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Potential Dietary Supplement-drug Interactions: Fat-soluble Vitamins

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***SUMMARY*. Dietary supplement marketing and use have exploded in popularity over the last two decades. Dietary supplements can interact with prescription and over-the-counter drugs in various ways. Some supplements can interfere with the way a drug is absorbed or metabolized, or they can increase or decrease the effectiveness of a drug. Some drugs can affect the metabolism of supplements, making them more or less potent. The existing clinical data concerning dietary supplement adverse events and drug interactions can be ambiguous and often contradictory, which makes it difficult for healthcare providers to counsel patients about supplements. This review was designed based on data obtained from relevant online research articles using the phrases dietary supplements-drug interactions, and fat-soluble vitamins up to June 2022 on PubMed and Google Scholar. The goal of this review was to look at the known fat-soluble vitamin supplement-drug interactions. Such an overview would make it easier for healthcare providers to communicate these documented interactions and contraindications to their patients, preventing significant adverse events and improving therapeutic outcomes.**

RESUMEN. La comercialización y el uso de suplementos dietéticos se han disparado en popularidad en las últimas dos décadas. Los suplementos dietéticos pueden interactuar con los medicamentos recetados y de venta libre de varias maneras. Algunos suplementos pueden interferir con la forma en que se absorbe o metaboliza un fármaco, o pueden aumentar o disminuir la eficacia de un fármaco. Algunos medicamentos pueden afectar el metabolismo de los suplementos, haciéndolos más o menos potentes. Los datos clínicos existentes sobre los eventos adversos de los suplementos dietéticos y las interacciones farmacológicas pueden ser ambiguos y, a menudo, contradictorios, lo que dificulta que los proveedores de atención médica aconsejen a los pacientes sobre los suplementos. Esta revisión se diseñó en función de los datos obtenidos de artículos de investigación en línea relevantes que utilizan las frases interacciones entre suplementos dietéticos y medicamentos y vitaminas liposolubles hasta junio de 2022 en PubMed y Google Scholar. El objetivo de esta revisión fue analizar las interacciones conocidas entre los suplementos de vitaminas liposolubles y los medicamentos. Tal descripción general facilitaría que los proveedores de atención médica comuniquen estas interacciones y contraindicaciones documentadas a sus pacientes, previniendo eventos adversos significativos y mejorando los resultados terapéuticos.

INTRODUCTION

Dietary supplements are manufactured products intended to supplement the diet including vitamins, minerals, amino acids, herbs, and botanicals. The increased consumption of supplements is supposed to provide health benefits; however, overconsumption may result in higher amounts of supplements that the body may be unable to tolerate. As a result, consumers are exposed to health risks due to excessive consumption of dietary supplements. The risk of

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supplements becomes more serious when consumed without medical supervision [1].

Among nutritional supplements; multivitamins, mineral supplements, calcium supplements, and omega-3 fatty acids or fish oil are considered to be the most consumed products. About a quarter of the supplements are used based on the advice of healthcare providers [2]. Thus, most dietary supplement usage is made by the consumer's decision. Despite their wide use, the health benefits of dietary supplements are questionable. Several diseases such as scurvy, beriberi, pellagra, and rickets are caused by a lack of vitamins. However, the vitamin content of a normal well-balanced diet is sufficient to avoid these diseases. There is no or limited evidence suggesting vitamins or any other dietary supplements can lower the risk of disease nor have health benefits in well-nourished individuals since studies aimed at determining the effects of supplements often give conflicting results [3-6].

In recent years, the consumption of nutritional supplements has grown tremendously. Patients may use dietary supplements to make them feel better, improve their health, and prevent or treat illness [7,8]. Therefore, this review series aims to identify the potential interactions of dietary supplements with the prescribed medications. In this first part of the review series, the potential interaction of fat-soluble vitamins with medications will be presented. In the upcoming instalments of this review series, other dietary supplements, including water-soluble vitamins and minerals, will be discussed.

Supplement-drug interactions

The interaction is an alteration of the drug's mechanism of action by the concomitant presence of a substance such as dietary supplements, food or other drugs that may increase or decrease the pharmacological effects of medications [9]. Three types of interaction can be identified: drug-disease; drug-drug; drug- supplement and Miscellaneous-drug interactions [9]. The reaction mode of drug combination is classified into three main categories of interaction: synergistic; antagonistic and null reaction [10]. Therefore, combined supplements-drug could potentiate the effects of the drug (synergistic), antagonize its effects by a decrease in therapeutic efficacy or there is no outcome impact [11].

The use of medications for chronic diseases can induce a risk of the development of subclinical or clinical micronutrient malnutrition which may develop gradually over the long-term use of medications. Dietary supplements can interact physically; chemically, physiologically or pathophysiological with a medication. Consequently, dietary supplements would alter the pharmacokinetic properties of medication, with a potential mutual impact of medications on micronutrient oral bioavailability [12]. For this review, table 1 shows the severity of rating scale categories of supplement-drug interactions that will be used for the description of the risks of adverse effects for the concomitant use of supplementation with prescribed medications. These Rating scale categories are only a guideline [13].

Vitamins

Vitamins are organic compounds and are required in limited quantities for optimal physical condition. Humans cannot produce sufficient amounts (if at all) of most vitamins, thirteen essential vitamins are available in formulated supplements. Vitamins play an essential role in many biochemical reactions of the human body and work as coenzymes or cofactors [14].

Relatively, high voluntary consumption of vitamin supplements and fortified food may be associated with higher than recommended dietary reference intake. Vitamin supplements can be considered as a medication with physiological and pharmacological effects, and consequently, adverse effects including drug interactions [15,16]. The Food and Drug Administration (FDA) determined that consumers of dietary supplements consider vitamins as safe supplements and can be used without prescription or the supervision of healthcare providers. The as-

Severe	Avoid combinations, serious supplement-drug interactions
Moderate	Avoid combinations; unless the benefits outweighed the risks
Minor	Supplement-drug interaction is small. Monitoring plan and (if possible) alternative drug consideration
Unknown	Not enough information is available

Table 1. Rating scale categories of supplement-drug interactions.

sociated adverse effects of vitamins are underreported and the FDA receives less than 1% of supplements-associated adverse events [17]. Certain vitamins are associated with potentially serious adverse reactions such as vitamin A at high intakes, while other vitamins have minor and reversible adverse events such as vitamin K [18,19].

Families of younger children are more likely to tell their physician about the use of vitamins but still, there is a gap in reporting the use of vitamins for children versus parents [20]. The potential risks and benefits of using vitamins concurrently with medications in children should be considered by parents and healthcare providers, and providers should ask about vitamin use and advise caution concerning potential interactions. In one survey of 1804 children visiting the pediatric emergency department (Canada) [21], one-third of the children using vitamins, had potential vitamin interactions with their prescribed medications in the preceding 3 months. Of these, two or more protentional interactions were identified. The major concern interactions were vitamin C with aspirin (33%), vitamins D, B6, folic acid and B12 with corticosteroids (29%), whereas niacin, folic acid and vitamin E with ibuprofen (15%). Pharmacokinetic interaction was about 60% of vitamin-drug interaction and modified absorption was the most. Despite numerous possible interactions, only 62% of parents/caregivers report that the child had vitamin supplementations to their general practitioner [20,21].

Although dietary supplements including vitamins have been found relatively safe and regulated as a food by the FDA, vitamins may be associated with potential health issues to consider their reclassification as OTC medications, as opposed to dietary supplements [19].

The potential fat-soluble vitamin adverse reaction with prescribed medication

Vitamin A

Iron. Interaction of vitamin A with iron absorption in the intestinal tract does not occur directly but acts by depletion of iron stores. Vitamin A acts by stimulating the manufacturing of transferrin by increasing iron moving from plasma to the tissues is another possible mechanism. Lower serum iron level is when high doses of vitamin A are taken, whereas low doses favor iron absorption [22]. Iron taken concurrently with vitamin A (antioxidant) may lead to hydroxyl radical production.

Hepatotoxic drugs. Both pexidartinib (anticancer) and pretomanid (antibacterial) are hepatotoxic and have a major risk of hepatotoxicity when taken concurrently with vitamin A. Consumption of vitamin A with hepatotoxic drugs in large amounts (*e.g.* carbamazepine, amiodarone, isoniazid, methotrexate, acetaminophen) also has a toxic effect on the liver. Taking vitamin A along with mipomersen requires liver function test monitoring since both drugs have the potential to elevate hepatic enzymes [19].

Tetracyclines antibiotics. The risk of intracranial hypertension can be increased when taking tetracyclines and vitamin A concurrently in high doses, Normal doses of vitamin A along with tetracyclines do not seem to cause this problem. Some of the tetracyclines include demeclocycline, minocycline are also associated with hepatotoxicity [23].

Warfarin. Vitamin A raises clotting time as does warfarin which increases bleeding tendency and toxicity problems of both drugs [24].

Atorvastatin. Over two years of treatment for high cholesterol with diet and HMG-CoA reductase inhibitors, blood vitamin A level is elevated. People on HMG-CoA reductase inhibitors, such as atorvastatin and fluvastatin, should have their vitamin A level checked if they wish to supplement [24].

Gabapentin. Anticonvulsant medications can indeed induce birth abnormalities. and their toxicity may be connected to low vitamin A levels in the blood. According to one controlled study, using numerous anticonvulsant medicines causes significant alterations in how the body consumes vitamin A [25].

Isotretinoin. Isotretinoin interacts with vitamin A, and the risk of hypervitaminosis A resulting from combining these medications may increase, a condition that stems from excessive vitamin A-related effects [26].

Minerals oils. Mineral oil has hindered the absorption of various minerals and supplements, notably vitamins A and C. Taking multivitamin-mineral supplements simultaneously should be avoided or taking them two hours before or after mineral oil [27].

Neomycin. Many nutrients, including vitamin A, can be reduced in absorption or eliminated by neomycin [27].

Thioridazine. Individuals on thioridazine exhibited greater blood levels of vitamin A than those who did not use the medicine. Thioridazine with vitamin A supplementation may

result in dangerously high vitamin A levels. People on thioridazine should exercise caution while supplementing with vitamin A and be on the lookout for adverse effects such as bone pain, headaches, dry scaly skin, and hair loss [28].

Retinoids. Some drugs increase vitamin A toxicity by pharmacodynamics synergism such as bexarotene which is classified as a retinoid used to treat skin problems from a certain type of cancer and etretinate that used to treat severe psoriasis. It is a synthetic aromatic retinoid [28].

Vitamin E

Statin. Patients non-treated with statin medication have lower levels of vitamin E compared to their treated counterparts. Altering of β-carotene and vitamin E concentration in the blood is likely to occur with statin use [29].

Chemotherapy. Since chemotherapy act by oxidative damage to cancer cells, it is better to avoid antioxidant supplementation. some oncologists suggested this idea. However, limited research does support the idea that an antioxidant can interact with oxidative damage to tumour cells [28].

Iron. Hydroxyl radical synthesis may be stimulated by vitamin E (antioxidant) and iron when taken together [19].

Warfarin. Anticoagulation (blood-thinning) is enhanced in patients treated with warfarin and taking vitamin E (up to 1,200 IU per day), this fact from an isolated case in 1974. While taking extra vitamin E (100 IU or 400 IU per day) did not cause clinical bleeding as assumed by another study discovery [19]. Despite advice to the contrary frequently supplied by doctors regarding this alleged connection, it now looks safe for persons taking warfarin to supplement vitamin E, since these precautions are based on a single case report from 1974 [28].

Aspirin. Vitamin E is supposed to be a blood thinner, but there have been insufficient studies to back up this claim. A double-blind trial of those who smoked discovered that taking aspirin and vitamin E in more than 50 IU per day resulted in a statistically significant increase in bleeding gums compared to taking aspirin alone (affecting one in three versus one in four with only aspirin). The authors found that vitamin E may enhance the risk of bleeding, particularly when coupled with aspirin [19].

Anticoagulants/antiplatelet. Vitamin E may potentiate the effects of anticoagulants and platelet inhibitors. Vitamin E is hypothesized to interfere with the actions of vitamin K-dependent clotting factors by inhibiting the oxidation of reduced vitamin K. This interference appears to be related to the amount of the drug and is stronger in people who already have a vitamin K shortage. One controlled clinical trial found that supplementation with only 50 mg/day of vitamin E increased subarachnoid hemorrhage in male smokers aged 55 to 74 years (n = 409) [30]. Thus, interaction is observed between vitamin E and heparin, fondaparinux, abciximab, antithrombin III, betrixaban, bivalirudin and argatroban.

Bile acid sequestrants. Bile acid sequestrants interfere with fat-soluble vitamins absorption including vitamin E [28].

Griseofulvin. In patients receiving vitamin E, blood level of griseofulvin was reported to be increased, allowing the drug dose to be halved and this reduction in the amount of griseofulvin should decrease the side effects of the drug [28].

Cyclophosphamide. Since cyclophosphamide is activated through an oxidation process, antioxidants (vitamin A, vitamin E, beta-carotene and others) may interfere with its activation [28].

Cyclosporine. In patients receiving vitamin E, blood level of cyclosporine was reported to be increased [29].

Selumetinib. Because selumetinib tablets include vitamin E, consumers should avoid vitamin E-containing combinations [31].

Vitamin D

Verapamil. It is yet unclear how verapamil and vitamin D interact with one another, however, verapamil's efficacy may be reduced by vitamin D [32].

Heparin. Osteopenia has been described in pregnant women who had heparin medication. Patients who were given large doses of heparin for several months had osteoporosis. Heparin has an impact on vitamin D activation [28].

Indapamide. Thiazide diuretics boost vitamin D activity. However, the possibility of a comparable impact with indapamide is still unknown [32].

Estrogen. When women received estrogen alone, their vitamin D blood level raised, whereas taking estrogen along with medroxyprogesterone returned vitamin D levels to pre-estrogen levels in postmenopausal women [28].

Anticoagulant. Vitamin D boosts anticoagulant activity based on a single letter published in the Journal of the American Medical Association in 1975 [33].

Lipase inhibitors. Orlistat impairs dietary

and supplementary vitamin D absorption since vitamin D is fat-soluble [34].

Bile acid sequestrants. Bile acid sequestrants have the potential to bind fat-soluble vitamins such as vitamin D [28,34].

Statins. Competition for cytochrome P450 3A4 (CYP3A4) activity is one possible reason for vitamin D-statin interactions. This enzyme, however, does not metabolize all statins. Pitavastatin and pravastatin show low interactions with metabolizing enzymes. Although more research is needed, it appears that only statins metabolized by CYP3A4 have the potential to interact with vitamin D intake [34].

Thiazide. Taking thiazide diuretics coinciding with vitamin D might conceivably create or worsen hypercalcemia because thiazide decreases urine calcium excretion while vitamin D supplementation increases intestinal calcium absorption [34].

Vitamin K

Vitamin E. These vitamins interact with each other by different mechanisms including competition for the enzymes especially that one to form menadione and also interfering with metabolism pathway including that for excretion of all forms of vitamin K [28], or competing for hydroxylation with cytochrome P450 thereby preventing the β-oxidation of the tail to form menadione. All of these mechanisms would decrease the production and/or availability of menaquinone-4. Vitamin E can inhibit the conversion of K1 to menadione, or it can potentiate vitamin K metabolism and excretion [35].

Warfarin. Warfarin works by interfering with vitamin K function to slow blood clotting. Warfarin's anticoagulant effects are reversed when coinciding with vitamin K [28].

Bile acid sequestrants. Bile acid sequestrants such as cholestyramine, colestipol and colesevelam prevent the absorption of fat-soluble vitamins K [32]. Even if no signs of coagulopathy are apparent at the start of therapy, caution should be exercised while treating a patient with long-term cholestyramine. The malabsorption of various fat-soluble vitamins during cholestyramine administration has been the focus of numerous researches. Although some show no influence of cholestyramine on the absorption of fat-soluble vitamins, others have found malabsorption. It can therefore be concluded that malabsorption of fat-soluble vitamins when using cholestyramine is an existing phenomenon [36].

Aminoglycoside antibiotics. Several incidents of significant bleeding among antibiotic users have been documented. This adverse effect might be caused by decreased vitamin K activity and/or decreased vitamin K synthesis by bacteria in the colon. According to one study, patients who used broad-spectrum antibiotics had reduced liver quantities of vitamin K2 (menaquinone), while their level of vitamin K1 (phylloquinone) remained normal. Several antibiotics appear to have a significant impact on vitamin K activity, while others may have little effect [28].

Minerals oils. Absorption restriction of vitamin K by mineral oil is the way of interaction between them. Mineral oil consumed on an empty stomach may assist in reducing interference ([27]).

The probable clinical interactions between fat-soluble vitamins and prescribed drugs are listed in Table 2, along with the relevant rating scale categories for interactions.

CONCLUSION

The FDA categorizes vitamins and supplements differently from drugs, as they are considered food products rather than medications. However, the FDA regulates the manufacturing and labeling of vitamins and supplements to ensure their safety and quality. For the fat-soluble vitamins, the FDA considers vitamin A, vitamin D, and vitamin E to be essential nutrients and provides daily recommended intake for these vitamins. Vitamin K, while also an essential nutrient, is not currently required by the FDA to have a daily recommended intake level. While the FDA considers these vitamins to be essential nutrients, in certain cases, high doses of certain fat-soluble vitamins can have harmful effects, especially when taken in combination with certain medications

Dietary supplements can contain potent active ingredients that can cause toxic effects or interact with other medications, leading to harmful side effects. It is also important to follow recommended dosages and not exceed the upper-referenced limit for any vitamin or mineral, as excessive amounts can be harmful. Additionally, the consumption of multiple supplements that contain the same nutrient can lead to toxicity. In conclusion, while vitamins play an important role in maintaining good health, they can also interact with medications and have potential adverse effects.

Vitamin	Prescribed drug	Clinical result of interaction	Rating scale categories	Source of data
Vitamin A	Iron	There is a negative effect on the absorption of iron	Unknown	22
	Hepatotoxic drugs	Increased hepatotoxicity	Major	19
	Tetracycline	The possibility of developing intracranial hypertension and hepatotoxicity	Major	23
	Warfarin	Increased anticoagulant effects	Major	24
	Atorvastatin	Elevated blood vitamin A level	Moderate	24
	Gabapentin	Toxicity linked to low vitamin A	Unknown	25
	Isotretinoin	Risk of hypervitaminosis A	Major	26
	Minerals oils	Impeded absorption of vitamins A and C	Minor	27
	Neomycin	Decreased the bioavailability of vitamin A	Minor	27
	Thioridazine	Increased blood levels of vitamin A and in severe cases, bone damage and hepatotoxicity may occur	Unknown	28
	Retinoids	Increased vitamin A toxicity	Major	28
Vitamin E	Statin	Altering of blood vitamin E level	Moderate	29
	Chemotherapy	Interact with antitumor activity	Moderate	28
	Iron	Hydroxyl radical production in the body may be enhanced	Moderate	19
	Warfarin	Increased anticoagulant effects	Moderate	19, 28
	Aspirin	Risk of bleeding	Unknown	19
	Anticoagulants / Antiplatelets	Increased anticoagulant effect and risk of bleeding	Major	30
	Bile acid sequestrants	Disrupt vitamin E absorption	Moderate	28
	Griseofulvin	Increased side effects of Griseofulvin	Unknown	28
	Cyclophosphamide	Affect the effectiveness of the chemotherapy treatment	Moderate	28
	Cyclosporine	Increased risk of side effects such as nephrotoxicity, tremors, and seizures	Moderate	29
	Selumetinib	Because Selumetinib tablets include vitamin E, consumers should avoid vitamin E-containing combinations	Major	31

(Cont.)

Vitamin D	Verapamil	Decreased Verapamil efficacy	Unknown	32
	Heparin	Osteopenia and osteoporosis	Unknown	28
	Indapamide	Effect on vitamin D level	Unknown	32
	Estrogen	Effect on vitamin D level	Unknown	28
	Anticoagulants	Increased anticoagulant effect	Unknown	33
	Lipase inhibitors	Impair vitamin D absorption	moderate	34
	Bile acid sequestrants	Effect on the bioavailability of vitamin A	Moderate	28, 34
	Statins	Disrupt vitamin D absorption	Major	34
	Thiazide	Hypercalcemia	Moderate	34
Vitamin K	Vitamin E	Decreased vitamin K bioavailability	Major	28, 35
	Warfarin	Decreased anticoagulant effect	Major	28
	Bile acid sequestrants	Possibility of vitamin K malabsorption	Moderate	32, 36
	Aminoglycoside	Risk of bleeding	Unknown	28
	Minerals oils	Possibility of vitamin K malabsorption	Moderate	27

Table 2.The potential fat-soluble vitamin clinical interactions with prescribed medication and their rating scale categories for interactions.

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