



## Vitamin K Deficiency: An Updated Review for Healthcare Providers

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### Abstract:

**Background:** Vitamin K is a fat-soluble vitamin essential for blood coagulation, bone metabolism, and cardiovascular health. Deficiency can lead to bleeding disorders, osteoporosis, and vascular calcification, with neonates being particularly vulnerable to life-threatening hemorrhage without prophylaxis.

**Aim:** This review examines the pathophysiology, clinical implications, and management strategies for vitamin K deficiency across populations, emphasizing evidence-based interventions to prevent complications.

**Methods:** A comprehensive analysis of current literature, clinical guidelines, and ongoing trials was conducted, focusing on diagnostic approaches, treatment protocols, and interprofessional care coordination.

**Results:** Vitamin K deficiency is preventable with appropriate supplementation. Intramuscular prophylaxis in newborns reduces VKDB incidence to near zero, while oral regimens require strict adherence. Adults

benefit from dietary adjustments or supplementation, particularly those with malabsorption or on anticoagulants. PIVKA-II testing provides reliable deficiency detection, and emerging research suggests potential roles in chronic disease mitigation.

**Conclusion:** Timely intervention and multidisciplinary collaboration are critical to optimizing outcomes. Neonatal prophylaxis remains a public health priority, and tailored approaches improve management in high-risk adults.

**Keywords:** Vitamin K, phyloquinone, VKDB, coagulation, prophylaxis, PIVKA-II

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## Introduction:

Vitamin K consists of a group of fat-soluble compounds that play a vital role in various physiological processes. These compounds serve as essential cofactors for vitamin K-dependent proteins, which are involved in critical functions such as blood coagulation, bone metabolism, and cardiovascular health. A deficiency in vitamin K can lead to serious health complications, including excessive bleeding, impaired bone development, osteoporosis, and an increased risk of cardiovascular disease. The National Academy of Science Food and Nutrition Board recommends a daily intake of 120 µg for adult men and 90 µg for adult women to maintain adequate vitamin K levels and support these physiological functions.[1] Vitamin K deficiency bleeding (VKDB) in newborns is classified into three distinct categories based on the timing of symptom onset. Early VKDB occurs within the first 24 hours after birth, classic VKDB presents within the first week of life, and late VKDB develops between one week and six months of age, with the highest incidence observed between two and eight weeks.[1][2] In addition to acquired deficiencies, hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) is a rare congenital disorder that may also present with bleeding symptoms during the neonatal period.[1][3] This condition further underscores the importance of vitamin K in maintaining proper hemostasis and overall health. The prevention and management of VKDB typically involve prophylactic vitamin K administration at birth, which has been shown to significantly reduce the incidence of bleeding disorders in infants.[2] Despite its established efficacy, ongoing research continues to explore optimal dosing strategies and long-term outcomes associated with vitamin K supplementation in both neonates and adults. Understanding the mechanisms of vitamin K metabolism and its role in health and disease remains crucial for developing effective clinical interventions.

## Etiology

Vitamin K deficiency arises from multiple factors, including inadequate dietary intake of vitamin K-rich foods such as leafy green vegetables, vegetable oils, and fermented products. Additionally, malabsorptive disorders—such as celiac disease, cystic fibrosis, and inflammatory bowel disease—can impair the intestinal absorption of fat-soluble vitamins, including vitamin K.[1][4] Prolonged antibiotic use may also contribute to deficiency by disrupting gut microbiota that synthesize menaquinones (vitamin K<sub>2</sub>).[1][5] Furthermore, medications such as warfarin and other vitamin K antagonists interfere with vitamin K metabolism by inhibiting the recycling of vitamin K epoxide, thereby increasing the risk of deficiency.[1][6] A comprehensive understanding of these etiological factors is crucial for the prevention, diagnosis, and management of vitamin K deficiency.

In neonates, vitamin K deficiency bleeding (VKDB) may result from maternal factors, such as the use of medications that interfere with vitamin K metabolism during pregnancy, or from insufficient placental transfer of vitamin K to the fetus.[1][2] Exclusively breastfed infants are at higher risk due to the low vitamin K content in human milk compared to formula.[1][2] In contrast, hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) is a rare autosomal recessive disorder caused by mutations in either the *GGCX* (gamma-glutamyl carboxylase) or *VKORC1* (vitamin K epoxide reductase complex subunit 1) genes.[1][3] This condition leads to impaired carboxylation of vitamin K-dependent proteins, resulting in decreased levels of coagulation factors II, VII, IX, and X, as well as anticoagulant proteins C, S, and Z.[1][3] Unlike acquired vitamin K deficiency, VKCFD requires genetic testing for definitive

diagnosis and often necessitates lifelong management with vitamin K supplementation or fresh frozen plasma in severe cases.[1][3]

## Epidemiology

Vitamin K deficiency is observed in approximately 8% to 31% of otherwise healthy adults, but it rarely leads to clinically significant bleeding in this population.[4][5][6] Hemorrhagic complications are more likely to occur in high-risk groups, including individuals with malabsorption disorders (e.g., celiac disease, cystic fibrosis, or chronic pancreatitis), severe liver disease, or those taking medications that disrupt vitamin K metabolism (e.g., warfarin or prolonged antibiotic use).[4][5][6] Neonates are particularly vulnerable to vitamin K deficiency due to inherently low vitamin K levels at birth. Classic vitamin K deficiency bleeding (VKDB) was first documented in 1894, characterized by bleeding manifestations typically arising on the second or third day of life.[2][7] Historically, when compounded by sepsis-induced coagulopathy, the incidence reached 600 cases per 100,000 infants, with a staggering 62% mortality rate.[2][7] Early VKDB is strongly associated with maternal use of vitamin K antagonists, such as anticonvulsants, during pregnancy. Without prophylactic vitamin K administration at birth, the incidence of early VKDB can be as high as 12%.[2][8] In modern practice, due to widespread neonatal vitamin K prophylaxis, the incidence of classic VKDB has significantly declined to an estimated 0.25% to 1.7% of cases.[2][8] Late VKDB, occurring between 2 weeks and 6 months of age, remains a concern, particularly in exclusively breastfed infants, with reported rates ranging from 4.4 to 72 cases per 100,000 births.[2][7][9] This form carries a high mortality rate (20%–50%) and is associated with severe neurological sequelae in survivors due to the high prevalence of intracranial hemorrhage.[2][7][9] Epidemiologic studies indicate a higher incidence of late VKDB in Asian populations, though the underlying reasons remain under investigation.[2][9] In contrast, hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) is an extremely rare autosomal recessive disorder, with fewer than 30 documented cases globally. It affects both sexes equally and requires genetic confirmation for diagnosis.[10]

## Pathophysiology

Vitamin K comprises a group of fat-soluble compounds structurally classified as 2-methyl-1,4-naphthoquinones, distinguished by variable alkyl substituents at the 3-position. Three primary forms exist: vitamin K1 (phyloquinone), the plant-derived form abundant in leafy greens and cruciferous vegetables; vitamin K2 (menaquinone), produced by gut microbiota and found in fermented foods; and the synthetic vitamin K3 (menadione), which is no longer used clinically due to its association with hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient infants.[2] Modern formulations utilize synthetic vitamin K1 (phytonadione) as a safer alternative.

The absorption and metabolism of vitamin K differ between its natural forms. Vitamin K1 requires bile salts, pancreatic enzymes, and dietary fats for efficient uptake in the jejunum and ileum, where it is incorporated into chylomicrons for systemic distribution.[11] In contrast, vitamin K2 is both synthesized by intestinal bacteria and obtained from dietary sources, with longer-chain menaquinones (e.g., MK-4 to MK-13) exhibiting distinct tissue distribution patterns and potentially superior bioavailability for extrahepatic functions.[4] Vitamin K serves as an essential cofactor for  $\gamma$ -glutamyl carboxylase (GGCX), which catalyzes the post-translational modification of glutamate residues to  $\gamma$ -carboxyglutamate (Gla) in vitamin K-dependent proteins. This carboxylation enables clotting factors II (prothrombin), VII, IX, and X to bind calcium and interact with phospholipid membranes, a critical step in coagulation cascade activation.[4] Inefficient carboxylation results in under-carboxylated proteins (e.g., PIVKA-II), which lack procoagulant activity and predispose to bleeding. The vitamin K cycle—regulated by vitamin K epoxide reductase (VKOR)—recycles oxidized vitamin K 2,3-epoxide back to its active hydroquinone form, a process inhibited by warfarin.[4][11]

Beyond coagulation, vitamin K activates anticoagulant proteins (C, S, Z), bone-related proteins (osteocalcin, matrix Gla protein), and vascular regulators. Under-carboxylated osteocalcin correlates with reduced bone mineral density and fracture risk, while deficient matrix Gla protein activity permits vascular calcification, contributing to cardiovascular disease.[4][12] Neonates are physiologically vitamin K-

deficient due to poor placental transfer, sterile intestines (limiting K<sub>2</sub> synthesis), and low breast milk vitamin K content. This results in elevated PIVKA-II levels and susceptibility to VKDB.[13] In contrast, hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) stems from mutations in *GGCX* (type 1) or *VKORC1* (type 2), disrupting carboxylation and causing deficiencies across all vitamin K-dependent proteins.[3][10]

### History and Physical Examination

Vitamin K deficiency in adults often presents with bleeding manifestations, including prolonged bleeding at venipuncture sites, easy bruising (ecchymoses), petechiae, or hemorrhage following minor trauma. A thorough medication history is crucial, as patients may be taking antibiotics (which disrupt gut flora-derived vitamin K<sub>2</sub> synthesis), anticonvulsants (e.g., phenytoin), or warfarin—all of which interfere with vitamin K metabolism. Physical examination typically reveals cutaneous signs of bleeding, such as purpura or mucosal hemorrhage, particularly in high-risk individuals with malabsorption disorders or liver disease. In neonates, vitamin K deficiency bleeding (VKDB) presents with distinct patterns based on timing. A common historical feature across all VKDB types is parental refusal of intramuscular vitamin K prophylaxis at birth. Early VKDB (onset <24 hours postpartum) is strongly linked to maternal use of vitamin K antagonists (e.g., warfarin, anticonvulsants) and manifests as severe, often life-threatening hemorrhage—intracranial, pulmonary, or intra-abdominal bleeding predominates. Classic VKDB (days 2–7) typically causes milder bleeding, such as umbilical oozing, gastrointestinal hemorrhage, or prolonged bleeding post-circumcision. Late VKDB (2 weeks–6 months) predominantly affects exclusively breastfed infants due to low breast milk vitamin K content; intracranial hemorrhage is the hallmark, with mortality rates of 20–50% and significant neurological morbidity in survivors.[14] Any unexplained neonatal bleeding warrants immediate laboratory evaluation. Hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) may mimic VKDB in severe neonatal cases, presenting with spontaneous or post-procedural hemorrhage (e.g., post-circumcision). Milder forms may present later with easy bruising, mucosal bleeding (epistaxis, gingival), or abnormal bleeding after surgery. Associated skeletal abnormalities (e.g., nasal hypoplasia, distal digital hypoplasia) and developmental delays may occur due to impaired carboxylation of bone-related proteins.[10]

### Evaluation

The diagnosis of classic vitamin K deficiency in adults is primarily based on coagulation studies, with prolonged prothrombin time (PT) being the most common initial finding. PT elongation occurs due to decreased levels of functional vitamin K-dependent clotting factors (II, VII, IX, X), though it typically requires approximately a 50% reduction in prothrombin levels before becoming abnormal.[15] While PT is responsive to vitamin K administration, it remains a nonspecific marker as it can be affected by various other conditions, including liver disease and warfarin therapy. A more sensitive indicator of vitamin K deficiency is protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-gamma-carboxy prothrombin (DCP). Unlike conventional coagulation tests, PIVKA-II directly reflects the presence of under-carboxylated prothrombin and demonstrates minimal variability related to age or other physiological factors, making it a more reliable biomarker for assessing vitamin K status.[16]

Nutritional vitamin K deficiency can be detected through elevated PIVKA-II levels, which become apparent when daily vitamin K intake falls below 60 mcg.[17] Neonates are particularly susceptible to vitamin K deficiency, with studies showing that 10–50% of newborns have elevated PIVKA-II levels at birth, increasing to approximately 70% by days 4–5 of life if vitamin K prophylaxis is not administered.[2] Direct measurement of plasma vitamin K levels, though theoretically useful, presents challenges due to significant variability influenced by analytical techniques, dietary lipid intake, and metabolic factors. Although liquid chromatography–tandem mass spectrometry (LC-MS/MS) offers precise quantification of vitamin K subtypes, its limited availability in routine clinical settings restricts its widespread use.[4]

The diagnostic criteria for vitamin K deficiency bleeding (VKDB) require a PT prolongation of at least four times the upper limit of normal, accompanied by one of the following: (1) normal or elevated platelet counts with preserved fibrinogen levels and absence of fibrin degradation products; (2)

normalization of PT within 30 minutes of intravenous vitamin K administration; or (3) elevated PIVKA-II/DCP levels.[2] In cases where hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) is suspected, confirmation requires genetic analysis of gamma-glutamyl carboxylase (*GGCX*) or vitamin K 2,3-epoxide reductase complex (*VKORC1*) genes, typically performed in specialized research laboratories.[10] This distinction is crucial, as VKCFD necessitates long-term management rather than transient vitamin K supplementation.

### **Treatment and Management of Vitamin K-Related Conditions**

The management of vitamin K deficiency and associated disorders varies depending on the patient population, underlying etiology, and clinical severity. Treatment strategies range from dietary modification to pharmacological supplementation, with specific protocols established for different clinical scenarios.

#### **Vitamin K Deficiency in Adults**

The National Academy of Science Food and Nutrition Board recommends a daily vitamin K intake of 120 µg for men and 90 µg for women to maintain adequate levels. For adults with confirmed deficiency, oral vitamin K1 (phytonadione) supplementation is the first-line treatment, with corrective doses typically ranging from 1 to 2 mg. Higher doses (up to 25 mg) may be required in severe cases. Patients on warfarin therapy who develop excessive anticoagulation may require 1 to 10 mg of oral vitamin K1 to reverse elevated INR, with peak effects observed approximately 24 hours post-administration. In cases of acute bleeding, intravenous (IV) vitamin K1 may be necessary for faster correction.

#### **Chronic Conditions in Adults**

Emerging evidence suggests potential benefits of higher-dose vitamin K supplementation (both K1 and K2) in chronic conditions such as osteoporosis and cardiovascular disease, where vitamin K-dependent proteins (e.g., osteocalcin, matrix Gla protein) play a regulatory role. However, standardized dosing guidelines remain under investigation, with ongoing randomized controlled trials evaluating optimal therapeutic ranges.[18]

#### **Prophylaxis in Newborns**

Neonatal vitamin K prophylaxis is critical in preventing vitamin K deficiency bleeding (VKDB). The most effective method is a single intramuscular (IM) injection of 0.5 to 1 mg vitamin K1 at birth, which nearly eliminates the risk of VKDB.[1][2][19] For parents who decline IM administration, an oral regimen may be considered, though it is less reliable. Common oral protocols include:

- **Option 1:** 2 mg at birth, followed by additional doses at days 4–6 and weeks 4–6.
- **Option 2:** 2 mg at birth, then 1 mg weekly for 3 months. Despite these alternatives, IM prophylaxis remains the gold standard due to its sustained efficacy.

#### **Vitamin K Deficiency Due to Malabsorption in Infants**

Infants with conditions impairing fat absorption (e.g., biliary atresia, cystic fibrosis) require aggressive vitamin K supplementation. Daily oral doses of 0.3 to 15 mg may be necessary, adjusted based on disease severity. If oral therapy fails, parenteral (IV or subcutaneous) vitamin K1 should be administered.[20]

#### **Treatment of Neonatal VKDB**

For active VKDB, immediate intervention with 1–2 mg of vitamin K1 via slow IV infusion or subcutaneous injection is essential. In cases of life-threatening hemorrhage, fresh frozen plasma (FFP) at 10–15 mL/kg should be administered alongside vitamin K to rapidly restore clotting factors.[14]

#### **Treatment of Hereditary Combined Deficiency (VKCFD)**

VKCFD, a rare genetic disorder, requires long-term management with high-dose oral vitamin K1 (10 mg, 2–3 times weekly). If oral absorption is inadequate, IV vitamin K1 may be substituted. For surgical

prophylaxis or acute bleeding, FFP (15–20 mL/kg) or prothrombin complex concentrates (PCCs) may be required. In refractory cases, recombinant factor VIIa can be considered.[10] Effective management of vitamin K-related conditions depends on tailored therapeutic approaches, ranging from dietary adjustments in mild deficiency to aggressive supplementation in severe or congenital disorders. While oral and IM vitamin K1 remain mainstays of therapy, emerging research continues to refine dosing strategies for chronic diseases. Neonatal prophylaxis remains a critical public health measure, with IM administration offering the most reliable protection against VKDB.

### Differential Diagnosis

Vitamin K deficiency must be distinguished from other bleeding disorders that present similar clinical manifestations. Inherited coagulation factor deficiencies (e.g., hemophilia A/B or factor VII deficiency) can mimic vitamin K-dependent coagulopathy but are characterized by persistent factor deficiencies unresponsive to vitamin K supplementation. Diagnostic confirmation requires specific factor activity assays. Additionally, acquired bleeding disorders secondary to liver disease or disseminated intravascular coagulation (DIC) may present with prolonged PT/INR but typically demonstrate additional laboratory abnormalities, including thrombocytopenia, elevated D-dimers, and reduced fibrinogen levels. A critical diagnostic consideration is differentiating between drug-induced vitamin K antagonism (e.g., warfarin therapy) and true deficiency states. While warfarin produces a similar coagulopathy by inhibiting VKORC1, its effects are distinguished by a clear medication history and normalization of coagulation parameters following vitamin K administration. Malabsorption syndromes (e.g., celiac disease, cystic fibrosis, or biliary obstruction) must also be identified, as they require targeted management of the underlying condition rather than simple nutritional repletion. Vitamin K deficiency in adults has been implicated in chronic diseases such as osteoporosis and vascular calcification, creating diagnostic overlap with age-related bone loss or atherosclerotic cardiovascular disease. The presence of under-carboxylated osteocalcin or matrix Gla protein may help establish a causal relationship. Finally, hereditary combined deficiency of vitamin K-dependent clotting factors (VKCFD) must be excluded through genetic testing in refractory cases, particularly when bleeding manifestations persist despite adequate vitamin K supplementation.

### Pertinent Studies and Ongoing Trials

Current research on vitamin K spans a wide spectrum of clinical applications, with 402 registered studies on ClinicalTrials.gov, including 136 active trials investigating vitamin K and its antagonists. These studies explore diverse therapeutic areas, ranging from comparative efficacy analyses between traditional vitamin K antagonists (e.g., warfarin) and direct oral anticoagulants (DOACs) to novel applications in chronic disease management. Several landmark studies have significantly advanced our understanding of vitamin K's role in chronic conditions:

1. **PREVEND (Prevention of Renal and Vascular End-Stage Disease) Study:** This large-scale cohort study examined vitamin K status in relation to cardiovascular and renal outcomes, demonstrating an association between low vitamin K levels and increased vascular calcification in patients with chronic kidney disease (CKD).[21]
2. **LASA (Longitudinal Aging Study Amsterdam):** Focusing on elderly populations, LASA identified correlations between vitamin K deficiency and age-related decline in bone mineral density, suggesting a potential protective role against osteoporosis.[22]
3. **ECKO (Vitamin K Supplementation in Postmenopausal Women with Osteopenia) Trial:** This randomized controlled trial evaluated the effects of vitamin K1 supplementation on bone turnover markers, revealing modest but significant improvements in bone health parameters among supplemented participants.[6]
4. **VIKI (Vitamin K Italian Dialysis Study):** Investigating CKD patients on hemodialysis, VIKI highlighted the high prevalence of functional vitamin K deficiency and its association with accelerated vascular calcification.[23]

5. **Japanese Osteoporosis Intervention Trial-03:** This study provided evidence supporting the synergistic effects of vitamin K2 (menaquinone-7) with standard osteoporosis therapies in reducing fracture risk.[24]

Ongoing research continues to explore vitamin K's pleiotropic effects, including its potential role in diabetes management, neurodegenerative diseases, and cancer prevention. These studies aim to clarify optimal dosing strategies and establish evidence-based guidelines for therapeutic applications beyond traditional coagulation management.

#### Treatment Planning for Vitamin K Supplementation

##### Adults

For maintaining adequate vitamin K levels and managing minor bleeding episodes in adults, oral vitamin K1 (phytonadione) supplementation is the first-line approach. The typical therapeutic dose ranges from 1–10 mg, adjusted based on the severity of deficiency and clinical context (e.g., warfarin reversal or nutritional deficiency). Subcutaneous administration may be used when oral absorption is uncertain, but bleeding is not life-threatening. Intravenous (IV) vitamin K is reserved for severe hemorrhage or acute coagulopathy requiring rapid correction, though caution is warranted due to the small risk of anaphylactoid reactions.

##### Neonates and Infants

The gold standard for prophylaxis in newborns is a single intramuscular (IM) injection of 0.5–1 mg vitamin K1 at birth, which nearly eliminates the risk of vitamin K deficiency bleeding (VKDB). This route is preferred due to its sustained release and 100% bioavailability. Oral vitamin K regimens (e.g., 2 mg at birth, repeated at 4–6 days and 4–6 weeks) may be considered for parents who decline IM administration, but they are less reliable and require strict adherence. If an infant vomits within 1 hour of an oral dose, the dose should be repeated. Oral vitamin K is contraindicated in:

- **Preterm infants** (due to immature absorption)
- **Neonates with cholestasis or malabsorption disorders** (e.g., biliary atresia, cystic fibrosis)
- **Infants with suspected bowel obstruction**

For infants with malabsorption, parenteral (IM or IV) vitamin K is necessary, with dosing adjusted based on severity (e.g., 0.3–15 mg/day).

##### Special Populations

- **Patients on warfarin:** Low-dose oral vitamin K (1–2.5 mg) can correct excessive anticoagulation without overriding warfarin's therapeutic effect.
- **Chronic kidney disease (CKD) or osteoporosis:** Emerging evidence supports high-dose vitamin K2 (menaquinone-7, 45–360 mcg/day) to mitigate vascular calcification and bone loss, though protocols remain investigational.

Treatment planning for vitamin K deficiency prioritizes route selection (oral for maintenance, IV for emergencies) and population-specific protocols (IM for neonates, adjusted dosing for malabsorption). Adherence to evidence-based prophylaxis in newborns remains critical to preventing VKDB.

##### Safety and Toxicity:

Vitamin K is recognized for its high safety margin, with no known toxicity associated with excessive dietary intake. Unlike other fat-soluble vitamins, vitamin K does not accumulate in the body to harmful levels, as excess amounts are efficiently metabolized and excreted. The synthetic form of vitamin K1, phytonadione, is available in both oral and parenteral formulations, including intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes of administration. While generally well-tolerated, rare anaphylactoid reactions have been reported, occurring in approximately 3 cases per 10,000 doses, with a higher incidence associated with IV administration. These reactions are thought to be mediated by the

emulsifying agent polyoxyethylated castor oil present in some injectable formulations rather than by vitamin K itself. The risk of adverse effects can be mitigated through several strategies. For IV administration, slow infusion rates not exceeding 1 mg per minute are recommended to minimize the likelihood of hypersensitivity reactions. In non-emergent situations, the IM or SC routes are preferred due to their lower risk profile. For patients with a history of hypersensitivity to injectable formulations, alternative preparations without polyoxyethylated castor oil may be considered. Additionally, oral administration of phytonadione is associated with an even lower incidence of adverse effects, making it the preferred route for long-term supplementation and minor deficiency correction. The safety profile of vitamin K is particularly relevant in neonatal populations, where large-scale prophylaxis programs have demonstrated an excellent tolerability record. Intramuscular administration of vitamin K to newborns has not been associated with significant adverse effects, supporting its status as the gold standard for prevention of vitamin K deficiency bleeding. The absence of toxicity concerns allows for flexible dosing strategies across different clinical scenarios, from nutritional supplementation to emergency reversal of anticoagulation. Ongoing pharmacovigilance continues to confirm the favorable risk-benefit ratio of vitamin K in both therapeutic and prophylactic applications [25].

### **Prognosis**

The prognosis of vitamin K deficiency depends on multiple factors, including severity, etiology, and timeliness of treatment. In adults, mild deficiencies often resolve with dietary adjustments or supplementation, yielding excellent outcomes. However, undiagnosed or prolonged deficiency may lead to clinically significant bleeding, osteoporosis, or cardiovascular complications due to impaired activation of vitamin K-dependent proteins. Prognostic assessment in adults is complicated by confounding variables such as comorbidities, concurrent malnutrition, and genetic variations in vitamin K metabolism.[4][12] For neonates, prognosis is heavily influenced by preventive strategies. Prophylactic vitamin K administration at birth dramatically reduces morbidity and mortality from vitamin K deficiency bleeding (VKDB). Late-onset VKDB carries the poorest prognosis, with intracranial hemorrhage occurring in 50% of cases and substantial associated mortality.[14] Hereditary combined deficiency (VKCFD) typically demonstrates a favorable long-term prognosis with regular vitamin K supplementation, though severe cases may require additional clotting factor support during bleeding episodes.[10] Early recognition and intervention remain critical for optimizing outcomes across all age groups.

### **Complications**

Vitamin K deficiency can lead to significant clinical complications due to its essential role in coagulation, bone metabolism, and vascular health. The most immediate and life-threatening complication is hemorrhage, resulting from impaired synthesis of functional vitamin K-dependent clotting factors (II, VII, IX, X). In neonates, this manifests as vitamin K deficiency bleeding (VKDB), which can cause fatal intracranial, gastrointestinal, or umbilical bleeding if untreated.[14] Adults with severe deficiency may experience spontaneous bleeding, hematoma formation, or prolonged hemorrhage following trauma or surgery.[4] Beyond coagulation disorders, chronic vitamin K deficiency contributes to impaired bone mineralization due to under-carboxylation of osteocalcin and matrix Gla protein. This leads to reduced bone density, increased fracture risk, and in pediatric populations, developmental skeletal abnormalities.[12] Emerging research also links insufficient vitamin K to vascular calcification and arterial stiffness, potentially exacerbating cardiovascular disease progression.[4][12] These complications underscore the importance of prophylactic measures in neonates and early detection in high-risk adults, particularly those with malabsorption disorders or on long-term antibiotics. Appropriate vitamin K supplementation can prevent most severe outcomes, highlighting its critical role in maintaining hemostasis and long-term health.[4][10][14]

### **Consultations**

The management of vitamin K deficiency necessitates a multidisciplinary approach to address its diverse clinical manifestations and underlying etiologies. Hematologists are essential for evaluating and managing coagulopathies, particularly in cases of severe bleeding or when differentiating between acquired

deficiency and inherited disorders such as VKCFD. Nutritionists or dietitians provide critical guidance on optimizing dietary intake of vitamin K-rich foods (e.g., leafy greens, fermented products) and tailoring supplementation regimens to individual needs. For patients with malabsorption syndromes (e.g., celiac disease, inflammatory bowel disease), gastroenterologists play a pivotal role in diagnosing and treating the primary condition to restore adequate vitamin K absorption. In chronic or severe cases, consultations with orthopedic specialists may be warranted to assess bone mineral density and fracture risk, while cardiologists can evaluate and mitigate potential cardiovascular complications linked to vascular calcification. For neonates, pediatricians are central to ensuring timely prophylactic vitamin K administration and monitoring for signs of VKDB, particularly in high-risk populations such as exclusively breastfed infants. In suspected hereditary cases, clinical geneticists facilitate diagnostic confirmation through genetic testing (e.g., *GGCX* or *VKORC1* mutations) and provide family counseling. This collaborative framework ensures holistic care, integrating nutritional, hematologic, gastrointestinal, and genetic perspectives to optimize outcomes and prevent complications across all age groups.

### **Patient Education**

Effective patient education is critical for preventing vitamin K deficiency complications, particularly in neonates. Parents should be informed about the importance of vitamin K prophylaxis at birth to prevent vitamin K deficiency bleeding (VKDB), a rare but potentially fatal condition. Healthcare providers must clearly explain that intramuscular (IM) vitamin K injection is the most effective method, providing complete protection with a single dose, whereas oral regimens require multiple doses and carry a higher risk of failure. Addressing parental concerns about safety, clinicians should clarify that the 1990 study suggesting a link between IM vitamin K and childhood cancer has been thoroughly refuted by subsequent large-scale studies, confirming its safety.[26] For adults, particularly those with malabsorption disorders, chronic liver disease, or on long-term antibiotics, education should focus on recognizing early signs of deficiency (e.g., easy bruising, bleeding) and the role of dietary sources (leafy greens, fermented foods) or supplements. Patients with osteoporosis or cardiovascular risk factors may benefit from discussions about emerging research on vitamin K's potential benefits for bone and vascular health, though they should be advised that evidence for routine high-dose supplementation remains investigational. Tailored, evidence-based counseling ensures informed decision-making and adherence to preventive measures, optimizing outcomes across all populations.

### **Other Considerations in Vitamin K Physiology and Testing**

Vitamin K serves as an essential cofactor for multiple physiological processes beyond coagulation, including the activation of anticoagulant proteins (C, S, Z), bone metabolism regulators (osteocalcin), and vascular protectants (matrix Gla protein). However, assessing vitamin K status presents challenges due to analytical limitations. Direct measurement of vitamin K concentrations is complicated by interference from dietary lipids, variability among vitamers (K1 vs. K2 subtypes), and heterogeneous tissue distribution. While liquid chromatography–tandem mass spectrometry (LC-MS/MS) offers precise quantification, its clinical availability remains limited. Protein induced by vitamin K absence or antagonist-II (PIVKA-II), an under-carboxylated form of prothrombin, has emerged as the most practical biomarker for functional vitamin K deficiency. Unlike direct vitamin K assays, PIVKA-II reflects hepatic vitamin K activity and correlates with clinical coagulopathy, making it valuable for diagnosing subclinical deficiency. Notably, vitamin K exhibits no known toxicity even at supraphysiological doses, as excess amounts are efficiently metabolized. However, rare anaphylactoid reactions (<0.03% incidence) have been reported with intravenous phytonadione, attributed to solubilizing agents rather than vitamin K itself. These insights underscore the need for nuanced clinical interpretation of vitamin K-related testing while reinforcing its broad safety profile.

### **Enhancing Healthcare Team Outcomes for Vitamin K Management**

Vitamin K plays a pivotal role in reducing morbidity and mortality in chronic conditions such as vascular calcification and osteoporosis, where supplementation may offer protective benefits for at-risk patients.[4] An interprofessional team—including physicians, nurse practitioners, pharmacists, and

dietitians—should collaborate to identify candidates for supplementation, optimize dosing, and monitor therapeutic responses. This team-based approach ensures comprehensive care, particularly for patients with malabsorption disorders or those on long-term antibiotics who are at higher risk of deficiency. For neonates, prophylactic vitamin K administration remains a critical intervention to prevent vitamin K deficiency bleeding (VKDB), a potentially fatal but entirely preventable condition. The gold standard is a single intramuscular (IM) injection (0.5–1 mg) within the first hour of life, which provides complete protection. For infants where IM administration is declined, a structured oral regimen (e.g., 2 mg at birth, repeated at 4–6 days and 4–6 weeks) must be strictly followed for at least 6 weeks to mitigate late-onset VKDB risk.[2] Patient and family education is essential to address misconceptions and emphasize the safety and necessity of prophylaxis. Clinicians should transparently discuss the absence of evidence linking vitamin K to childhood cancer, countering outdated concerns. By fostering collaboration among pediatricians, nurses, and pharmacists, healthcare teams can ensure universal prophylaxis adherence, significantly reducing preventable neonatal morbidity and mortality.

### **Conclusion:**

Vitamin K plays an indispensable role in hemostasis, skeletal integrity, and vascular health, with deficiency posing significant risks across all age groups. For neonates, the prevention of vitamin K deficiency bleeding (VKDB) through universal intramuscular prophylaxis stands as one of modern medicine's most successful public health interventions, reducing mortality from hemorrhagic complications. The safety and efficacy of this approach are well-established, with oral regimens serving as a secondary option requiring meticulous adherence. Clinicians must address parental concerns with evidence-based counseling, dispelling outdated myths linking prophylaxis to childhood malignancies. In adults, vitamin K deficiency often arises from malabsorption, medication interactions, or inadequate dietary intake. Prompt diagnosis—supported by PIVKA-II testing—and targeted supplementation can prevent bleeding diatheses and mitigate long-term sequelae such as osteoporosis and cardiovascular calcification. Emerging research highlights vitamin K2's potential in chronic disease management, though further trials are needed to define standardized protocols. The management of hereditary conditions like VKCFD underscores the importance of genetic testing and lifelong monitoring, while interprofessional collaboration ensures holistic care for complex cases. Pharmacists optimize dosing, dietitians tailor nutritional strategies, and specialists address organ-specific complications. Ultimately, the integration of neonatal prophylaxis, public education, and personalized adult care forms the cornerstone of vitamin K deficiency management. By combining preventive medicine with advances in diagnostics and therapeutics, healthcare teams can significantly reduce the global burden of vitamin K-related morbidity. Future research should focus on refining supplementation strategies for chronic diseases and expanding access to diagnostic tools in resource-limited settings.

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## الملخص:

**الخلفية:** يُعد فيتامين ك من الفيتامينات القابلة للذوبان في الدهون، ويؤدي دورًا أساسيًا في تخثر الدم، واستقلاب العظام، وصحة القلب والأوعية الدموية. وقد يؤدي نقصه إلى اضطرابات نزيف، وهشاشة العظام، وتكلس الأوعية، ويُعد حديثو الولادة الأكثر عرضة للنزف المهدد للحياة في حال عدم تلقيهم للوقاية.

**الهدف:** تستعرض هذه المراجعة الجوانب الفيزيولوجية المرضية والآثار السريرية واستراتيجيات التدبير لنقص فيتامين ك لدى مختلف الفئات، مع التركيز على التدخلات المبنية على الأدلة لتقليل المضاعفات .

**المنهجية:** أُجري تحليل شامل للأدبيات الطبية الحديثة، والإرشادات الإكلينيكية، والتجارب السريرية الجارية، مع التركيز على وسائل التشخيص، وبروتوكولات العلاج، وتنسيق الرعاية بين التخصصات.

**النتائج:** يمكن الوقاية من نقص فيتامين ك عبر المكملات المناسبة. الوقاية عبر الحقن العضلي عند حديثي الولادة تقلل بشكل شبه كامل من الإصابة بنزف نقص فيتامين ك، في حين تتطلب الأنظمة الفموية التزامًا صارمًا. البالغون يستفيدون من تعديل النظام الغذائي أو المكملات، لا سيما من يعانون من سوء الامتصاص أو يتناولون مميعات الدم. اختبار PIVKA-II يُعد وسيلة دقيقة للكشف عن النقص، وتشير الأبحاث الحديثة إلى دور محتمل للفيتامين في الحد من الأمراض المزمنة.

**الاستنتاج:** التدخل المبكر والتنسيق متعدد التخصصات أمران أساسيان لتحقيق أفضل النتائج. تظل الوقاية عند حديثي الولادة أولوية في الصحة العامة، وتُعد الأساليب المصممة وفقًا للحالة فعالة في إدارة الحالات عالية الخطورة لدى البالغين.

**الكلمات المفتاحية:** فيتامين ك، فيلوكينون، نزف نقص فيتامين ك (VKDB) ، التخثر، الوقاية، PIVKA-II