependent calcification on vascular system

Carboxylation is one of the post-translational modifications on proteins and is essential for the activity of VKDPs. The activation of VKDPs, which includes coagulation factors, OC, MGP, Gas-6, GRP, and periostin, is achieved by carboxylation of the proteins' Glu residues [33, 34]. The carboxylation of VKDPs happens in the case of an abundance of vitamin K, which is required for the activation of the GGCX enzyme (**Figure 1**) [35]. This enzyme adds carboxyl groups on Glu residues of VKDPs and converts them to Gla (**Figure 2**) [35]. This conversion enables the Gla residues to capture free Ca^{2+} ions that are circulating in the vascular system [36, 37]. For instance, there are five Glu residues on MGP, which is the only protein known as an inhibitor of arterial calcification. The Glu residues on the protein are carboxylated and converted to Gla, the active form of the protein. Without being activated, MGP is unable to hold free Ca^{2+} ions, which are eventually deposited in the vascular system and cause VC, such as calcium deposits and atherosclerotic plaques (**Figure 3**) [38, 39]. After the

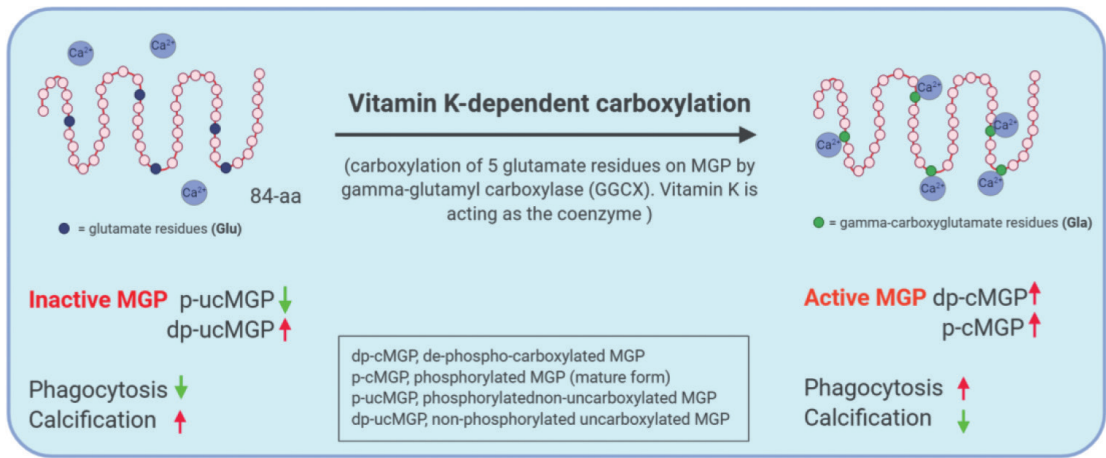


Figure 1.
Vitamin K-dependent post-translational carboxylation of MGP protein.

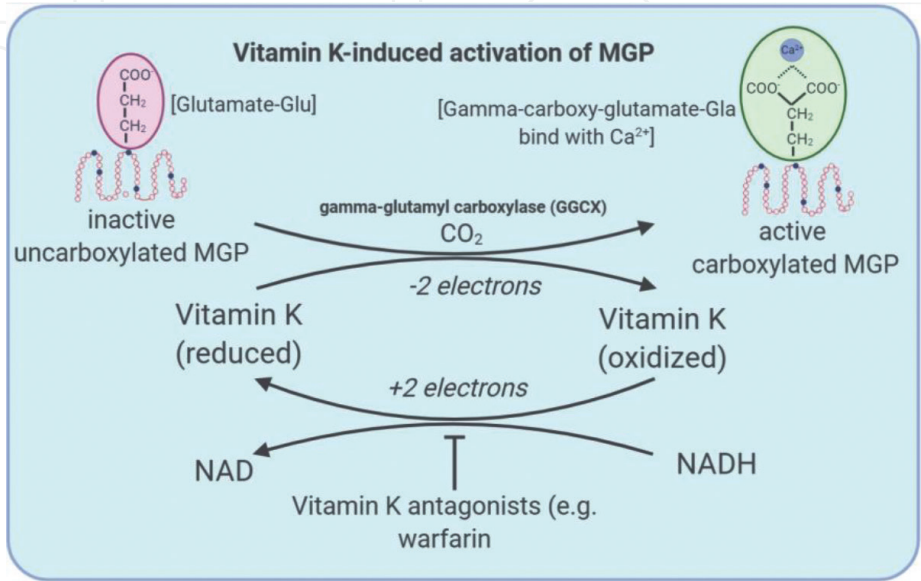


Figure 2.
General overview of vitamin-K induced activation of VKDPs.

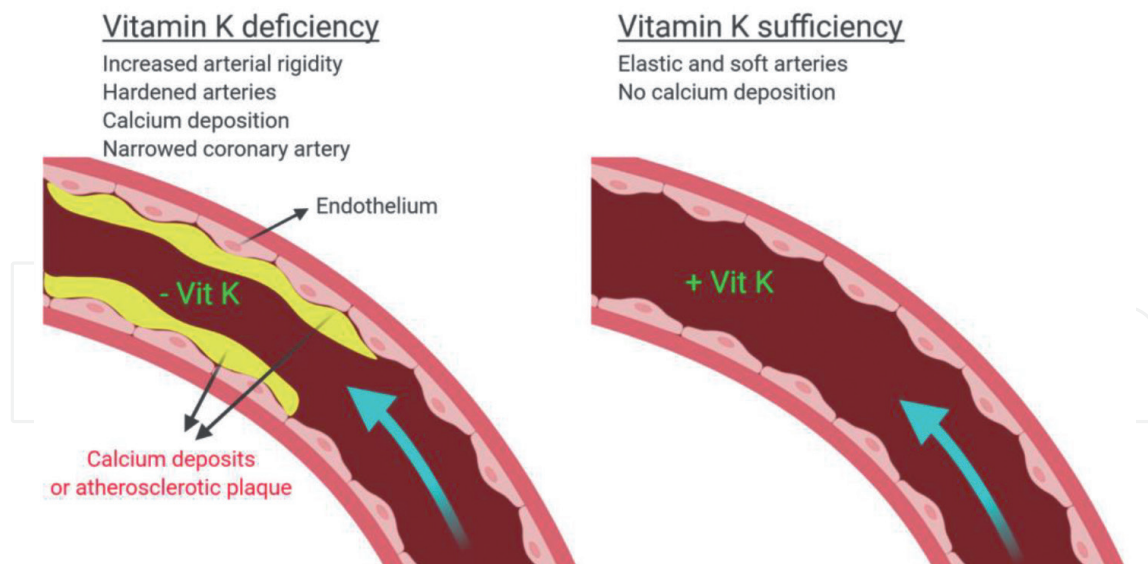


Figure 3.
The consequences of vitamin K deficiency in vascular system.

inflammation and hyperlipidemia, the soft-tissue mineralization phenomena occur in vascular smooth muscle cells (VSMCs), leading to their hardening and differentiation into osteoblast-type cells [40]. In addition to the mineralization phenomena, it has been hypothesized that active forms of MGP proteins may attach to the calcified crystals in the vasculature resulting in apoptotic bodies and vesicles. Another assumption is their potential to hinder VSMCs' trans-differentiation into an osteogenic phenotype [34, 41, 42]. A three-year clinical study by Shea et al. with 229 patients who were routinely given dietary vitamin K versus 223 patients in the placebo group showed that the addition of dietary vitamin K significantly correlated with decreased levels of calcium in coronary arteries [43]. In addition to carboxylation, post-translational phosphorylation of serine residues occurs on MGP. The enzyme casein kinase adds phosphate groups on three serine residues, regulating the secretion of protein into the extracellular matrix [44]. The unique relationship among circulating MGP forms, aortic stiffness, and arterial calcification was proposed in a recent article by Roumeliotis et al. [37]. The study has shown that more than one form of the MGP protein can be detected in the circulation and extracellular matrix governed by the degree of carboxylation and phosphorylation of the protein (**Figure 1**) [37].

5. Statins effect on vitamin K2 function

Statins, or more precisely, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase-inhibiting molecules, are a family of molecules that interfere with cholesterol synthesis and induce the uptake of the low-density lipoproteins (LDLs) in the body [45]. Available as a prescription since 1987 [46], statins today are one of the most commonly prescribed medications worldwide [47]. However, some researchers are starting to suggest that physicians may be overprescribing statins to their patients [48–50]. A recent study published in the *Annals of Internal Medicine* journal found that the statins' potential side effects seem to outweigh the benefits for people whose 10-year CVD risk is approximately 7.5–10% [51]. The United States Food and Drug Administration's consumer update from 2017, named "Controlling Cholesterol with Statins," states that statins have been linked to associated muscle

symptoms and a high chance of developing type 2 diabetes in patients [52]. It seems crucial to understand the exact phenomena behind statins' mechanism of action and clarify the medical community's created bias [53]. One potential explanation is given by the Kinjo Gakuin University group led by Harumi Okuyama, who suggests that statins may have an essential role in the increased probability of developing diabetes and arteriosclerosis [54] via the inhibition of vitamin K2 synthesis [55]. Researchers have indicated that statins may inhibit vitamin K2 production via the inhibition of geranylgeranyl diphosphate (GGPP) synthesis by HMG-CoA reductases (**Figure 4**) [56]. Some authors hypothesize that prolonged HMG-CoA reductase suppression by chronic statins treatment could adversely affect patients by diminishing the vitamin K2 supply to their bodies [56]. This phenomenon may be an essential factor in diabetes, atherosclerosis, and osteoporosis causation. The recently aggregated data from available randomized controlled trials and observational studies suggest a 10 to 45 percent higher risk of new-onset development of diabetes mellitus type 2 in statin patients than non-users [57]. Studies have shown that postmenopausal women taking statins are 150% more likely to develop type 2 diabetes [58]. In a large clinical study (n = 2,142), Cederberg et al. show a 46% increase in the risk of developing diabetes alongside decreased insulin secretion and overall body sensitivity to insulin [59]. Furthermore, particular varieties of statins—simvastatin and atorvastatin—showed a dose-dependent effect on insulin sensitivity and its secretion in patients [60]. These clinical observations may collectively suggest a relationship between statins' inhibition of Vitamin K2 and GGPP production and statins' influence on insulin

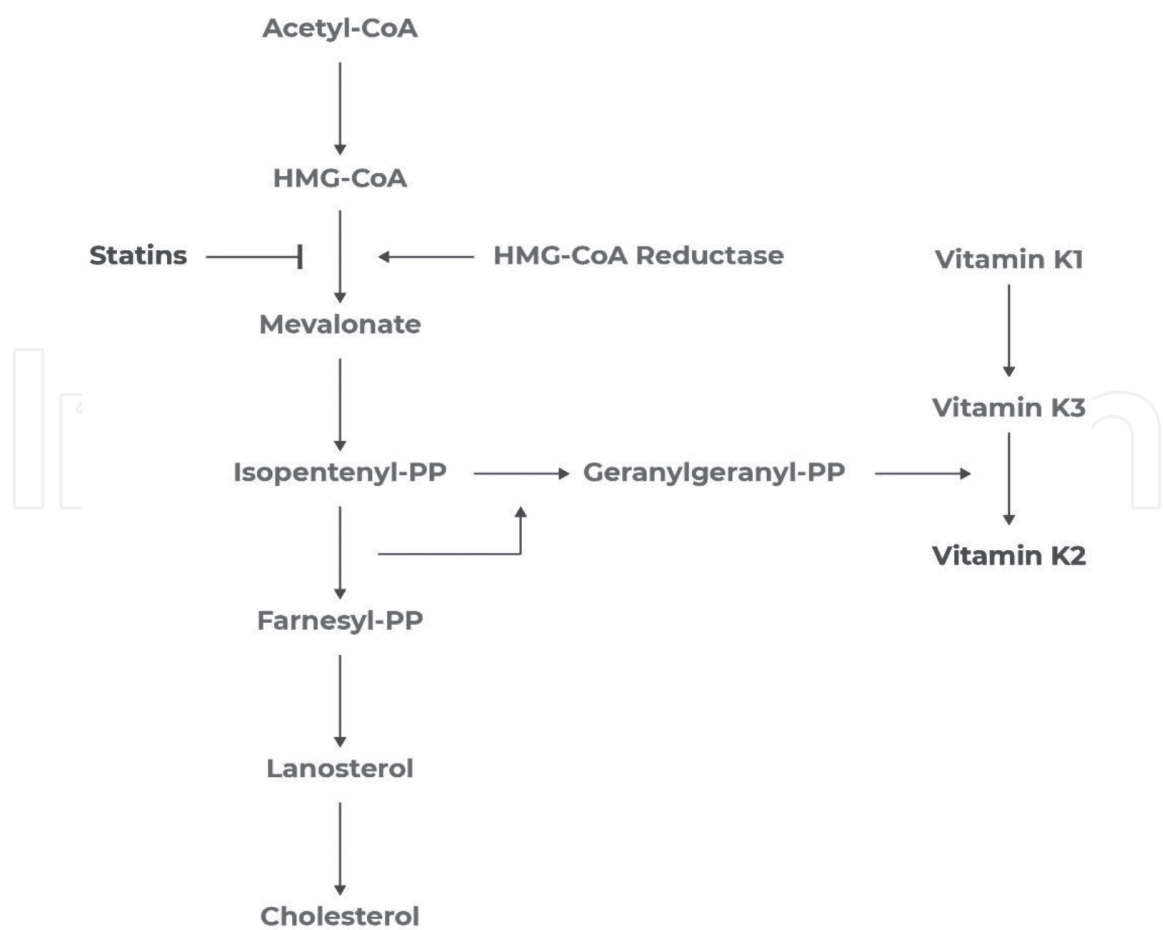


Figure 4. Statins and vitamin K2 related biochemical pathways. Statins inhibit HMG-CoA reductase in the mevalonate pathway. Geranylgeranyl-PP is essential for the synthesis of vitamin K2 from vitamin K1.

synthesis, secretion, and sensitivity. Insufficient levels of vitamin K2 may be linked to atherosclerosis and other CVDs [61]. In the large population-based Rotterdam study (n = 7,983 men and women, age > 55 years), Geleijnse et al. report a positive correlation between the reduced risk of CHD with regular dietary consumption of vitamin K2 [59]. The authors hypothesize the link between the depletion of vitamin K2 levels and severe coronary artery calcification in patients.

Several clinical studies have demonstrated that administering vitamin K2 (but not vitamin K1) was an effective method of osteoporosis fracture prevention in patients [62, 63]. Studies have shown that vitamin K2 up-regulates bone markers' expression and sustains lumbar bone mineral density in patients [63]. Pre-clinical and clinical evidence shows that statins may have an essential role in reducing the supply of vitamin K2 to the tissues through the body. Additional studies are required to explore the mechanisms for statin-associated diseases that were identified in pre-clinical and clinical studies, including diabetes, atherosclerosis, osteoporosis, chronic kidney disease, and cancer, and the effects of the various types of statins on the vitamin K2 synthesis, delivery, and accumulation in the body.

6. Physiological roles of vitamin K on CV functions

There is growing preclinical and clinical evidence of the crucial role of vitamin K in VC prevention [64]. Several VKDPs are regulated by vitamin K share entirely Gla, which is the remarkable amino acid produced by the posttranslational modification of the vitamin K-mediated enzyme GGCX [65]. The prothrombin molecule is carboxylated at ten glutamyl residues to produce the active form of prothrombin. These Gla are deposited at the amino-terminal domain of all VKDP, which share a common amino acid sequence [66]. Studies have shown that Gla also regulates calcium due to the placement of Gla in calcium-binding sites of the protein [67].

Available literature has limitations regarding the average requirement of vitamin K for normal homeostasis. In 2001, the United States Pharmacopeia Health and Medicine Division established adequate intake (AI) values based on median intake values reported by the National Health and Nutrition Examination Survey (NHANES) III; the AI value for vitamin K1 was set to 90 µg/dl for adult females and 120 µg/dl for adult males [67, 68]. This study does not advocate that this concentration of vitamin K will be enough to maintain the carboxylation of VKDPs. Undercarboxylated, biologically inactive Gla proteins are caused by vitamin K deficiency, resulting in the synthesis of calcification, which is considered a risk factor for VC and CVD [67, 68].

CVD is a cluster of abnormal conditions, such as CHD, and influences the functions of the heart and blood vessels that supply blood to various parts of the body [69]. Heart diseases and stroke are the primary causes of death and disability worldwide. According to the American Heart Association 2020 report, the age-adjusted death rate of CVD is 219.4 per 100,000, which means that someone is dying of CVD every 37 seconds, with a total of 2,353 deaths from CVD each day in the U.S. Consistent with these data, there are approximately 795,000 new or recurrent strokes each year, as well as approximately 401 deaths from stroke each day, based on data for previous years [70]. CVD-related diseases, such as angina, carotid artery diseases, and peripheral artery diseases, are characterized by the formation of fatty deposits in the arteries, which is known as atherosclerosis. These deposits consist of calcium, cellular waste products, fatty substances, cholesterol, and fibrin (a clotting material in the blood), which ultimately leads to narrowing and blockage of the arteries and

reduced blood flow to the heart muscle. Studies have shown that lifestyle, healthy diets, vitamins, and physical activity may have a potential role in preventing the development of CVD [71, 72].

There is compelling evidence that vitamin K is involved in various biological processes in the body and mediates anti-calcification, anti-cancer, bone-forming, and insulin-sensitization effects, and plays a vital role in the prevention management of CVD (**Figure 5**) [72]. It has been reported that vascular deficiency of vitamin K can lead to CVD by increasing calcium deposition and coronary artery calcification because vitamin K-synthesized osteocalcin and MGP strongly inhibit VC by regulating bone metabolism. Previous studies have shown a strong association between reduced intake of vitamin K and the development of coronary calcification, advocating that adequate vitamin K intakes can prevent CVD [73, 74]. The involvement of vitamin K in VC by the carboxylation of MGP has been confirmed in various animal studies that; MGP-knock out mice died within two months due to VC-induced rupturing of blood vessels followed by short stature, osteopenia, and fractures [75]. Sweatt et al. hypothesized that in rodents, a specific calcium-mediated and vitamin K-dependent Gla region in MGP protein is involved in binding bone morphogenetic protein-2 (BMP-2) that may link the age-related arterial calcification and low carboxylation of MGP [76]. Vitamin K antagonist warfarin has been shown to antagonize vitamin K-dependent carboxylation of MGP, leading to extensive VC [77]. However, vitamin K intake can suppress arterial calcification after treatment with warfarin in rats [78]. VKDPs, such as MGP and Gas-6, have the ability to protect the vasculature and have an essential role in blood coagulation by preventing tissue calcification and cell death in VSMCs and arterial vessel walls [79]. Several clinical observational studies have hypothesized that chronic dietary supplementation of both vitamins K1 and K2 may negatively correlate with risks of VC and CVD [79].

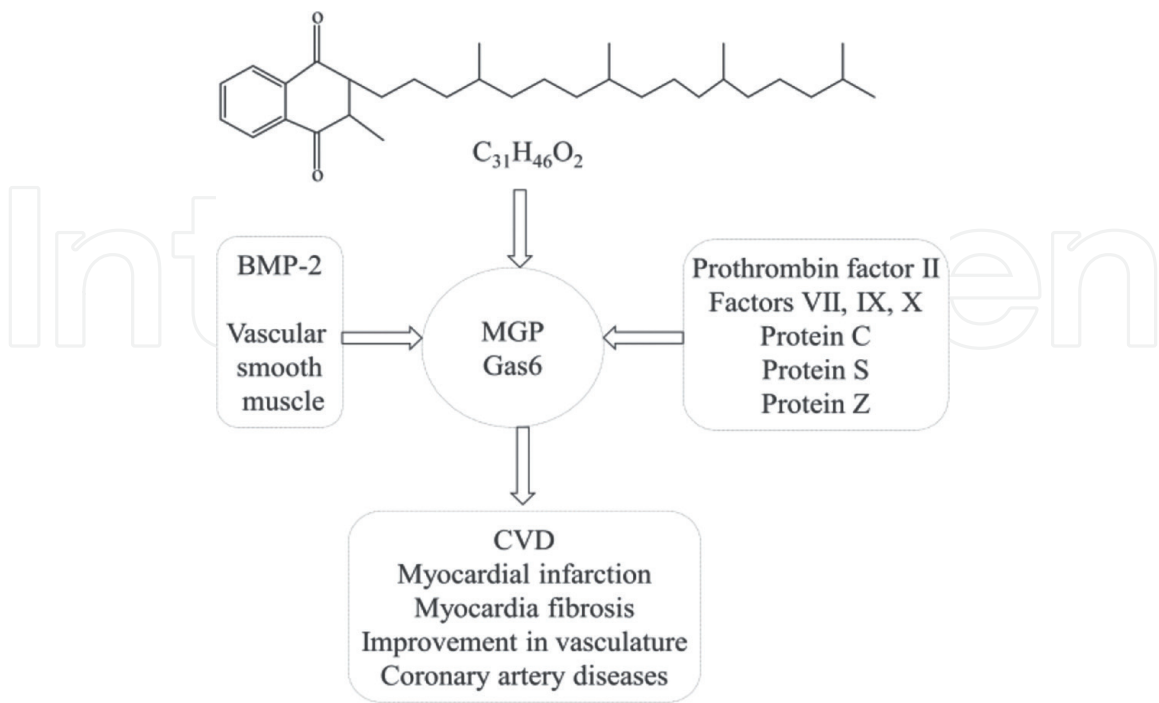


Figure 5.
A model showing the therapeutic potential of vitamin K against various cardiovascular diseases (CVD). MGP and Gas6 are vitamin K dependent proteins, which are activated by carboxylation. Subsequently, Gas6 exerts inhibitory effects on the apoptosis of endothelial cells and VSMCs, thus preventing angiostasis and protecting blood vessels and improved various heart diseases.

Additionally, subtypes of vitamin K2 (MK4 to MK9) have been examined in the Prospect-EPIC cohort, which consists of 16,057 women, aged 49–70 years old with no history of CVD [79]. This study concluded that a high intake of menaquinones (MK7, MK8, and MK9) could protect against CVD. However, this kind of protection has not been observed with vitamin K1 (phylloquinone) against CVD in other cohort observations [79, 80]. Notably, a Nurses' Health Study conducted with 72,874 female nurses aged between 38 and 65 years old has confirmed that vitamin K1 and lower risk of CVD is not significant because vitamin K1 intake may be a substitute marker for a healthy diet rather than an independent risk factor for CHD [81]. Nevertheless, data from National Health and Nutrition Examination Surveys examined the data of 5296 individuals with a minimum age of 50 years and concluded that vitamin K1 shows an independent assessment of high arterial pulse pressure [69]. In another prospective cohort study, 7216 participants were assessed by different types of vitamin K intake and mortality [82]. This study concluded that a high vitamin K intake is linked to the reduced risk of CVD in a Mediterranean population [82]. Vitamin K has shown promising results against vascular calcification in vitamin K-deficient individuals. Further research is justified to explore a relationship between vitamin K supplementation and the prevention of CVD.

7. Therapeutic role of vitamin K

CVD is a public health burden and a serious challenge to the health system throughout the world. CVD is a leading cause of death globally, with approximately 18 million deaths in 2015; the World Health Organization (WHO) forecasts that approximately 23.3 million deaths could occur from CVD by 2030 [83, 84]. The WHO has defined CVD as a *“group of illnesses that affect the heart and blood vessels”* [83]. These conditions include CHD and cerebrovascular disease. Scientific evidence has shown that factors related to nutrition have an important role in the development of CVDs and that these dietary factors may contribute to the differences in the morbidity and mortality from CVD seen in various regions of the world [83].

Different forms of vitamin K exist in the diet sourced from plants and animals [83, 85–88]. Vitamin K2 is usually a product of bacterial synthesis; however, meat, dairy, and fermented food products provide a minimal amount of vitamin K-2 [86, 88, 89]. Discovered in 1936, vitamin K has been known as an enzyme co-factor for the carboxylation of VKDPs [85, 86, 89]. Its key function in the synthesis of clotting factors in the liver has made the relationship between vitamin K and coagulation of blood a well-known phenomenon; however, recent studies are offering more insight into the diversity of functions associated with vitamin K [85, 86, 89, 90]. Many disease conditions related to the activities of vitamin K are now being described [89]. The carboxylation or activation of VKDPs requires vitamin K as a cofactor to the GGCX enzyme and occurs in the liver [83, 85, 86, 89]. The process converts specific Glu into calcium-binding Gla residues [86, 89, 90]. The uncarboxylated forms of the VKDPs are inactive, and carboxylation turns them into active and functioning proteins [86]. Some of the VKDPs that are carboxylated in the liver include clotting factors, such as factor II (prothrombin) and factor X [86]. Studies have confirmed that the process of activation of VKDPs also occurs outside the liver in smooth muscle cells. The extracellular matrix MGP protein is produced by smooth muscle cells and inhibits soft-tissue mineralization by binding to Ca^{2+} ions to the vascular walls [44, 83, 85, 86]. MGP is a VKDP with Gla and serine residues. MGP is activated via carboxylation of the Gla residues, followed by phosphorylation of the serine residues

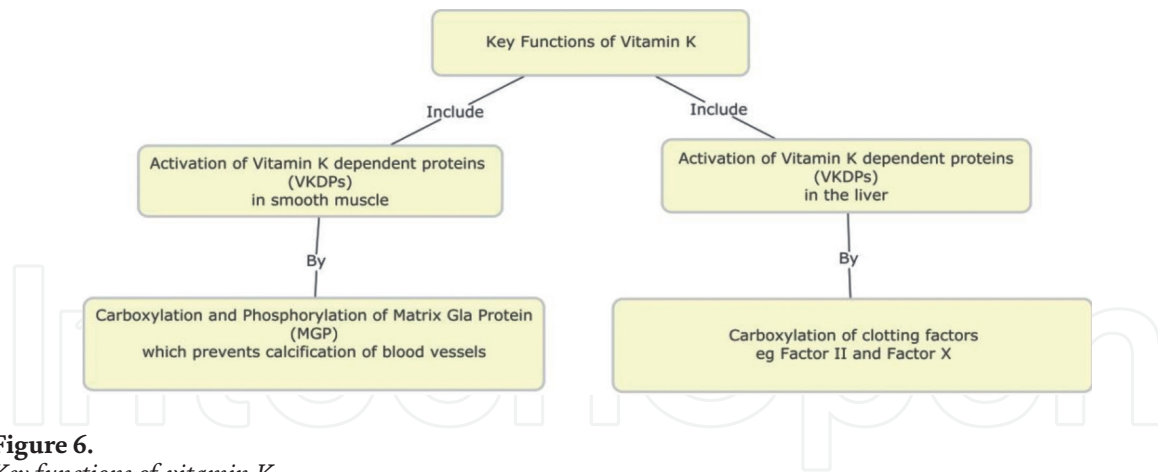


Figure 6.
Key functions of vitamin K.

[44, 86]. Vitamin K is essential to the carboxylation and phosphorylation of MGP as the enzyme co-factor [44, 86]. Carboxylation of MGP leads to its structural changes, which are very important for its ability to bind to calcium crystals [44]. Although MGP becomes inactivated when there is vitamin K deficiency and leads to VC, a high intake of vitamin K can reverse conditions [44, 83, 85, 86]. MGP secreted by chondrocytes and VSMCs has been shown to inhibit VC and was described as the most potent natural inhibitor of calcification in the human body [44]. Apart from inhibition of calcification, MGP has also been recognized as having the ability to reverse the calcification process [44]. The protection of MGP from VC occurs via its high binding affinity to new crystals of hydroxyapatite, which prevents their increase within the vascular wall [44]. MGP also stimulates arterial macrophages, leading to phagocytosis and apoptosis of the MGP-hydroxyapatite complex (**Figure 6**).

A sub-optimal level of vitamin K in the body is associated with an increased risk of adverse health outcomes, especially in adult and elderly populations. Studies have linked vitamin K deficiency with CVD, insulin resistance, and inflammation, as well as cognitive impairment [13, 83, 85, 87]. A lack of vitamin K has been shown to lead to an increased risk of calcification of blood vessels and CVD due to the presence of nonfunctioning Gla proteins [44, 83, 85, 86]. Vitamin K deficiency may cause increased calcium deposition in the walls of the blood vessels, leading to calcification of the coronary artery, and ultimately, CVD [13, 83]. Earlier observational studies have also established a relationship between low vitamin K intake with calcification of blood vessels; other observations have suggested that high vitamin K supplementation in the diet may reduce long-term CVD risks [13, 83, 85]. An increased intake of dietary vitamin K is also associated with a decrease in the risk of all-cause mortality, as concluded by a study of a Mediterranean population with a high risk of CVD [83].

8. Vitamin K and inflammation

Inflammation is a recognized contributor to the progression and onset of diseases related to aging, such as osteoarthritis, CVD, and other similar diseases [85, 89]. The production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), C-reactive protein (CRP), and interleukin-6 (IL-6), has been found to be interfered by vitamin K. These findings were demonstrated in a cross-sectional study that showed a relationship among the high levels of vitamin K supplementation, the low levels of pro-inflammatory cytokines, and diminished inflammation in the body [85, 89]. Leptin

hormone has a proinflammatory effect, menadione (VK3) has an apoptotic effect in Hepatocellular carcinoma through inhibiting leptin and through ROS generation which made VK3 a potential vitamin in preventing hepatocyte survival [91].

9. Conclusion

New insights about the activities of vitamin K and its crucial protective role in CVD development have emerged. Good association between dietary vitamin K2 and CVD is now clinically established. The role of inhibitory effect of statins in synthesis of vitamin K2 should be emphasized. However, there is still a need for prospective in-depth studies to improve the current understanding of this critical relationship and apply such knowledge to prevent CVD and improve its outcomes. Research should focus on understanding the function and regulation of new proteins that enhance or inhibit vascular calcification as well as the combination of vitamin D with other therapeutic drugs. Prospective studies may assess the vitamin K status using multiple biomarkers to provide insight on the relationship of vitamin K to vascular calcification and CVD.

Conflict of interest

All authors declare that there is no conflict of interest.

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