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ANALYSIS OF GENERAL AND SPECIFIC PHARMACOLOGICAL PROPERTIES OF FAT-SOLUBLE VITAMINS

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Abstract: Vitamins are essential micronutrients that are either insufficiently or cannot be synthesized endogenously, and the main way that we obtain them is through our diet. Vitamins can be classified as either water-soluble or fat-soluble, and the fat-soluble vitamins—which include vitamins A, D, E, and K—are essential for many physiological processes, including coagulation, immune function, bone health, and vision. This review covers the biochemistry, transport, and functions of these vitamins, emphasizing deficiency syndromes and possible toxicities. Numerous physiological processes depend on fat-soluble vitamins, such as vitamins A, D, and E. Deficits in these vitamins have been linked over the last 20 years to a higher risk of cancer, type II diabetes, and several immune system problems. Furthermore, there is mounting evidence that these vitamins interact, particularly between A and D. This improved clinical correlation with disease has led to a large increase in laboratory requests for vitamin assays as well as translational clinical research. Measurements of the most often used blood markers for determining the body's fat-soluble vitamin (FSV) status are 25-OHD (vitamin D), retinol (vitamin A), and α-tocopherol (vitamin E). The accurate measurement of FSV in blood faces several challenges. Their physical and chemical characteristics, the lack of measurement standardization, and the shortcomings of the methods currently employed for quantification are some of these challenges. In order to identify the current obstacles for the quantification of blood vitamins A, D, and E, this study aims to provide a brief overview of the metabolism and interactions of FSV.

Key words: Vitamins A, D, E, K, fat-soluble vitamins, vitamin deficiency, emphasizing deficiency syndromes.

Introduction. The word "vitamin" was coined from two terms, vital and amine, but the letter "e" was removed because it was later realized that not all of them are amines. Vitamins are small organic molecules that are not synthesized endogenously in sufficient amounts, which highlights their importance in our diet at all life stages, from neonatal to geriatric life. Vitamins are organic essential micronutrients (needed at minute levels) that cannot be synthesized by vertebrates but are required to perform specific biological functions for normal growth and the maintenance of a human's health. The 13 recognized vitamins are categorized based on how soluble they are in fat or water, which further influences their pharmacokinetic characteristics [1-3]. In the presence of fats, the intestines effectively absorb the fat-soluble vitamins (A, D, E, and K) that are the primary subject of this review. This review covers the biochemistry, transport, and roles of vitamins, emphasizing deficiency syndromes and potential toxicities. Vitamins are essential micronutrients that cannot be synthesized endogenously or in inadequate amounts, and the main way that we obtain them is through our diet. Vitamins can be classified as either water-soluble or fat-soluble, and include vitamins A, D, E, and K. Vitamins that are fat-soluble are essential for a variety of physiological processes, including immune function, coagulation, bone health, and vision [4-7]. Vitamins are tiny organic substances that are often consumed through food and are necessary in trace levels for a variety of biological processes. Based on how soluble they are in fat and water, the thirteen recognized vitamins are separated into two classes. When fat is present, the intestines absorb the fat-soluble vitamins (FSV) A, D, E, and K.

Clinical manifestations of classic vitamin deficits include increased oxidative cell stress (vitamin E), osteomalacia (vitamin D), night blindness (vitamin A), and hemorrhage (vitamin K). Other possible actions of FSV have been found in recent studies, especially with regard to vitamins A and D [8-11]. Classical deficiencies of those vitamins were historically directly linked to a number of pathological manifestations, including hemorrhage (from vitamin K deficiency), oxidative stress (from vitamin E deficiency), night blindness (from vitamin A deficiency), and osteomalacia (from vitamin D deficiency). However, in the last ten years, vitamins, especially A and D, have been linked to more complex disorders, including autoimmune diseases and cancer. In this review, each fat-soluble vitamin will be described in detail, along with its function at every stage of life and in relation to different-sex requirements [12-16]. The goal of this review is to briefly describe the metabolism and interactions of FSV as a prelude to highlighting the current challenges for the quantification of blood vitamins A, D, and E. Because deficiencies of these two FSV have also been indirectly linked to cancer, type II diabetes mellitus, and a number of immune system disorders, laboratory requests have considerably increased in the last ten years. Throughout this review, the abbreviation "FSV" is used to indicate vitamins A, D, and E [17-20].

The main purpose of the presented analytical manuscript is to provide a brief overview based on many years of scientific research devoted to the analysis of the general and specific pharmacological properties of the specificity of fat-soluble vitamins.

The term "vitamin A" refers to retinol and related compounds that demonstrate the biological activity of retinol. The primary forms of vitamin A are retinol, retinoic acid, and retinal, while retinyl palmitate is the main form that is stored in the liver. The resurgence of interest in vitamin A is related to the actions of retinoid acid as an endocrine and paracine hormone. Retinoic acid is believed to be crucial for the differentiation and development of embryonic stem cells as well as for the maintenance of healthy structure and function of epithelial cells. Additionally, retinoic acid may play a role in the metabolism of vitamin A in the liver. Although vitamin A's most well-known function is related to sight, it is also hypothesized that vitamin A regulates the macronutrient metabolism of proteins, lipids, and carbohydrates [1,2,7,9]. The carboxylic form of vitamin A, known as all-trans-retinoic acid, is also believed to inhibit the growth of tumor cells in vitro and may be involved in regulating cell apoptosis. It is primarily obtained through diet, either as provitamin A compounds (carotenoids, particularly β-carotene) from pigmented vegetables and fruits or as preformed vitamin A (primarily as retinyl esters) from animal sources. Normally, 70–90% of vitamin A is absorbed by the gut in the presence of intestinal juice and bile salts. In the intestinal lumen, the brush-border retinyl ester hydrolase hydrolyzes retinyl esters to retinol and free fatty acids before enterocytes can absorb them [4-8].

Vitamin D is a prohormone that has been linked to a number of diseases, both directly and indirectly. The most common form of vitamin D in blood is 25-hydroxyvitamin D, and its active form is 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3). Historically, vitamin D deficiency has been linked to osteomalacia in adults and rickets in children.28 Low levels of vitamin D have been linked to bone fractures and other clinical manifestations. Over the past 20 years, a significant number of studies have focused on the biological roles of vitamin D. The optimal blood level of vitamin D is linked to the immune system, the general health of bone, and the immune system. Additionally, vitamin D status has been linked to risk status for cardiovascular disease and stroke [4-9]. Low levels of vitamin D and its metabolites have also been indirectly linked to the development of breast cancer; the active form of vitamin D, 1,25-(OH)2D3, and the vitamin D receptors (VDRs) are thought to have a regulatory effect on normal and breast cancer cell growth and differentiation; additionally, 1,25-(OH)2D is believed to play a role in TNF-α expression, which induces apoptosis of cancer cells. Low levels of vitamin D were also found in patients with HIV and respiratory infections, which may be related to the role of vitamin D in immunity [5,8,9,10].

The two naturally occurring groups of vitamin E are tocopherols and tocotrienols. Each of these groups has four isomers (α, β, γ, and δ) depending on the number and position of methyl groups on the chromanol ring. A diet high in γ-tocopherol is typically the primary source of vitamin E, but α-tocopherol is the predominant form in the bloodstream and is associated with numerous biological activities in both humans and animals. Vitamin E is important for the normal morphology of erythrocytes and is thought to be involved in slowing down the aging process because it is essential for the elimination of reactive oxygen species (ROS), which are involved in cell destruction.58 This vitamin also inhibits platelet aggregations, which may make it protective against the atherosclerotic process and cardiovascular disease. Additionally, it has been suggested that vitamin E has a protective role against arthritis, cataracts, neurological disease, and immunological disorders. Its health significance is primarily related to its antioxidant properties, but it has recently been correlated with non-antioxidant activities as well [8-15]. The majority of food sources contain vitamin E, so vitamin E deficiency is most frequently linked to genetic or malabsorption disorders like cystic fibrosis, chronic hepatitis, and gastrointestinal disorders. However, epidemiologically, vitamin E deficiency is more common in developing countries than in industrial ones because of inadequate vitamin intake and the high prevalence of infectious diseases related to oxidative stress processes, like AIDS and malaria [6,7,9,11].

The liver needs vitamin K to manufacture a number of blood clotting proteins. While bacteria generate vitamin K2 homologs (menoquinones), plants synthesize vitamin K1. Both dietary sources and the gut microbiota's production of vitamin K are available to the human body. Vitamin K levels are lower in cereals, dairy products, meats, and fruits, and higher in dark-green leafy vegetables. A Food and Nutrition Board committee determined that people should consume between 70 and 140 µg daily. The lower end of that range was predicated on the idea that intestinal synthesis provides half of the daily vitamin K intake, while the other half is provided by the diet. The consumption that comes solely from diet is represented by the upper end of the spectrum. It has been believed that dietary intake of vitamin K does not require monitoring because the average American diet contains 300 to 500 µg per day and there are no instances of vitamin K toxicity or deficiency in the general population [9-15].

Fat-Soluble Vitamin Interaction. Studies in rats showed that a high intake of vitamin A reduced the toxicity of hypervitaminosis D. In a different human study based on a nested case-control model, the blood level of 25-OHD3 was inversely associated with colorectal cancer among those with lower retinol intake. Vitamin D deficiency (<50 nmol/L) and a high level of retinol (>2.8 µmol/L) has also been linked to an increased risk of osteoporotic fractures. One FSV supplementation has been shown to affect other FSV levels in blood: vitamin D3 supplementation (800 IU/D for 6 months) either by itself or in combination with calcium (2 g/d for 6 months) raised 25-OHD3 levels by 48% and decreased α-tocopherol by 14%; vitamin D3 supplementation dropped serum 25-OHD2 levels by 48%, although this was deemed statistically insignificant; however, vitamin D3 supplementation had no impact on retinol levels among the 85 study participants [5-12]. Although vitamin A and vitamin E have been measured together on a regular basis, it is the molecular interaction between vitamins A and D that is currently attracting research interest regarding their regulatory roles in gene expression. 1,25-(OH)2-D3 forms a complex with the vitamin D receptor (VDR), which can then form a heterodimer with the retinoid X receptor (RXR), which in turn triggers gene expression; retinoic acid and endocrine receptors, including thyroid hormone receptors, can also form a heterodimer with RXR, which again regulates gene expression; given the common link between RXR and high doses of vitamin A, it is hypothesized to attenuate the heterodimer formation of VDR and RXR [14-20].

Clinical relevance. Preventing fat-soluble vitamin shortages and toxicities requires a multidisciplinary team of medical specialists. Physicians, medical assistants, dieticians, pharmacists, and patients are all members of the interprofessional team. For instance, a neonate's darker complexion and exclusive breastfeeding are risk indicators for vitamin D inadequacy that a doctor must identify. Clinicians are in a position to identify atypical signs and symptoms in high-risk patients and report their findings to the physician because they frequently spend the most time with patients. They play a crucial role in identifying concerning signs early on, like headaches and seizures brought on by vitamin-A intoxication. In addition to performing primary and tertiary prevention of excess or shortage of fat-soluble vitamins, dieticians and nutritionists are crucial in adjusting a patient's diet and making sure their nutritional requirements are met [1-11].

Discussion. Age and gender are important factors in determining the micronutrient needs of healthy individuals. Among these micronutrients are vitamins that are needed in trace amounts for optimal metabolism, homeostasis, and a healthy lifestyle, and that function as coenzymes in a number of biochemical reactions. Most previous research has focused on issues related to a particular vitamin or stage of life, with most studies only reporting the effects of either excess or deficiency. Vitamins are divided into two categories: water-soluble and fat-soluble components, such as vitamins A, D, E, and K. These vitamins have been shown to play an undeniable role in a number of physiological processes, including immune regulation, vision, bone, and mental health [3-8]. However, the fat-soluble vitamins are now regarded as a preventative measure for a number of illnesses, including asthma, rickets disease, autism, and gestational diabetes. For the first time, a thorough understanding of the coordination of the four distinct fat-soluble vitamin requirements throughout the human life cycle—from conception to pregnancy to adulthood and senility—as well as a thorough evaluation of the interactions between them and their underlying mechanisms of action—are provided in this review. To emphasize the various daily needs and impacts, the impact of sex on each vitamin is also shown at each stage of life [11-15]. To sum up, this review article is regarded as an updated, thorough summary that clarifies the possible function of fat-soluble vitamins at every stage of a person's life. While vitamin D seems to serve as a buffer against gestational diabetes and preeclampsia, vitamin A has been shown to be necessary for the fetus's normal morphological development during pregnancy. However, it was discovered that while vitamin K lowers the risk of coagulopathy in pregnant women, vitamin E plays a crucial role in lowering the risk of low birth weight babies. It has also been noted that since certain vitamins, including vitamin D, have strong preventive value, vitamin supplementation during lactation may be beneficial [3-8]. In infants and children, vitamin D serves as a preventive measure against rickets, asthma, and autism. Additionally, it was emphasized that fat-soluble vitamins, when taken in the right amounts, are essential for the healthy development, maintenance, and operation of tissues. However, because they can be hazardous, it is important to administer them at the right dosages. In order to help clinicians choose the optimum regimen and to draw attention to the need for more research in that area, the study highlights the notable differences in the daily vitamin requirements of males and girls. It has also been emphasized how GM and fat-soluble vitamins interact. But only in the cases of vitamin A and D was the relationship between genital tissues and fat-soluble vitamins described, indicating a promising area that requires more research. Further research on the functions of fat-soluble vitamins in a number of clinical disorders, including cancer, autoimmune illnesses, infectious diseases, and neurodegenerative diseases, is warranted by our findings [15-20].

Conclusions. While there are still gaps in the traceability chain, the ability to compare results across laboratories and over time is limited. Therefore, it is necessary for all parties (including clinical institutes for measurement standardization and manufacturers of in vitro diagnostic medical devices) to collaborate in order to address the current challenges related to standardization, with clear traceability and demonstrated commutability.

Traditionally, we have measured individual fat soluble vitamins to look for isolated deficiencies in relation to disease. However, there is growing evidence of interactions between these vitamins, particularly between vitamins A and D, and it would be useful to measure these FSV simultaneously within a single analytical method.

The analyte will be charged via the ionization process after the LC first separates the analytes from its sample matrix. In the first quadrupole (Q1), the charged molecules (precursor ions) will be chosen based on their mass-to-charge ratio (m/z). The collision cell (Q2) breaks up the precursor ions between them and high-purity gas (such as nitrogen gas). The second quadrupole's m/z can then be used to choose the broken molecules (product ions) (Q3).

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