Review

Fat Soluble Vitamins Role in Health Promotion

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Abstract:
Vitamins as a class of essential nutrients in trace quantities are required for normal growth, and reproduction. They are studied in two categories; fat soluble vitamins and water soluble vitamins that are functional in many ways to maintain healthy immune system response for disease prevention, and to improve cognitive functions. The main aims of the present review are on vitamins discovery and classifications, fat soluble vitamins biological functions, conditions of deficiency/toxicity on human health promotion, their possible effect/s regarding COVID-19 infection and common neurological and genetic diseases. For this purpose many basic related literatures as well as new advances on fat soluble vitamins were assessed. Investigations indicated that malabsorption in fat-soluble vitamins is of particular significance in Cystic Fibrosis. In addition, in Parkinson's and Alzheimer's patients a diet rich in antioxidant vitamins recommended for their protective role and improvement of the cognitive functions. Furthermore, it is recognized that fat soluble vitamins use, especially vitamins A & D supplements during COVID-19 days in light of their safe and therapeutic range could be beneficial. However, their possible preventive role and/or supportive therapy against COVID-19 are yet controversial. Further clinical studies worldwide will hopefully define their role/s in reducing the severity and complications of the infection. In addition, in the absence of specific treatment for COVID-19 to date, as well as reducing the risks for other deficiency conditions, looking for alternative approaches like improving the availability, affordability and acceptability of healthy diets for all, specifically for the most vulnerable groups are important.

Keywords: Fat Soluble Vitamins- Deficiency- Toxicity- Covid-19 Infection- Immune System.

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Introduction

The discovery of the vitamins was a major scientific achievement in understanding of health and disease. The major period of discovery began in the early nineteenth century and ended at the mid-twentieth century. In 1912, Casimir Funk originally purposed the term "vitamine". Funk believed that some human diseases, were caused by chemical deficiencies of factors of the same type. Because each of these factors had a nitrogen-containing component known as an amine, he called the compounds "vital amines," a term that he later shortened to "vitamines." The final "*e"* was dropped later when it was discovered that not all of the vitamins contain nitrogen and, therefore, not all are amines (1). By the last half of last century, all vitamins were identified, their chemical structures were determined and natural sources from which vitamins can be obtained were described in detail (2-3).Vitamins are a class of essential nutrients and organic compounds that are required in trace quantities (in micrograms to milligrams quantities per day) for normal health, growth, wellbuilt immune system and reproduction. Some vitamins can be synthesized in varying concentrations by humans. Generally this endogenous synthesis is not enough to cover daily needs and so dietary intake is required. If a vitamin is absent from the diet or is not properly absorbed by the body, a specific deficiency disease may develop (1-3). There are thirteen vitamins that are recognized. Based on their solubility, they are divided into fat-soluble variants (A, D, E and K) and water-soluble variants (B and C). The former mainly bind to nuclear receptors of the cells and affect the expression of specific genes (4). The latter mainly constitute a cofactor for the enzyme, affecting the enzymatic activity (5-6). Furthermore, the alphabetic nomenclature indicates the chronology of vitamins discovery; however; the subsequent observation that vitamin B consisted of multiple compounds, gave rise to numerical nomenclature. The gaps in numbering are due to the removal of several substance that were initially described as vitamins (6-8). Water-soluble vitamins travel freely through the body and are not effectively stored. The excess amounts usually excreted by the kidneys. The body needs water-soluble vitamins in frequent, and small doses. These vitamins are not as likely as fat-soluble vitamins to reach toxic levels. Fat-soluble vitamins (A,D,E,K) need bile acid micelle solubilization to be digested .They are absorbed in intestinal tract with the help of dietary fats(7) , transported, and stored in fatty tissue and the liver for longer periods of time. In addition, they are not excreted as easily as water-soluble vitamins (7-9). There are many publications involving both groups of vitamins (8-11) , however, in the present review, fat soluble vitamins dietary sources, biological functions, state of deficiency/toxicity on human health promotion , their possible effect/s regarding COVID-19 infection, a two year global pandemic, and common neurological and genetic diseases are discussed.

Fat soluble Vitamins

Vitamin A

Vitamin A (retinol) is an essential nutrient needed in small amounts by humans for the normal function of the visual system, growth and development, maintenance of epithelial cellular integrity, immune function, neuronal differentiation and influences on the secretion of neurotransmitters in the brain, and reproduction. It is not a single vitamin but a collection of compounds known as retinoids. Retinoids occur naturally in the human body. The most active retinoid has been found to be retinoic acid. Some foods such as meat, fish, eggs, and dairy foods provide retinols (Preformed vitamin A), which the body can use directly as vitamin A. Others provide pro-vitamin A or carotenoids; generally in the form of alpha/beta/gamma carotene compounds. They are dietary precursors of retinol that the body converts into vitamin A. Carotenoids are dark-colored pigments and are found in vegetables such as carrots, sweet potatoes, spinach and other leafy green vegetables; and fruit such as cantaloupes and apricots (12-13). There are more than 500 known carotenoids. The most common type of them is beta-carotene that is an antioxidant and protects cells from damage caused by free radicals (14-16). It is also specifically contributes to the orange color of vegetables and fruits. Vitamin A functions at two levels in the body: the first is in the visual cycle in the retina of the eye; the second is in all body tissues where it systemically maintains the growth and soundness of epithelial cells and membrane regulation (from skin to mucous to teeth and to bones) metabolism (17). Furthermore, it has anti- oxidative [13-14] properties and a major role in immune system (18). In the visual system, the major consequence of vitamin A deficiency is ocular dysfunction with abnormal dark adaptation (night blindness), conjunctival and corneal xerosis (thickening) which can lead to blindness (19-20). Night blindness in which it is difficult or impossible to see in relatively low light is usually an indicator of inadequate available retinol, but it can also be due to a deficit of other nutrients that are critical to the regeneration of rhodopsin, such as protein and zinc, and to some inherited diseases, such as retinitis pigmentosa. In the eye, the symptoms and signs, together referred to as xerophthalmia. It ranges from the milder stages of night blindness and Bitot spots to the potentially blinding stages of corneal xerosis, ulceration and necrosis (keratomalacia). The various stages of xerophthalmia are regarded both as disorders and clinical indicators of vitamin A deficiency. At the second level, the growth and differentiation of epithelial cells throughout the body are affected by vitamin A deficiency (VAD). In VAD case, in epithelial tissues, goblet cell numbers are reduced and causes mucous secretions to diminish. As a consequence, cells lining protective tissue surfaces fail to regenerate and differentiate, hence they flatten and accumulate keratin. Both factors-the decline in mucous secretions and loss of cellular integrity-reduce the body’s ability to fight infections (21). Classical symptoms of xerosis (drying) and desquamation of dead surface cells as seen in ocular tissue (i.e. xerophthalmia) are the external evidence of the changes also occurring to various degrees in internal epithelial tissues. Vitamin A deficiency has also been linked to impaired mechanisms of host resistance to infection, poor growth and increased mortality in a study of mothers and children [19]. Furthermore, Cystic Fibrosis is a known risk factor of VAD because of liposoluble vitamin malabsorption due to pancreatic insufficiency (21). Cystic fibrosis (CF) is a genetic disorder that affects multiple organs and causes disease in the lungs, digestive systems and pancreas. In people with CF, the pancreas often does not produce enough enzymes to allow the body to absorb digested food properly. Pancreatic insufficiency affects up to 90% of people with CF, whereby fat malabsorption occurs and pancreatic enzyme replacement is required to prevent malnutrition (21). Fat soluble vitamins (A, D, E and K) are co-absorbed with fat and thus deficiency of these vitamins may occur (20). Vitamin A deficiency can be defined as a serum retinol (SROL) concentration less than 0.70 µmol/L (18). However, SROL levels may be influenced by albumin and retinol binding protein as well as acute illnesses with infection and inflammation (22). Levels of SROL should be measured while individuals are clinically stable (20,23). Furthermore, concentration of vitamin A, do not play a role in the pathogenesis of Parkinson’s disease (PD) (24). Carotene deficiency has no defined serum concentrations (25). However, as long as vitamin A levels are normal, adverse clinical manifestations of β-carotene deficiency are unknown (15). Because vitamin A is fat soluble and can be stored, primarily in the liver, routine consumption of large amounts of vitamin A over a period of time can result in toxic symptoms, including hepatotoxicity, bone abnormalities and joint pain, headaches, vomiting, and skin desquamation. Furthermore, it may contribute to osteoporosis and hip fractures. Hyper-vitaminosis A appears to be due to abnormal transport and distribution of vitamin A and retinoids caused by overloading of the plasma transport mechanisms (26-27). On the other hand, excessive carotene in the diet can temporarily yellow the skin, a condition called carotenemia, a harmless, reversible yellowing of the skin (15). In general, most authors consider excessive intake of carotene as nontoxic (15-16). It is commonly seen in infants fed largely mushed carrots.VAD is most common in populations consuming most of their vitamin A needs from pro-vitamin carotenoid sources and where minimal dietary fat is available (28). About 90% of ingested preformed vitamin A is absorbed, whereas the absorption efficiency of pro-vitamin A carotenoids varies widely, depending on the type of plant source and the fat content of the accompanying meal (29). Where possible, an increased intake of dietary fat is likely to improve the absorption of vitamin A in the body. VAD can occur in individuals of any age. However, it is a disabling and potentially fatal public health problem for children under 6 years of age. VAD related blindness is most prevalent in children under 3 years of age (30). Women of reproductive age are also thought to be vulnerable to VAD during pregnancy and lactation because they often report night blindness (31-32) and because their breast milk is frequently low in vitamin A (33-34). There is no consistent, clear indication in humans of a sex differential in vitamin A requirements during childhood. Growth rates, and presumably the need for vitamin A, from birth to 10 years for boys are consistently higher than those for girls (35). Furthermore, in light of vitamin A pulmonary and immunological roles, oral supplementation of vitamin A is currently being investigated in the treatment of severe acute respiratory syndrome coronavirus-2 (SAR- CoV-2), later named COVID-19 by the WHO. Pathology of COVID-19 involves a complex interaction between COVID-19 and the immune system. In addition, COVID-19 has been found to persuade inflammatory responses, especially involving liver, lung, and kidney, which further increase the risk of depletion of vitamin A stores (36-37).

Vitamin D

Vitamin D encompasses a number of fat-soluble secosteroids with a physiological role in mineral homeostasis, primarily calcium, magnesium, and phosphate. They are in turn needed for the normal mineralization of bone and skeletal health, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D in its natural form, cholecalciferol, is acquired through dietary sources, such as oily fish, mushrooms, and egg yolks, but is also produced through de novo synthesis in the dermis of the skin from dehydrocholesterol(cholesterol like precursor) by exposure to UVB rays from the sun or other sources (38). The version made in the skin is referred to as vitamin D3 (colecalciferol) whereas the dietary form can be vitamin D3 or a closely-related molecule of plant origin known as vitamin D2 (ergocalciferol). From a nutritional perspective, both of the above forms are inactive. They are metabolized similarly in humans, are equal in potency, and can be considered equivalent. Regardless of the route of entry, 99% of endogenous or dietary vitamin D, are transformed into the active form; [1,25-dihydroxy vitamin D or1,25-(OH)2D / calcitriol] after being hydroxylated twice. First hydroxylation happens in the liver that produces [25-hydroxyvitamin-D or 25(OH) D/calcidiol], which is the most abundant circulating metabolite of the vitamin D. The second hydroxylation occurs in the kidneys that produces [1,25-dihydroxy vitamin D or 1,25-(OH)2D / calcitriol] (39-40). This active form regulates the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins. Clinical assays measure 1,25-(OH)2D2 and 1,25-(OH)2D3, collectively called 1,25-(OH)2D. Similarly, calcidiol is measured as 25-OH-D but it is a mixture of 25-OH-D2 and 25-OH-D3. In calcium homeostasis, 1,25-(OH)2D works in conjunction with parathyroid hormone (PTH) to produce its beneficial effects on the plasma levels of ionized calcium and phosphate (41-42) . The physiologic loop starts with the calcium receptor of the parathyroid gland (43). When the level of ionized calcium in plasma falls, PTH is secreted by the parathyroid gland and stimulates the tightly regulated renal enzyme 25-OH-D-1-α-hydroxylase to make more 1,25-(OH)2D from the large circulating pool of 25-OH-D. The resulting increase in 1,25-(OH)2D (with the rise in PTH) causes an increase in calcium transport within the intestine, bone, and kidney. All these events raise plasma calcium levels back to normal, which in turn is sensed by the calcium receptor of the parathyroid gland. The further secretion of PTH is turned off not only by the feedback action of calcium, but also by a short feedback loop involving 1,25-(OH)2D directly suppressing PTH synthesis in the parathyroid gland. This model clearly demonstrates that sufficient 25-OH-D must be available to provide adequate 1,25-(OH)2D synthesis and hence an adequate level of plasma calcium. Furthermore, numerous recent studies have focused on the plasma levels of 25-OH-D and PTH to gain an insight into vitamin D status and there is a strong presumptive relationship of this variable with bone status (39,44-47) . Vitamin D deficiency is prevalent at all ages, especially in elderly. Vitamin D not only regulates the calcium homeostasis and skeletal health but also regulates the physiological and pathological processes, such as cell proliferation, differentiation, and anti-oxidative stress (48-50) .Children with a lack of vitamin D may suffer from rickets (bone deformity) and adults may develop osteoporosis and osteomalacia. Additionally, vitamin D deficiency is also associated with cardiovascular diseases, muscle weakness, diabetes mellitus, cancers, and multiple sclerosis (51). The relationship between vitamin D and Parkinson's disease (a multi-factorial disease) has gradually attracted attention (52). Many non-interventional studies found that the high levels of serum vitamin D can reduce the risk of Parkinson's disease (PD) (53-55), and several clinical intervention trials also proposed that vitamin D supplementation can attenuate the deterioration of the Parkinson's disease and reduce the occurrence of fractures in patients with PD (56-57). Furthermore, epidemiological and clinical studies suggest that vitamin D has a positive effect on (PD). In a cohort study, over 7000 serum samples were collected for measuring the 25-hydroxy vitamin D level, and meanwhile, the occurrence of PD was instigated over a 30-year follow-up period. The results showed that individuals with higher serum vitamin D concentrations had a lower risk of PD (58). Evatt et al. also noted consistent findings (59). PD patients with lower 25-hydroxy vitamin D levels may exhibit more severe symptoms compared with normal controls (60-61). Unsurprisingly, a randomized, double-blind, placebo-controlled trial found that vitamin D3 supplementation (1200 IU/day for 12 months) significantly prevented the deterioration of PD patients (62). However, further studies are still needed to clarify the definitive correlations between vitamin D and PD. It has also been reported that vitamin D deficiency co-exists in patients with COVID-19. Dark skin color, increased age, the presence of pre-existing illnesses and vitamin D deficiency are features of severe COVID disease (63). Moreover, vitamin D has been suggested to play a role in COVID-19, as two ecological studies indicated that the rate of infection was higher in countries at higher latitudes and/or lower vitamin D status (64-65). In recommending intakes for vitamin D, it is recognized that in most locations in the world in a broad band around the equator (between latitudes 42°N and 42°S), the most physiologically relevant and efficient way of acquiring vitamin D is to synthesize it endogenously in the skin from 7-dehydrocholesterol by sun (UV) light exposure. In most situations, approximately 30 minutes of skin exposure (without sunscreen) of the arms and face to sunlight can provide all the daily vitamin D needs of the body (66). However, skin synthesis of vitamin D is negatively influenced by factors which may reduce the ability of the skin to provide the total needs of the individual (66). Examples of such factors are; Latitude and season- both influence the amount of UV light reaching the skin; The ageing process-thinning of the skin reduces the efficiency of this synthetic process; Skin pigmentation-the presence of darker pigments in the skin interferes with the synthetic process because UV light cannot reach the appropriate layer of the skin; Clothing-virtually complete covering of the skin leaves insufficient skin exposed to sunlight; Sunscreen use-widespread and liberal use of sunscreen, though reducing skin damage by the sun, deleteriously affects synthesis of vitamin D. Because not all of these problems can be solved in all geographic locations, particularly during winter, it is recommended that individuals correct their vitamin D status by consuming the amounts of vitamin D appropriate for their age group (Table 1) (67). It is rare for an individual to have vitamin D toxicity and the adverse effects of high vitamin D intakes- hypercalciuria and hypercalcaemia- do not occur at the recommended intake levels as in Table 1. In fact, it is worth noting that the recommended intakes for all age groups are still well below the lowest observed adverse effect level of 50µg/day and do not reach the "no observed adverse effect level" of 20µg/day (47,68-69).

Vitamin E

Vitamin E is the major lipid-soluble antioxidant in the cell antioxidant defense system and is synthesized by plants and exclusively obtained from diet. Natural vitamin E includes two subgroups: tocopherols and tocotrienols; and they can further be divided into four lipophilic molecules, respectively: α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. The major difference between tocopherols and tocotrienols is the side chain. Tocopherols have a saturated phytyl tail, while tocotrienols possess an unsaturated isoprenoid side chain (70). Because of this unsaturated side chain, the tocotrienol is superior to the tocopherol as an antioxidant by increasing the molecular mobility through lipid membranes and by accepting electrons readily (70). In addition to its potent antioxidant capacity, vitamin E is involved in many physiological processes such as immune function (71), cognitive function, physical performance (72-73) , regulation of gene expression and skin health. Vitamin E is located primarily within the phospholipid bilayer of cell membranes and its major biological role is to protect poly unsaturated fatty acids (PUFAs) and other components of cell membranes and low-density lipoprotein (LDL) from oxidation by free radicals. Elevated levels of lipid peroxidation products are associated with numerous diseases and clinical conditions (74). Although vitamin E is primarily located in cell and organelle membranes where it can exert its maximum protective effect, its concentration may only be one molecule for every 2000 phospholipid molecules. This suggests that after its reaction with free radicals it is rapidly regenerated, possibly by other antioxidants (75). The requirement for vitamin E is relate to the (PUFAs) content of cellular structures and therefore, depends on the nature and quantity of dietary fat, which affects such composition. Hence, the minimum adult requirement for vitamin E is not certain and no specific recommendations regarding the intake of vitamin E have been made officially, and the optimal supplementation dosage of mixed tocopherols is still undetermined. But is probably not more than 3 to 4 mg (4.5-6 IU) for α-tocopherol per day for those who ingest a diet containing the minimum of essential fatty acids (76). Foods rich in vitamin E include canola oil, olive oil, margarine, almonds and peanuts. One can also get vitamin E from meats, dairy, leafy greens and fortified cereals. Vitamin E is absorbed in the presence of bile and from the small intestine. Most tocopherol enters the bloodstream via lymph, where it is associated with chylomicrons and very low density lipoproteins. The vitamin is stored in most tissue, with the largest amount stored in adipose tissue. Some of the tocopherol deposition is in association with lipoproteins in cellular membranes. Rapid exchange of tocopherol occurs between the erythrocyte membranes and plasma lipoproteins. When physiological amounts are administered, only a small fraction of the dose appears in urine (77-78). The assessment of the vitamin E requirement for humans is confounded by the very rare occurrence of clinical signs of deficiency because these usually only develop in infants and adults with fat malabsorption syndromes or liver disease, in individuals with genetic anomalies in transport or binding proteins, and possibly in premature infants (79-81). This suggests that diets contain sufficient vitamin E to satisfy nutritional needs. Vitamin E appears to have very low toxicity, when obtained from food sources alone. It has no documented evidence of toxicity. However, evidence of pro-oxidant damage has been found to be associated with supplements, but usually only at very high doses (for example at >1,000 mg/day) (82-83). A few other studies suggest that tocopherols appear to inhibit platelet aggregation through the inhibition of protein kinase C (PKC) and the increased action of nitric oxide synthase (84-85). Furthermore, it has been suggested that vitamin E supplementation (200-400mg/day) may be appropriate therapeutically to moderate some aspects of degenerative diseases such as Parkinson's disease (PD) [(86). However, two population-based studies did not find the association between vitamin E intake and risk of PD (87-88). To date, there is little evidence regarding the use and/or dosage of vitamin E as a prophylactic or therapeutic agent against COVID-19 (89). Overall vitamin E supplementation improves overall immune functions, reduces respiratory tract infection incidences, severity, lowers virus load in lung tissues, and increases the antibody titers, particularly in the elderly (90-92). Malnourished individuals should benefit from the inclusion of vitamin E supplementation in COVID-19 management. The Alzheimer's disease (AD) Cooperative Study in 1997 showed that vitamin E may slow disease progression in patients with moderately severe AD (93). High doses of vitamin E delayed the loss of the patient's ability to carry out daily activities and their consequent placement in residential care for several months. In another study, it was found that subjects with AD had reduced concentrations of plasma antioxidant micronutrients, suggesting that inadequate antioxidant activity is a factor in this disease. High plasma levels of vitamin E are associated with a reduced risk of AD in older patients and this neuroprotective effect is related to the combination of different forms of vitamin E rather than to α-atocopherol alone (94).

Alzheimer's disease occurs as a result of protein oxidation and lipid peroxidation via a free radical mechanism, where the beta amyloid protein induces cytotoxicity through a mechanism involving oxidative stress and hydrogen peroxide, leading to neuronal cell death and finally AD. Vitamin E can block the production of hydrogen peroxide and the resulting cytotoxicity (95-97). Moreover, Vitamin E is the major naturally occurring lipid-soluble non-enzymatic antioxidant protecting skin from the adverse effects of oxidative stress including photo-aging. It protects the skin from various deleterious effects due to solar radiation by acting as a free radical scavenger (98) and it is an important ingredient in many cosmetic products. Experimental studies have indicated that vitamins C and E have important protective effects in the aging process and brightening of the skin (99-100). The results have revealed significant improvements in the skin tone and increase in homogeneity. Furthermore, vitamin E is one of the treatment for yellow nail syndrome (101-102). Yellow nail syndrome includes slow growing, opaque yellow nails with exaggerated yellow curvature. In addition, the antioxidant supplementation through vitamins E and C and the mineral zinc has been seen to apparently enhance the antioxidant protection against oxidative stress and allow less time for wound healing (103).

Vitamin K

Vitamin K refers to a family of compounds with a common 2-methyl-1,4-naphthoquinone (104-105) but differ in the structures of a side chain at the 3-position. Vitamin K is needed for a unique post-translational chemical modification in a small group of proteins with calcium-binding properties, collectively known as vitamin K-dependent proteins or Gla proteins. They function in coagulation, bone development, and cardiovascular health. Vitamin K exists naturally in two bioactive forms; as vitamin K1 (phylloquinone) and vitamin K2 (menaquinone) (105-108). Vitamin K1 contains a phytyl side chain and is synthesized by plants and algae. It is mainly found in green leafy vegetables as well as olive oil and soyabean oil. In addition, it is the main circulating form of vitamin K and is primarily provided by dietary sources. Whereas vitamin K2 consists of a group of menaquinones, which are characterized by the length of their isoprenoid side chain. Furthermore, vitamin K2 is created in the human gut by bacteria and it is found in small amounts in chicken, butter, egg yolks, cheese and fermented products (better known as natto) (109-111).Today, menaquinones are generally called MK-n, where "n "signifies the number of isoprenoid units. With regard to preventive and therapeutic aspects, menaquinone-4 (MK-4) and menaquinone-7 (MK-7) are among the most important forms of vitamin K2 with 4 and 7 isoprenoid units, respectively (106,112-113). There is a third, synthetic form K3 (menadione), the use of which has been replaced by a synthetic form of vitamin K1 due to the potential for toxicity in infants with glucose-6-phosphate dehydrogenase deficiency (114) . Although vitamin K1 (phylloquinone) in blood must have been derived exclusively from the diet, it is not known whether circulating vitamin K2 (menaquinones) such as MK-7 are derived from the diet, intestinal flora, or a combination of these sources. Vitamin K1 is the major source (>90%) in the human diet and is absorbed in the jejunum and ileum, transported by chylomicrons in circulation, and is dependent on bile, pancreatic enzymes, and dietary fat content (115). In addition, it is known to be selectively distributed in a number of hepatic and non- hepatic tissues. The biological role of vitamin K is to act as a cofactor for a specific carboxylation reaction that transforms selective glutamate (Glu) residues to g-carboxyglutamate (Gla) residues

(104,116). The reaction is catalysed by a microsomal enzyme, g-glutamyl, or vitamin K-dependent carboxylase, which in turn is linked to a cyclic salvage pathway known as the vitamin K epoxide cycle. The four vitamin K-dependent pro-coagulants (factor II or prothrombin, and factors VII, IX, and X) are serine proteases that are synthesized in the liver and then secreted into the circulation as inactive forms (zymogens). Their biological activity depends on their normal complement of Gla residues, which are efficient chelators of calcium ions. In the presence of Gla residues and calcium ions these proteins bind to the surface membrane phospholipids of platelets and endothelial cells and together with other cofactors, form membrane-bound enzyme complexes. When coagulation is initiated, the zymogens of the four vitamin K-dependent clotting factors are cleaved to yield the active protease clotting factors and thus preventing bleeding (104,116-117). Two other vitamin K dependent proteins, protein C and protein S, play a regulatory role in the inhibition of coagulation. The function of protein C is to degrade phospholipid-bound activated factors V and VIII in the presence of calcium. Protein S acts as a synergistic cofactor to protein C by enhancing the binding of activated protein C to negatively charged phospholipids. There is evidence that protein S is synthesized by several tissues including the blood vessel wall and bone and may have other functions besides its well-established role as a coagulation inhibitor. Both vitamin K1 and vitamin K2 are required for the γ-glutamyl carboxylation of all vitamin K-dependent proteins (106) .Although mammalian bacterial intestinal flora are able to produce vitamin K2, the amount produced is thought to be negligible (106) . Vitamin K is present in the other body tissues as well, including the brain, heart, pancreas, and bone (36, 118-119). It is rapidly metabolized in the liver and excreted in the urine and bile (115). This rapid metabolism accounts for its relatively low blood levels and tissue stores compared to the other fat soluble vitamins. Furthermore, vitamin K can have a serious interaction with anticoagulants such as warfarin (Coumadin) antagonizing its activity and leading to the depletion of vitamin K dependent clotting factors. Most individuals taking warfarin are advised to avoid vitamin K-containing foods, such as green leafy vegetables (120). Vitamin K deficiency can be exacerbated further when warfarin is initiated (121). In addition, vitamin K deficiency can contribute to significant bleeding, poor bone development, osteoporosis, and increased cardiovascular disease. Vitamin K Deficiency Bleeding (VKDB) is rare and it is potentially life threatening bleeding disorder of early infancy. Because vitamin K stores are low at birth and its concentration in human milk is low as well. Most multi dose oral regimens provide protection for all except for a small group of infants with undetected hepatobiliary disease (122-123). In adults, primary vitamin K-deficient states that manifest as bleeding are almost unknown except when the absorption of the vitamin is impaired as a result of an underlying pathology (104,124) or during long term antibiotic or anticoagulant treatments (125). Naturally occurring vitamin K (K1 and K2) toxicity is extremely rare. However, a synthetic form of vitamin K (menadione) or K3 has been associated with neonatal haemolysis and liver damage, and therefore, no longer used therapeutically (6) .Thrombosis is a frequent manifestation of COVID-19 that contributes to poor outcomes. It has been proposed that pneumonia induced extrahepatic vitamin K depletion lead to accelerated elastic fiber damage and thrombosis in severe COVID-19 patients due to impaired activation of matrix Gla Protein or (MGP) and endothelial protein S respectively (126-127) .

Discussions

Each fat soluble vitamin as well as other trace elements (128) has multiple and essential biological functions for human health. In summary; vitamin A is essential for normal vision, epithelial cell integrity, and epithelial proliferation and immunity (18). The major cause of blindness in children worldwide is xerophthalmia (19) caused by vitamin A deficiency. It is also pivotal in the maintenance of innate cell mediated and antibody mediated responses (129). In a study on vitamin A, Field et al, reported vitamin A has a capacity to resist infection (130). In this regard, several studies reported that vitamin A and related compounds have a potentially beneficial role and could be a promising option in the treating of COVID-19 pandemic by preventing lung infection (131-133). Vitamin D, promotes absorption and metabolism of calcium and phosphorus. It is required for bone health and has a role in immune function and incidence of cancer, type 1 diabetes, autoimmune disease and heart disease (3-6,134-137). Promising results indicated that vitamin D supplement is essential in treating respiratory tract infection, including COVID-19 (63-64) , and pulmonary fibrosis as well (138). Furthermore, it is indicated that during the COVID-19 pandemic, it is crucial that all people in the hospital, including the patients and staff, take vitamin D supplement to raise 25(OH)D concentrations as an essential step in preventing infection spread (139). However, initial testing of vitamin D level at an interval is advocated to determine the dosing levels required. The best defined role for vitamin E is an antioxidant activity for polyunsaturated fatty acids (PUFAs) within the membranes, or preventing cell membrane oxidation, and maintaining neurological functions. The antioxidant system mainly consists of two subtypes: firstly, enzymatic antioxidant system, including superoxide dismutase (SOD), catalase (CAT), and glutathioneperoxidase (GSH-Px), and secondly, nonenzymatic antioxidant system, including vitamin C, vitamin E, glutathione, melatonin, alpha-lipoic acid, carotenoids, and trace elements copper, zinc, and selenium (74,128). Furthermore, oxidative stress refers to the imbalance between the oxidation system and antioxidant system that results in excessive accumulation of oxidative substances. Reactive oxygen and nitrogen species and other free radicals that result from oxidative stress are potential causes of cell membrane damage (74,140). In general diseases causes an increase in oxidative stress; therefore, consumption of foods rich in antioxidants, which are potentially able to quench or neutralize excess radicals, may play an important role in modifying the development of disease. Although limited clinical data is available to establish a link between oxidative stress and viral infection due to COVID-19, many lines of evidence (141-143) still suggested that overproduction of reactive oxygen species and deprived antioxidant system play a significant role in the pathogenesis and severity of COVID-19. It is often suggested that the onset of severe lung injury in COVID- 19 patients is based on the activation of the oxidative stress mechanism coupled with an innate immune response (144-146). Furthermore, vitamin E supplementation may lead to the protection and improvement of lung tissue in Cystic Fibrosis patients. However, future studies are needed to look at this issue more specifically (147). The letters (A, B, C and so on) were assigned to the vitamins in the order of their discovery. The one exception was vitamin K which was assigned "K" from "Koagulation" by the Danish researcher Henrik Dam (2,8,148). Beyond coagulation (149), vitamin K and vitamin K –dependent proteins are essential for calcification (maintaining bone and cardiovascular health), energy metabolism and inflammation (149-150). Other important roles of vitamin K is its ability to act as a potent antioxidant reducing the lipid peroxidation in the cell by producing vitamin K hydroquinone, a robust radical scavenging species (151-152). Furthermore, vitamin K has been found to have an anti-inflammatory activity (153). Reduced vitamin K levels have also been reported in COVID-19 patients (126) and one of the most common laboratory findings in these patients is the elevation of D-dimers (154-155). This deficiency reduces the functional levels of coagulation factors II, VII, IX, and X, predisposing them to develop coagulopathy and increasing hemorrhage risk (156-157) and DIC (Disseminated Intravascular Coagulation) formation. Coagulophaty and DIC appear to be associated with high mortality rates. The other laboratory markers recommended by the International Society of Thrombosis and Hemostasis (ISTH) for monitoring DIC formation are fibrinogen, prothrombin time, and platelet count (158). Also, low vitamin K level appears to be associated with increased elastin degradation (159) preferably degrading the lung tissue and resulting in breathing difficulty in COVID-19 patients. For the treatment of COVID-19 induced coagulopathy, the use of an anticoagulant is recommended (158). Moreover, evidence for benefits of routine vitamin K supplementation for people with Cystic Fibrosis is currently weak. However, no harm was found and until further evidence is available, the present recommendation by National guidelines should be followed (124,160). Furthermore, literatures review indicated that fat soluble vitamin deficiency malabsorption is of particular significance in Cystic Fibrosis (20-21,160). In Parkinson's disease vitamins may play a protective role, however, they cannot control the progression of the disease (83) and a diet rich in antioxidant vitamins recommended to improve the cognitive functions of Alzheimer's patients (95). Table2 summarizes the main biological functions of the fat soluble vitamins and their deficiency/toxicity cases in human health.

Conclusion

The importance of adequate and balance nutrition is vital in regulating the body's homeostasis. In this regard, a diet rich in fat soluble vitamins (A,D,E,K) are considered essential in small quantities for normal health, maintaining healthy immune system response for disease prevention, and improving cognitive functions (Table2). Use of these vitamins especially vitamins A & D supplements during a two year global pandemic COVID-19 , in light of their safe and therapeutic range is also recommended. However, their possible preventive role and/or supportive therapy against COVID-19 are yet controversial. Further future clinical studies worldwide will hopefully define their role/s in reducing the severity and complications of the infection. In addition, in the absence of specific treatment for COVID-19 to date, as well as reducing the risks for other deficiency conditions, looking for alternative approaches like improving the availability, affordability and acceptability of healthy diets for all, specifically for the most vulnerable groups are important.

Conflict of Interest

None.

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Tables

Table 1- Recommended Nutrient Intakes (RNIs) for Vitamin D, by Group

Groups	RNI (mg/day)[a]
Infants and children	
0–6 months	5
7–12 months	5
1–3 years	5
4–6 years	5
7–9 years	5
Adolescents	
10–18 years	5
Adults	
19–50 years	5
51–65 years	10
65+ years	15
Pregnant women	5
Lactating women	5

[a] Units: for vitamin D, 1 IU = 25ng, 40 IU = 1µg, 200 IU = µ5g,400IU = 10µg, 600 IU = 15µg, 800 IU = 20µg. IU-International Units

Table2: Fat Soluble Vitamins Biological Functions & Deficiency/ Toxicity Disease Cases in Human Health

Vitamins	Biological Function	Deficiency Disease Cases	Toxicity Disease Cases	Sources
A (Retinol)	Normal vision Maintenance of epithelial cellular integrity Neuronal differentiation Antioxidant activity Immune response Reproduction	Xerophthalmia Night blindness. Keratinization of the central Epithelium. Dry mucous Membranes. Low resistance to infection. Cystic Fibrosis is a known risk factor of VADa . Oral supplementation is currently being investigated in the treatment of Covid-19.	Hepatotoxicity-Bone Abnormality. Headache &Skin Desqamation	E Eggs-Meat Dairy products Vegetables
D (C (Cholecalciferol)	Mineralization of bones & skeletal health Hom Homeostasis of calcium, phosphorus, &magnesium	Rickets in children. Osteomalacia in adults & Osteaporosis increased risk for PDb & Covid-19	Rare	Oily fish, Mushrooms Egg Yolks
E (α- (Tocopherol)	Powerful antioxidant for polyunsaturated fatty acids (PUFAs) within the membranes Preventing cell membrane oxidation, Maintaining neurological functions. Cognitive function, physical performance, Regulation of gene expression and skin health. The vitamin is stored in most tissue, with the largest amount stored in adipose tissue. Vitamin E is one of the treatment for yellow nail syndrome	Rare. Only in infants & adults with an inherited or acquired condition that impairs the vitamin absorbance and in those who cannot absorb dietary fat or have rare disorders of fat metabolism. Decreased antioxidant activity in ADc . Little evidence for prophylactic or therapeutic agent against Covid-19	Low except at very high Supplement doses. Hemorrhagic toxicity	Canola Oil Olive Oil Margarine Almonds Peanuts E Meats, Dairy Le Leafy Greens Fortified Cereals.
K (Phylloquinone)	Coagulation/ Blood Clotting Essential for maintaining bone and Cardiovascular health, and metabolism. Acting as a potent antioxidant Reducing the lipid per oxidation in the cell by producing vitamin K hydroquinone. It also has an anti inflammatory activity.	In Adults, primary vitamin K Deficient states manifest as bleeding are unknown except when the absorption of the vitamin is impaired or during long term antibiotic or anticoagulant treatment . Vitamin K Deficiency Bleeding (VKDB) is rare and it is potentially Life threatening bleeding disorder of early infancy .Thrombosis in Covid - 19 patients with elevation of D-dimers.	N Naturally occurring vitamin K (K1 &K2) toxicity is rare. Menadione (K3), synthetic Form that causes liver Damage & neonatal haemolysis no longer used therapeutically .	Green leafy vegetables Olive Oil & Soyabean Oil

a-VAD- Vitamin A Deficiency; b-PD-Parkinson’s Disease; c-AD -Alzheimer’ Disease