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The Indications and Potential Complications of Supplementing with Fat-Soluble Vitamins

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Abstract

There is a seemingly infinite list of available formations of over-the-counter supplements, including vitamins. According to Grand View Research, the nutritional supplement industry has grown in popularity in recent years, increasing its worth to an estimated 140 billion dollars in 2020 globally, with vitamins accounting for 31.4% of the revenue. An estimated half of Americans take a daily vitamin or supplement. With the increasing number of people supplementing, the incidence of disease should be trending down. This literature review focuses on fat-soluble vitamins, vitamin A, D, E, and K. Supplementation of these vitamins proposes the prevention of chronic diseases such as cardiovascular disease and cancer. The mechanism behind this theory is logical; these vitamins act as antioxidants preventing damage within our body. This literature review aims to analyze the possible benefits of supplementing with fat-soluble vitamins and investigate the risks of supplementing with fat-soluble vitamins.

Supplementing these vitamins has a role when there is an overt deficiency; otherwise, there is little evidence to support the other preventative health claims. The overall recommendations are to obtain these vitamins naturally by consuming whole foods such as animal products and vegetables. The latest research suggests vitamins, like many other components, are needed to keep our bodies healthy, and our bodies require a balance for our bodies to function correctly. Additional research is necessary to have definite recommendations, especially when recommending the specific amounts required daily and the upper limit. A discussion with a medical provider is encouraged to ensure the safety of the supplement and an appropriate amount.

Keywords: Vitamin A, Vitamin D, Vitamin E, Vitamin K, deficiency, hypervitaminosis, multi-vitamin, supplement

Introduction

Vitamins are compounds necessary for adequate and efficient metabolism within the human body. The body is unable to synthesize most of these vitamins, requiring collection through diet. These organic substances divide into two categories based on the site of accumulation within the body, water-soluble or fat-soluble.

The water-soluble vitamins include vitamin C and every vitamin B form. These vitamins are hydrolyzed in the stomach, absorbed through the lining of the upper small intestine, and rapidly distributed directly into the circulation, utilized by the various organ systems. The kidneys excrete the excess in the form of urine. The excreted water-soluble vitamins do not deposit within the body. Therefore, replenishment of these vitamins requires daily intake.

The fat-soluble vitamins include A, D, E, and K. In contrast to water-soluble vitamins, these vitamins are not hydrolyzed and distributed throughout the body by the circulatory system. These vitamins require activation by the liver and kidney before being utilized. After utilizing these vitamins, these vitamins are stored in adipose tissue and within organ systems, allowing the replenishment of these vitamins to be less frequent (Fairfield, 2021).

The focus of this literature review is each of the fat-soluble vitamins. The method and effectiveness of intake for each vitamin will be associated with the recommended dietary intake and the prevalence of toxicity and deficiency in the general population. These considerations allow recommendations of identifying and initiating supplementation to the appropriate people who could benefit from supplementation of fat-soluble vitamins.

Statement of the Problem

A healthy intake of vitamins and minerals is encouraged for overall health. The recommended intake of both categories of these vitamins is a delicate balance. Each vitamin has

a naturally occurring origin, such as plants, animal products, and sunlight. There is an estimated average requirement, recommended dietary allowance or adequate intake, and a tolerable upper intake level; however, each recommendation is debated and differs for each person (Newman et al., 2019). These values are labeled as international units (IU) or microgram (mcg). However, some vitamins are more difficult to obtain for various reasons such as the preference of diet, availability of nutrients, food intolerances, and underlying health conditions. Vitamin deficiencies have been a historical concern worldwide.

In developed countries, fortifying these harder-to-obtain vitamins into commonly consumed foods has drastically decreased the frequency of deficiency (Fulgoni et al., 2011). This fortification of bread, milk, cereals, orange juice allowed vitamin intake that reached the recommended dietary allowance. Most Americans meet the recommended dietary allowance of many micronutrients. The fortifications of vitamin A and D have made the most impact on deficiency when examining the fat-soluble vitamins (Fulgoni et al., 2011). Even with this fortification, vitamin deficiencies persist but are rare in developed countries (Newman et al., 2019).

Besides fortification, there are additional ways these vitamins can be consumed, including over-the-counter supplements. The vitamin supplementation industry is becoming a massive business in developed countries. These supplements could include a multi-vitamin with variable concentrations of several vitamins, or a single vitamin with varying concentrations can be purchased. With the growing popularity of these over-the-counter supplements, the estimated amount of supplement usage in adults compared to previous years has increased in the United States (Kantor et al., 2016). When dietary intake alone is inadequate in meeting the estimated average requirement, over-the-counter supplementation is beneficial. This supplementation is

supportive in many instances of deficiency; however, these vitamins are often consumed without recommendation or supervision by a medical professional. With the immense variety of formulations and concentrations, it is difficult to determine the exact amount of each vitamin an individual acquires daily. Many of these over-the-counter supplements have amounts exceeding the recommended dietary allowance. When considering the chemistry of fat-soluble vitamins, consuming quantities higher than the recommended dietary allowance for extended periods can lead to toxicity (Blomhoff, 2001). With the increased intake of supplements, the National Poison Data System and Toxic Exposure Surveillance System have reported an increasing number of supplement exposures and toxicities, with the reported amount of over 21,000 cases annually (Rao et al., 2017). These toxicities are related to all supplements and not only fat-soluble vitamins.

Research Question

With the increasing popularity of over-the-counter vitamins and considering the chemistry of water-soluble and fat-soluble vitamins, the research before this literature review guided two questions. First, what conditions and considerations indicate supplementation with fat-soluble vitamins, and how should this be completed? Second, what are the potential risks of exceeding the recommended dietary allowance without medical supervision for each of the fat-soluble vitamins?

Methods

A comprehensive literature review was conducted utilizing research databases. These databases included PubMed, Clinical Key, Access Medicine, DynaMed, and UpToDate. The keywords included fat-soluble vitamins, vitamin A, retinoids, vitamin D, calciferol, vitamin E, alpha-tocopherol, vitamin K, phytonadione, deficiency, toxicity, hypervitaminosis, antioxidants,

prooxidants. The articles were limited to include 2010 to the present. The articles included meta-analyses, peer-reviewed journal articles, and systematic reviews.

Literature Review

A literature review includes studies promoting supplementation of fat-soluble vitamins and discouraging the overuse of these same vitamins. The first researched vitamin is vitamin A, also referred to as retinoids. The research shows this vitamin deficiency is not as standard within the population, and toxicity is more common since the use of preformed vitamin A in supplements. The most researched is vitamin D, also referred to as calciferol. Several studies are showing the benefits of vitamin D supplementations, especially in regions without direct sunlight. The last two fat-soluble vitamins are vitamin E and K, also named alpha-tocopherol and phytonadione, respectively. Deficiencies and toxicities of these vitamins at not common in the general population.

Vitamin A: Incidence of Deficiency and Toxicity, Appropriate Supplementation

Vitamin A is a subclass of fat-soluble vitamins, also referred to as retinoids. There are two primary forms of vitamin A, provitamin A and preformed vitamin A, among others occurring within the body depending on the type of form consumed, level of activation, and reservoir location (O'Byrne & Blaner, 2013). Provitamin A and preformed vitamin A both require activation. The most common form of provitamin A, beta-carotene, is found in plant sources. These forms are inefficient in creating vitamin A within the body, resulting in incidences of deficiency and the unlikelihood of toxicity. The metabolism of provitamin A into vitamin A requires feedback regulation. The activation is dependent on vitamin A status within the body. These forms are efficiently activated into vitamin A and do not require feedback regulation. The limited feedback regulation increases the risk of toxicity (Seres & Motil, 2021).

Vitamin A and its derivatives are essential for metabolism. It plays a vital role in immunity and vision (O'Byrne & Blaner, 2013). There are conflicting suggestions of recommended dietary allowance of vitamin A. According to the National Institute of Health, the recommended dietary allowance estimates 900 mcg (3,000 IU) for males and 700 mcg (2,333 IU) for females. The tolerable upper intake is 3,000 mcg (10,000 IU) for the average adult. With a multivitamin supplement and food fortified with preformed vitamin A, the intake level can easily exceed the recommended dietary allowance. The increasingly popular fish liver oil and cod liver oil capsules also contain high levels of preformed vitamin A. Along with these supplements, meal supplement bars, shakes, and gumballs contain additional supplementation vitamin A (Penniston & Tanumihardojo, 2003). There are vitamin D supplements that contain preformed vitamin A as well.

Although deficiency of vitamin A is rare within developed countries, it is essential to highlight that those specific populations would benefit from supplementation. According to the National Institutes of Health, overt vitamin A deficiency is diagnosed at a blood serum level of less than 0.7 mcmol/L. Vitamin A deficiency is the consequence of inadequate intake, including eating disorders and limited access. Other causes of deficiency involve malabsorption diseases such as cystic fibrosis, gastric bypass surgery, primary biliary cirrhosis, or chronic giardiasis, to name a few (Zalesin et al., 2010). Another population in which vitamin A supplementation is recommended is during lactation. Lactation promotes a state of nutrition depletion, and with the risks of congenital disabilities to be no longer an issue, the benefits of supplementation outweigh the risks. According to the National Institute of Medicine, the recommended dietary allowance during lactation is 1,300 mcg, increased from 700 mcg in the average adult woman.

Besides using vitamin A supplementation to combat overt deficiency, few incidences have proven to be beneficial. When looking at vitamin A supplementation and its effects on health, the idea is that supplementing with fat-soluble vitamins, including vitamin A would reduce the risk of cardiovascular disease, cancer, and other chronic disease states. The mechanism behind this idea encompasses how vitamin A acts as an antioxidant. An antioxidant protects the cells against free radicals. Free radicals cause damage at the molecular level since they contain an unshared electron. This unshared electron can steal an electron from adjacent molecules through oxidation, leading to disrupted molecular configuration and damage (Oettgen, 2019).

This antioxidant nature of vitamin A promotes the debate of the role of vitamins supplementation in cancer prevention. The research is different depending on the exact vitamin, the derivative of the vitamin use, the supplemented concentration, and the type of cancer (Greenwald et al., 2007). A double-blind observational study conducted over five to eight years researched male smokers and the incidence rate of lung cancer when consuming supplemental beta-carotene compared to the placebo of smokers with no supplementation. During the trial, each participant within the beta-carotene group received 20 mg a day. The participant criteria included men between 50-69 years who smoke five or more cigarettes a day. Other exclusion criteria included previous cancer diagnosis or another severe illness diagnosis. Prior supplementation of vitamin A was not allowed. The participants were stratified based on the type and quantity of cigarettes smoked; results were adjusted based on cigarette tar content. Among the 29,133 participants, there was a 16% increase in lung cancer incidence after supplementing with beta-carotene, an unexpected result since beta-carotene is considered the safer derivative of vitamin A found naturally in plants. An even more unexpected finding of a 39% increase in lung

cancer rates following supplementation of beta-carotene and retinyl palmitate combined, another derivative of vitamin A. The elevated incidence was independent of tar content within the cigarettes. When supplementing with beta-carotene, each category of cigarettes had a significantly higher risk of developing lung cancer regardless of tar content, with ultralight cigarettes showing an HR of 1.31, 95% CI [0.91 to 1.8] and nonfiltered cigarettes showing an HR of 1.22, 95% CI [0.91 to 1.64]. The nicotine content is similar with ventilated cigarettes with an HR of 1.23, 95% CI [0.98 to 1.54] and nonfiltered cigarettes with an HR of 1.22, 95% CI [0.91 to 1.64]. The strengths of this study include the randomized trial, large sample size, and quantifying data on smoking behavior. The weaknesses include the sample consisting of only male participants (Middha et al., 2019).

During pregnancy, the intake of essential micronutrients directly affects the fetus's health and development alongside maintaining the mother's overall health. An increased intake of several important micronutrients is proven to be beneficial for the fetus's health. When considering the fat-soluble vitamins in pregnancy, consuming the recommended dietary allowance is vital while not exceeding the tolerable upper intake limit (Hovdenak et al., 2012). Vitamin A plays a role in ensuring a healthy birth weight and ocular, bone, skin, and mucosa development. During pregnancy, there should be regulation of the consumption of vitamin A since it is teratogenic in concentrations above 3,000 IU a day (Bastos et al., 2019). This amount has dramatically decreased compared to the previously estimated amount of 15,000 IU a day (Rothman et al., 1995). The regulation is crucial during the first trimester when teratogenic effects occur. Overconsumption of vitamin A during the first trimester has led to congenital malformations of the central nervous, cardiovascular system, or spontaneous abortion. For this reason, supplementation or ingestion of foods rich in vitamin A is contraindicated during

pregnancy (Bastos et al., 2019). Another study found that when vitamin A or beta-carotene supplementation in pregnant women remains within the recommended dose, it does not reduce all-cause maternal, fetal, or infant mortality (West et al., 2011). Overall, supplementation of vitamins during pregnancy should be a shared decision between the patient and their medical provider.

Along with pregnancy, there are other conditions in which vitamin A supplementation should be highly regulated. With chronic kidney disease, vitamin A accumulates since the kidneys are vital in the metabolism and excretion of vitamin A. In healthy kidneys, dietary vitamin A is converted to retinol then stored in the liver before activating into the active form of retinoic acid. The excess vitamin A is degraded and excreted by the kidneys. In late-stage chronic kidney disease, the serum levels of vitamin A elevate without supplementation ($p=0.03$). These elevated levels of vitamin A correlate with higher calcium levels ($p<0.001$), which has its associated risks. One limitation of this observational study was the small sample size. (Manichavasagar et al., 2014).

Since vitamin A is a fat-soluble vitamin, there is an incidence of toxicity if taken in excess. There are two different excess methods, including sudden extreme intake, this is uncommon, but the effects are less harmful than chronic excess. In chronic excess of vitamin A, the adipose tissue stores vitamin A causing an extended time of higher levels of the vitamin. The storage of excess vitamin A results in a harmful elevation of vitamin A after discontinuing excess intake. Liver damage is the most common outcome of prolonged excess vitamin A levels, but other symptoms include increased intracranial pressure, dizziness, nausea, pain in joints or bones, coma, and death. The excess levels of vitamin A are attributed to performed A, as compared to the beta-carotene. Alternatively, the consumption of excess beta-carotene relates to

the most common adverse effect of developing an orange tint to the skin, which is benign and reversible (Johnson & Russel, 2015).

The use of over-the-counter vitamins for chronic disease prevention is a common occurrence. This systematic review examines the evidence related to the benefits and potentials harms of vitamin supplements. The United States Preventative Services Task Forces determined there is insufficient data to recommend the use of vitamin supplements to prevent chronic disease. With the help of beta-carotene supplements, a form of vitamin A, the Task Force discouraged their use, considering the augmented risk of lung cancer in the smoker when supplementing with beta-carotene (Fortmann et al., 2013).

In conclusion, Vitamin A supplementation has its indications to include instances of deficiency and increased nutrition depletion. Considering the delicate balance of vitamin A, it is encouraged to have adequate medical supervision while supplementing. The issue with supplementation of preformed vitamin A in the form of vitamin A has a higher likelihood of toxicity (Penniston & Tanumihardojo, 2003).

Vitamin D: Incidence of Deficiency and Toxicity, Appropriate Supplementation

There are two different types of vitamin D: D2 and D3. D2, also labeled ergocalciferol, is found in plant sources, while D3 or cholecalciferol's sources are animal products. Vitamin D deficiency is one of the more common vitamin deficiencies in developed countries with its two primary sources, diet and sun exposure. Vitamin D requires hydroxylation before the body can utilize the nutrient. This hydroxylation occurs within the liver resulting in the product of calcidiol. The kidneys hydrolyze the calcidiol to the final product of calcitriol. This homeostatic mechanism prevents overproduction of vitamin D intoxication from the primary source of sun exposure; this mechanism is nonexistent when regulating dietary vitamin D, including

supplements (National Institutes of Health, 2021). Vitamin D has several functions, including promoting calcium absorption to maintain adequate serum calcium for healthy bone mineralization during bone growth and remodel. The vitamin also has roles in reducing inflammation, cell growth, and immune function (Jones et al., 2014).

There have been multiple revisions to the recommended dietary allowance of each fat-soluble vitamin. The recommended dietary allowance is based on the general population and does not account for individual needs. These suggestions differ between developed countries (Passeron et al., 2019). According to the National Institute of Health, the recommended dietary allowance of vitamin D is 15 mcg (600 IU) for the average adult. These recommendations do not increase with pregnancy. The tolerable upper intake of vitamin D is 100 mcg (4,000 IU) for the average adult. If the concentrations exceed the recommended dietary allowance, adverse effects can occur, especially with long-term use (Biesalski et al., 2017). The recommended serum level of vitamin D for the average adult is greater than 32 ng/ml, but recommendations vary from 25 ng/ml to 100 ng/ml (Passeron et al., 2019). Most of the body's vitamin D is synthesized by the skin and sourced from the sun's UVB rays. Sunscreen use during sun exposure helps prevent skin cancers, but is the sunscreen limiting the amount of vitamin D synthesized by the body? In theory, sunscreen should decrease the amount of serum vitamin D by blocking UVB rays from the skin. A meta-analysis conducted by a panel of dermatologists predicts that sunscreen had no significant effect on serum vitamin D levels. Randomized control trials are unethical with exposing the control group to ultraviolet radiation without sunscreen protection. Alternatively, questionnaire-based studies report no correlation between sunscreen use and serum vitamin D levels. Questionnaire-based studies have drawbacks such as limited controls, compliance, and confounding factors (Passeron et al., 2019).

Five to thirty minutes of sun exposure in the late morning to afternoon is adequate to achieve the desired amount of vitamin D synthesis (Holick, 2007). The amount of Vitamin D from the sun ultimately depends on geographic location and the amount of sun-exposed skin. A study utilized 120 participants over six weeks. Exclusion criteria for the participants include prior vitamin D supplementation, non-Caucasian skin tone, and skin disorders. The study identified serum vitamin D measurements parameters to include deficient at less than five $ngml^{-1}$, sufficient of greater than 20 $ngml^{-1}$, and an optimal level of greater than 32 $ngml^{-1}$. Serum vitamin D was collected for a baseline and at each following week during the duration of the study. During the six weeks, the measured serum vitamin D levels increased by 10.4 $ngml^{-1}$ from 17.6 $ngml^{-1}$ totaling 28 $ngml^{-1}$. These measurements are statistically calculated to the requirement of nine minutes of 35% of exposed skin in the summer months to reach the desired serum level in San Diego. In the winter months at the exact location, it requires thirty-nine minutes. When comparing summer and winter sunlight at higher latitudes, the amount of the sun is insufficient at latitudes above 35-40 degrees north. The strengths of this study controlled the dietary intake of participants, study duration, and interval of vitamin D measurements. The weaknesses of the study include the small sample size and the statistically calculated geographic location estimates (Rhodes et al., 2010).

When looking specifically at fat-soluble vitamins, vitamin D deficiency remains common in the United States. The deficiency is related to decrease sun exposure, the most common source of vitamin D (Newman et al., 2019). An estimated 37% of adults experience deficiency due to inadequate sun exposure and poor dietary intake. Since vitamin D deficiency is common, there are ample supplements containing vitamin D. Vitamin D deficiency is associated with increased risk for developed cardiovascular disease, dementia, Alzheimer's disease, certain cancers such as

colon and breast, respiratory infections, and asthma. Several risk factors for vitamin D deficiency include liver disease, kidney disease, pregnancy, breastfeeding, limited sun exposure, malabsorption, poor nutritional intake, drug interactions, pigmented skin, age, and a high body mass index (Waterbury, 2018).

The combination of vitamin D and calcium is routine when treating bone health. Osteopenia and osteoporosis affected an estimated 56 million Americans in 2010. Osteoporosis-related fractures total over two million each year. The meta-analysis of randomized controlled trials supports calcium and vitamin D as prevention for fracture risk. The meta-analysis utilized literature databases to select 30,970 participants. The combination of calcium and vitamin D supplementation is statistically significant, specifically reducing the risk of hip fracture with an HR of 0.70, 95% [0.73-0.98] and the overall risk of fracture with an HR of 0.85, 95% [0.73-0.98] (Weaver et al., 2015).

There is a theory that vitamin D supplementation can lower blood pressure and decline the incidence of hypertension. The mechanism behind this theory relates to vitamin D's role in regulating the activity of the renin-angiotensin system. Supplementation of vitamin D can decrease this system's activity by lowering renin, aldosterone, and angiotensin levels, resulting in lower blood pressure. A meta-analysis with 4,744 participants focusing on vitamin D supplementation in cases with no prior vitamin D deficiency had no significant reduction of both systolic with an HR of -0.68 mmHg, 95% CI [-2.19 to 0.84] and diastolic with an HR of -0.57 mmHg, 95% CI [-1.36 to 0.22] (Golzarand et al., 2016). The doses of vitamin D supplementation varied between 200 to 12,000 IU a day. One subset of the study that observed a significant decrease in blood pressure parameters was individuals who consumed 800 IU a day for less than

six months ($p<0.001$). When supplementation exceeded six months, there was no significant decrease (Golzarand et al., 2016).

Although toxicity from vitamin D supplementation is not a common concern, overconsumption has serious adverse effects. Before recommending supplementation of vitamin D, the recommendation is to test for deficiency. The levels of vitamin D are clinically measured using the levels of D2 and D3 within the blood measured as 25-hydroxyvitamin D3, otherwise known as calcidiol. These levels may not accurately reflect stores of vitamin D within the liver, muscles, and adipose since vitamin D is lipid-soluble (Zarubtaj et al., 2019). Numerous studies show that serum calcium and phosphate levels rise above standard limits after vitamin D intoxication, even while serum vitamin D remains low.

There have been increasing reports of intoxication-related to the misuse of vitamin D supplements (Taylor & Davies, 2018). Hypervitaminosis D from diet and sun exposure alone is nearly inconceivable since the synthesis of endogenous vitamin D within the skin regulates feedback mechanisms. With vitamin D toxicity, the usual symptoms include hypercalcemia, confusion, apathy, recurrent vomiting, abdominal pain, polyuria, polydipsia, and dehydration. Although these symptoms are typically a consequence of vitamin D toxicity, there are instances where no symptoms result from the toxicity. When toxic levels of fat-soluble vitamins occur, this study found the elevated levels remained for up to eight weeks following cessation of the supplement (Rahesh, 2019). Because of this, supplementation with vitamin D needs careful consideration to avoid adverse effects (Razzaque, 2017).

Along with the inability to accurately measure the stores of vitamin D throughout the body, the optimal amount of serum 25-hydroxyvitamin D3 levels is debatable. A meta-analysis showed vitamin D supplementation results in changes in calcium metabolism, which includes

risks of hypercalcemia and hypercalciuria (Malihi et al., 2016). The risk of hypercalcemia increases when the individual is taking a thiazide diuretic. Thiazide diuretics are a common medication that can decrease urinary calcium excretion (Robien et al., 2013).

There is an idea that vitamin D supplementation increases incidences of kidney stones; however, a meta-analysis indicated there was no significant increase in kidney stone formation following vitamin D supplementation ($p=0.72$), with and without additional calcium supplementation. (Malihi et al., 2018). The meta-analysis included 3,150 participants supplementing over 2,800 IU a day for a year.

The same meta-analysis reviewed the possibility of other long-term adverse effects secondary to vitamin D. The studies suggest long-term high-dose vitamin D supplementation did not increase total adverse events compared to placebo in 1,731 participants from 10 studies ($p=0.61$). However, throughout the included studies, there was a trend for supplemental vitamin D to increase the risk of hypercalcemia in 2,598 participants from ten studies ($p=0.05$). The severity of symptoms typically correlates with the severity of hypercalcemia. The meta-analysis did not disclose the values related to hypercalcemia. Complications of hypercalcemia vary from asymptomatic to severe depending on the magnitude of abnormality, along with underlying co-morbidities. The strengths of the meta-analysis are the large sample size, the ability to exclude studies not meeting criteria, and the controls including calcium intake over all the studies utilized. The weakness includes the difference in definition in excess vitamin D and its toxicity levels between studies (Malihi et al., 2018).

When supplementing with vitamin D aimed at lowering blood pressure, one cohort of individuals within the study showed increased blood pressure levels. Individuals with an increased body mass index showed a significant increase in blood pressure parameters

independent of baseline health ($p < 0.001$). The mechanism behind this elevation is unclear, but the increased amount of adipose tissue that causes higher vitamin D levels is required to be effective is the most recent idea (Golzarand et al., 2016).

Vitamin E: Incidence of Deficiency and Toxicity, Appropriate Supplementation

Vitamin E is the third fat-soluble vitamin discussed during this literature review. Like the other fat-soluble vitamins, vitamin E can be found naturally within dietary sources, mainly plant products. There are two forms of vitamin E, tocopherols and tocotrienols. Among the tocopherols and tocotrienols exist several isoforms. These isoforms have variable biological activity within the liver and small intestine. The isoform secreted by the liver is alpha-tocopherol. This secretion results in blood and cellular concentrations that consist primarily of alpha-tocopherol. Much of the research related to vitamin E revolved around alpha-tocopherol for this reason (National Institutes of Health, 2021).

Vitamin E plays an essential role in an individual's overall health by acting as an antioxidant, like vitamin A. In addition to its antioxidant property, it has a role in immune function, cell signaling, and genetic regulation. The National Institute of Health has a recommended dietary allowance of vitamin E is 15 mg (22 IU) for the average adult. This recommendation remains during pregnancy or lactation. The tolerable upper limit of vitamin E is 1,000 mg (1,492 IU) for the average adult. Both deficiency and toxicity related to vitamin E are rare within developed countries. The most common adverse effect of hypervitaminosis E is hemorrhage because of the interruption of coagulation pathways, specifically platelet aggregation (Pastori et al., 2013).

Like vitamin A, vitamin E acts as an antioxidant within the human body. Recall, antioxidants protect against the damaging effects of free radicals. Because vitamin E acts as an

antioxidant, the theory is that the consumption of vitamin E prevents the development of chronic disease. Even though vitamin A demonstrated no evidence in preventing chronic disease, vitamin E supplementation may promote protection against the development of coronary heart disease and possibility other chronic disease states.

Coronary artery disease is a result of buildup in the arteries that supply the heart muscle. This buildup of plaque is related to the amount of cholesterol within the bloodstream, called atherosclerosis. Several risk factors for developing coronary artery disease include hypertension, dyslipidemia, diabetes, obesity, inactive lifestyle, and smoking. The prevention or delay of coronary artery disease with the consumption of vitamin E consists of two primary mechanisms. The first mechanism is from the vitamin inhibiting the oxidation of low-density lipoprotein cholesterol, the cholesterol essential for the development of atherosclerosis (Ziegler et al., 2020). The second mechanism consists of vitamin E preventing the formation of blood clots (Glynn et al., 2007). Even with these proposed mechanisms of protection, the randomized clinical trials suggest hesitation. When looking at the effect of vitamin E on each risk factor, the results are inconsistent. In an observational study of 3,507 participants, increased vitamin E intake significantly lowers systolic blood pressures ($p=0.012$). The strengths of this study include the moderate sample size and the detailed observation of diet. The drawbacks to this study were that the participants with higher vitamin E intakes had an overall healthier diet with less smoking and drinking alcohol (Kuwabara et al., 2014). A meta-analysis comprising eighteen trials totaling 839 participants summarized a significant decrease in systolic blood pressure following vitamin E supplementation compared to the placebo of no supplementations noting an HR of -3.4 mmHg, 95% CI, [-6.7 to -0.11] and $p>0.001$. There was no significant effect on diastolic blood pressure (Emami et al., 2019). Despite these findings, three separate clinical trials utilizing antioxidant

therapies for hypertension management produce controversial results (Sorriento et al., 2018). One consideration about these studies looking at heart disease is that most studies involve patients with existing risk factors.

Vitamin E and its effects on cancer and neurological disease are comparable to the results of heart disease. A study consisting of 29,367 men analyzed the incidence of prostate cancer when supplementing with vitamin E. The exclusion criteria included a previous cancer diagnosis, no previous prostate screening, and men who did not provide a dietary history. The supplementation cohort took an average of 300 IU daily over the eight-year study. The study concluded no correlation between vitamin E intake and the incidence of prostate cancer. The strengths of this study were the large sample size, the eight-year duration of the study, and the monitored dietary intake. A weakness includes not excluding known cancer-causing agents such as cigarette smoking. Another disadvantage is not excluding individuals with a family history of prostate cancer (Kirsh et al., 2006).

Vitamin E is considered neuroprotective because of its antioxidant activity since free radicals play a substantial role in many disease states, including Alzheimer's disease and cancer (Fukui, 2019). However, at this time, vitamin E supplementation is not recommended in slowing the decline of neurological function (Espeland, 2006; Isaac et al., 2008).

Vitamin K: Incidence of Deficiency and Toxicity, Appropriate Supplementation

Vitamin K is the final fat-soluble vitamin discussed with this literature review. There are two primary forms of vitamin K: phylloquinone and menaquinones. The primary sources of vitamin K are plants in the form of phylloquinone or the production by bacteria within the gut in menaquinones. Vitamin K is essential in hemostasis, bone metabolism, and other functions. The incidence rate of vitamin K deficiency and toxicity is rare in the United States (Seres & Motil,

2021). According to the National Institute of Health, the recommended dietary allowance of vitamin K in an average adult is 120 mcg for males and 90 mcg for females. These recommendations do not change with pregnancy or lactation. The National Institute of Health does not state a tolerable upper limit for vitamin K.

The population with the highest incidence of vitamin K deficiency is neonates. Neonates are most prone to become deficient because the bacteria that produce vitamin K in an adult's intestine has not colonized the neonates' intestine, potentially leading to deficiency. Because of the high prevalence of deficiency, administering an intramuscular dose of vitamin K at birth prevents vitamin K deficiency bleeding in neonates. The injection is clinically more effective than the oral form of vitamin K (Marchili et al., 2018).

Vitamin K deficiency is a risk factor in developing osteoporosis since vitamin K is involved in osteocalcin synthesis. Research on the effects of vitamin K on bone health and the prevention of osteoporosis is underway. A study of 381 postmenopausal women receiving supplementation of one mg of phylloquinone (vitamin K1) indicated no significant improvement of serum markers of bone turnover and the bone mineral density of the pelvis and spine. A drawback of this study was the limited study duration of one year. The subjects were also already postmenopausal, limiting osteoporosis prevention potential (Binkley et al., 2009). In addition, a meta-analysis that utilized the EMBASE database investigated 222,292 participants who indicated no significant increase of total circulating osteocalcin when supplementing with either phylloquinone or menaquinone (Chen et al., 2019). It is important to note that these studies are difficult to conduct without combining vitamin D supplementation, which, as previously discussed, is essential in preventing osteoporosis.

Another potential benefit of vitamin K is its role in vascular calcification. Vascular calcification is a significant risk factor for coronary artery disease. Vitamin K is a component of the protein that has a role in preventing vascular calcification. An observational study looking at 564 individuals supplementing with vitamin K found a correlation between high doses of vitamin K and the decreased risk of coronary artery calcification. The supplementation of menaquinone (vitamin K2) demonstrated an HR of 0.80, 95% CI [0.65-0.98]. Limitations of this study were the sample size and the variable supplementation of menaquinone (Beulens et al., 2009). A meta-analysis of 222,592 participants assessed the correlation between vitamin K and the incidence of cardiovascular disease. The analysis associated increased incidence of cardiovascular disease with a vitamin K deficiency marker with an HR of 1.84, 95% CI [1.48-2.28], confirming vitamin K deficiency is a risk factor in cardiovascular disease development. The meta-analysis identified the weakness of a small number of studies available (Chen et al., 2019). The development of research is complicated since the contraindication of vitamin K supplementation and anticoagulation therapy, a therapy commonly employed in individuals with increased risk of coronary artery disease.

As previously stated, vitamin K toxicity is uncommon; however, several circumstances inhibit the use of vitamin K supplementation. Since vitamin K plays a vital role in the coagulation pathway, it is essential to closely monitor vitamin K intact with patients who require warfarin therapy. Vitamin K-rich foods or supplements can dramatically affect the patient's international normalized ratio (INR).

Discussion

The chemistry of fat-soluble vitamins makes them unique compared to other vitamins since they are stored within the body and can act as additional reservoirs. For optimal health, it is

vital to maintain the preferred intake of each vitamin respectively. The deficiency of these vitamins has been decreasing following the fortification of familiar food sources and the increasing popularity of over-the-counter supplements. Even with these interventions, deficiency remains a concern, especially with vitamin D. However, with other fat-soluble vitamins, deficiency is rare. The anticipation of supplementation of these fat-soluble vitamins will be variable between individuals based on diet, food intolerance, underlining health conditions, and sun exposure.

The efficient and healthiest method of obtaining these micronutrients is through natural dietary intake. However, the popularity in the supplement industry has drastically increased in recent years. The average adult with a healthy diet does not need to purchase a vitamin supplement, especially a single vitamin supplement.

Natural food sources should be the primary sources when obtaining the recommended dietary allowance of all the micronutrients. When utilizing over-the-counter supplements, the forms of these micronutrients often differ from the natural sources, affecting how the body uses them. The body has mechanisms in place to activate and regulate the desired amount of each micronutrient, but these mechanisms are only valuable when converting the forms found in natural sources (Lentjes et al., 2019).

This literature review dealt with each fat-soluble vitamin individually. More frequently, these vitamins consist of a multivitamin. The same considerations are applied when purchasing a multivitamin. An estimated 51% of Americans take a multivitamin containing 100% of the recommended dietary allowance of at least nine micronutrients. A typical multivitamin contains three fat-soluble vitamins without vitamin K. The formulations of multivitamins have various combinations for personalization.

Multivitamins or single vitamin supplements that are taken should be the lowest dose available. The formulations with high amounts of single to several vitamins have the potential to lead to toxicity. This risk multiplies when taking a combination of a multivitamin in addition to a supplement with a single vitamin (Biesalski et al., 2017).

In conclusion, if an individual with no known deficiencies wants to supplement with the belief of promoting health and chronic disease prevention, it is safer to supplement with one multi-vitamin to avoid consuming excess instead of consuming several different vitamins.

Applicability to Clinical Practice

When determining if vitamin supplementation is necessary, a medical provider should take a thorough history of symptoms, diet, sun exposure, and medical conditions. If a supplement proves beneficial, a multivitamin is recommended before individual vitamin formulations (Macpherson et al*.,* 2013). If an overt deficiency exists, then dietary and supplemental intake of that vitamin should be discussed and customized to meet the specific concentrations needs. After initiation of the supplements, the deficiency requires monitoring periodically.

When considering the use of an over-the-counter supplement, there are several items to consider. First, have a conversation with a medical professional before starting a supplement. While there are indications for several of the supplements we previously discussed, individuals often meet their recommended dietary allowance from their diet. If there is a concern of deficiency, additional education on achieving adequate nutrition is the next step. The second item to be considered is Food Drug and Administration (FDA) approval. Many of the supplements on the market are FDA approved, but several are not. FDA approval is necessary for reassurance the supplement and its contents are accurately labeled. An explanation for the over ingestion of these vitamins is related to the limited regulation of these over-the-counter

supplements. Supplements are categories by the Federal Food and Drug Administration as "products." This category has minimal quality regulation compared to the supervision of prescription medications. There has been severe intoxication of fat-soluble vitamins and other supplements due to the mislabeling or conflicting concentrations (Saljoughian, 2021). The last considerations highlighted in this literature review is the price of the supplement. It is unnecessary to spend additional money on a supplement if a cheaper option is also FDA-approved.

Individuals who are recommended to supplement with all the fat-soluble vitamins and other vitamins and minerals are individuals with malabsorption disorders and eating disorders. Other individuals who would benefit from several different vitamins and minerals are individuals with an increased requirement, such as pregnant women, breastfeeding mothers, or athletes (Weisberg et al., 2004).

The groups of individuals listed previously would benefit from vitamin A supplementation. When supplementing with vitamin A, the safer form of beta-carotene should be utilized compared to the other forms.

There are subsets of populations that vitamin D supplementations are proven to be beneficial. Another population subset who should take supplemental vitamin D is individuals with limited sun exposure, especially in winter. As stated previously, individuals who live above 35-40 degrees north latitude require additional vitamin D supplementation. Individuals with darker skin absorb less UVB and should also supplement. These individuals should take additional vitamin D no matter the amount of sun exposure. Another subset of individuals who should supplement with vitamin D are individuals at high risk for developing osteoporosis. According to UpToDate, the suggested amount is 600 to 800 IU a day (Rosen, 2021).

When considering vitamin E supplementation, some specific individuals would benefit. The first occurrence is with premature infants less than 1,500 grams. Implementing vitamin E into their regimen might reduce complications related to the retina (Brion et al., 2003). The other specialty population with vitamin E supplementation in patients with abetalipoproteinemia, a genetic disorder resulting in poor absorption of dietary fat. These individuals require large doses of vitamin E, along with other nutrients (Traber et al., 2006). Typical over-the-counter supplements provide more than 67 mg of vitamin E, which is substantially higher than the recommended dietary allowance; however, toxicity remains uncommon (National Institutes of Health, 2021).

Vitamin K has similar indications for supplementation as the previous vitamins. The main concern with supplemental vitamin K is the interaction with warfarin. Warfarin is a common anticoagulant medication utilized by millions of Americans. Vitamin K can affect how warfarin works, altering the patient's INR. This interaction can lead to severe consequences for the patient. Patients on anticoagulation therapy such as warfarin are educated about appropriate vitamin E intake.

In conclusion, before any supplementation to an individual's regimen, a conversation with a healthcare professional should be completed. If there is a suspected deficiency, serum levels should be completed before initiation for confirmation of deficiency. If an overt deficiency is found, sufficient dietary intake should be attempted prior to supplementation. Education before beginning a supplementation is essential to maximize absorption and increase efficacy.

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