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Effects of Fat-Soluble Vitamins on Immune System

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***Abstract*: The immune system protects the body from invading microorganisms and chemicals. It protects against deadly illnesses and communicable diseases in this way. Its proper operation is critical for survival. Vitamins and trace elements must be consumed in sufficient amounts for the immune system to operate properly. Immune activities are suppressed by micronutrient insufficiency, which affects the innate T-cell-mediated immune response and the adaptive antibody response, as well as the balanced host response. This increases infection susceptibility, as well as morbidity and mortality. Infections, on the other hand, exacerbate micronutrient deficits by lowering nutrient intake, increasing losses, and interfering with utilization via modifying metabolic pathways.**

***Keywords*: Vitamin, Immune system, COVID-19, Cancer, Micronutrients.**

1. Introduction

The principal fat-soluble micro constituents (FSMs) in the human diet are fat-soluble vitamins (A, E, D, and K), carotenoids, and phytosterols [1]. Recent revelations that several proteins are involved in the absorption of these substances in the intestine could have a significant impact on their recommended dietary allowances (RDAs) [1]. After micellar solubilization, a bile salt-dependent process, fat-soluble vitamins are absorbed and processed or stored in the liver [2]. Deficiencies occur as a result of steatorrhea because fat malabsorption is accompanied by fat-soluble vitamin malabsorption [2]. Different FSVs have different structures, characteristics, and functions, making simultaneous analysis in food samples problematic [3]. Vitamins A, D, E, and K are fat-soluble vitamins that are lipophilic, hydrophobic compounds made up of isoprenoid units, the same building blocks that are used to make cholesterol. They are carried in the bloodstream bound to lipoproteins or more specific carrier proteins due to their hydrophobic nature [4].

2. Effects of Fat-Soluble Vitamins

A. Vitamin A

Vitamin A plays an important role in epithelial morphology, epithelial keratinization, stratification, differentiation, and functional maturation of epithelial cells, according to recent research green and Mellandy reported in 1928 that VitA might boost organisms' anti-inflammatory responses, coining the term "anti-inflammation vitamin." [5].

Vitamins can also prevent bone marrow cells' natural apopt osis, increasing myeloid cells in the bone marrow, spleen, and peripheral blood, demonstrating that VitA is involved in bone marrow homeostasis management [6].

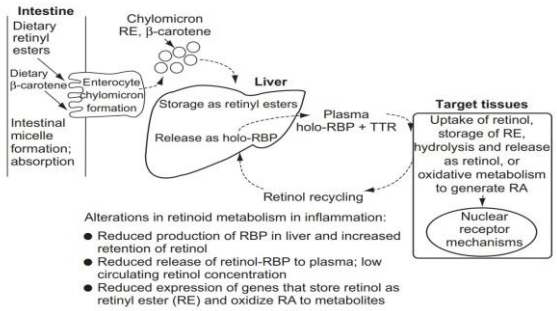

Fig. 1. A diagram depicting the major steps in vitamin A metabolism, as well as a description of the effects of inflammation and infection on retinol transport [7]

Vitamin A is an immunological enhancer that potentiates the antibody response, maintains and restores the integrity and function of all mucosal surfaces, and is essential for both innate and adaptive immunity. It is stored in the form of retinol. The retina is essential for vision [8]. And retinoic acid behaves like a hormone, attaching to two receptors (RAR and RXR) and influencing over 500 genes [8].

Vitamin A aids in the multiplication and maintenance of epithelial cells, particularly those in the lungs. It is a key regulator of lung differentiation and maturation, and maternal VAD during pregnancy may have long-term consequences for the offspring's lung health. Early retinoid deprivation causes lung agenesis in pregnant mice, but later deprivation results in faulty amelogenesis [10]. Vitamin A also has an effect on epithelial cells and innate immune cells that are found on mucosal surfaces. The ALDH1A enzymes essential for the conversion of retinaldehyde to the end-metabolite RA are expressed in dendritic cells of the gut and epithelial cells of the respiratory tract [11]. In cell differentiation, embryogenesis,

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apoptosis, and other processes, vitamin A has pleiotropic effects. Many epithelial tissues, including the mammary gland, are known to be involved in the maintenance, differentiation, and function of retinoic acid and its precursor retinol [12]. Although various options are investigated, the anti-cancer action of retinyl acetate (Vitamin-A acetate, VAA), chosen as a typical retinoid material, is related to its ability to conduct immunopotentiation [13]. Obesity and obesity-related disorders such as insulin resistance, type 2 diabetes, hepatic steatosis and steatohepatitis, and cardiovascular disease can all be affected by vitamin A. Many of the documented relationships are attributed to retinoic acid, the transcriptionally active version of vitamin A. However, retinol-binding protein 4 (RBP4) and aldehyde dehydrogenase 1A1 are both implicated in vitamin A metabolism [14].

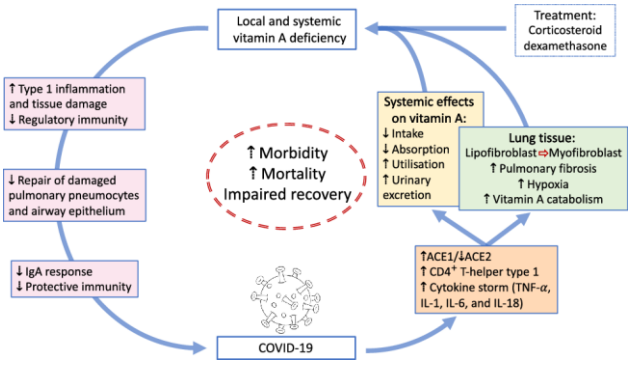

Fig. 2.
Vitamin A's role in infection resistance and recovery: implications for SARS-CoV2 [9].

B. Vitamin E

Vitamin E is a powerful lipid-soluble antioxidant that is found in higher concentrations in immune cells than in other blood cells, making it one of the most effective nutrients for immune function modulation [15]. T cell activity is influenced by vitamin E in two ways: directly by changing T cell membrane integrity, signal transduction, and cell division, and indirectly by influencing inflammatory mediators produced by other immune cells [15].

Vitamin E suppresses protein kinase C (PKC) activity via activating protein phosphatase 2A, which increases PKC-dephosphorylation. It has been shown to inhibit PKC in many cells, resulting in platelet aggregation inhibition, reduced proliferation of monocytes, macrophages, neutrophils, and vascular smooth muscle cells, and decreased superoxide production in neutrophils and macrophages. It may alter the interaction of membrane proteins and the translocation of enzymes to the plasma membrane, altering the activity of signal transduction enzymes [16]. Given that it is the most important lipophilic radical scavenging antioxidant in vivo, vitamin E's major activity is as an antioxidant. Vitamin E scavenges free radicals primarily through a hydrogen atom transfer reaction, yielding a non-radical product and a vitamin E radical, which can then react with another radical to produce a stable product, attack lipids, or regenerate vitamin E by reacting with a reducing agent like vitamin C or ubiquinol [17]. Higher levels of -tocopherol have been linked to a lower risk of asthma development in humans, however, the link between -tocopherol and asthma development is unclear [18]. Preterm birth can disrupt the normal development of the lungs because of maternal prenatal variables such as nutrition. Maternal -tocopherol consumption has been demonstrated to be a key growth factor for fetal respiratory system development and other outcomes, among other nutrients [18].

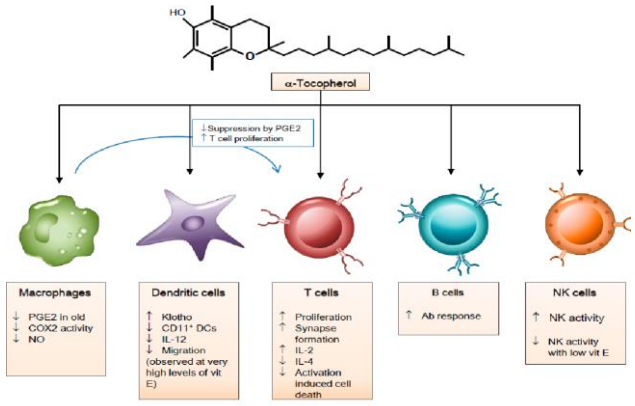

Fig. 3. Vitamin E's immunomodulatory impact on immune cells, PGE2 stands for prostaglandin E2; COX2 stands for cyclooxygenase 2; NO stands for nitric oxide; CD stands for Clusters of Differentiation; DCS stands for dendritic cells; IL-12 stands for interleukin-12; Ab stands for antibody; NK stands for natural killer [19].

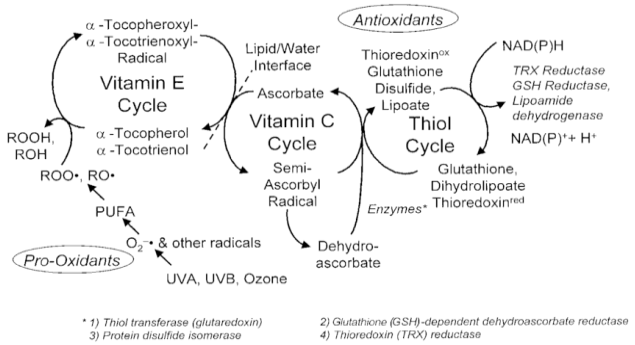

Fig. 4. The relationship between vitamin E, vitamin C, and the thiol redox cycle is depicted in this antioxidant network [20]

C. Vitamin D

Vitamin D's primary functions are to maintain calcium homeostasis and support bone health. Vitamin D increases calcium absorption in the small intestine and promotes osteoclast differentiation and bone calcium reabsorption. Vitamin D also aids in the mineralization of the collagen matrix in the skeleton. Vitamin D is taken through the diet or produced in the skin in humans [21]. On dendritic cells, vitamin D exerts a tolerogenic effect (DCs) 8. Vitamin D decreases DC proliferation, maturation, survival, and differentiation in vitro, resulting in a reduced ability to activate T cells [22], [23]. Simultaneously, it has a direct regulatory effect on T cells, limiting their proliferation as well as the generation of interleukin (IL)17 and interferon (IFN) [24]. Vitamin D supplementation may have a complex effect on immunological activation in people with CF. It also suggests that if administered in greater quantities, vitamin D2 could be a non-inferior substitute for the currently prescribed vitamin D3 [25].

Vitamin D has several possible beneficial impacts on vascular function. Calcitriol (1,25-dihydroxy vitamin D3), a biologically active form of vitamin D, binds to an intracellular target receptor to control the expression of genes involved in vasoregulation, inflammation, and thrombosis [26], [27]. Vitamin D metabolism disturbances are widespread in patients with end-stage renal disease (ESRD) and may contribute to vascular dysfunction [28]. In a carcinogen-induced model in the hamster, vitamin D compounds were shown to prevent cancer formation the vitamin D receptor (VDR) was found in human cancer cells and growth arrest was seen in vitro[29]-[31]. While the exact role of vitamin D in immune function regulation is still unknown, many studies have shown that vitamin D signaling affects monocyte/macrophage differentiation, T cell function, and cytokine production [32]-[34].

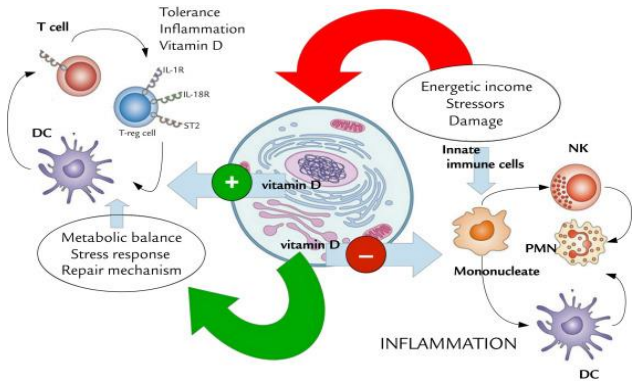

Fig. 5. Graphic depicting vitamin D's function as a pro-survival chemical. Stress and damage signals (red arrow) enter the cell and cause vitamin D to operate as an anti-stress and/or anti-inflammatory agent. To restore energetics and redox hemodynamics, the same mechanism supports and activates (green arrow) a tolerogenic, T-helper 2-type, M2-type, and regulatory T-cell (T-reg) type anti-inflammatory response. PMN = polymorphonuclear leukocyte; DC = dendritic cell; IL = interleukin; NK = natural killer [35]

Vitamin D regulates the stress and damage response, which is primarily governed by the immune system, allowing cells to maintain their energy and survival homeostasis (mainly through the inflammatory response) [35].

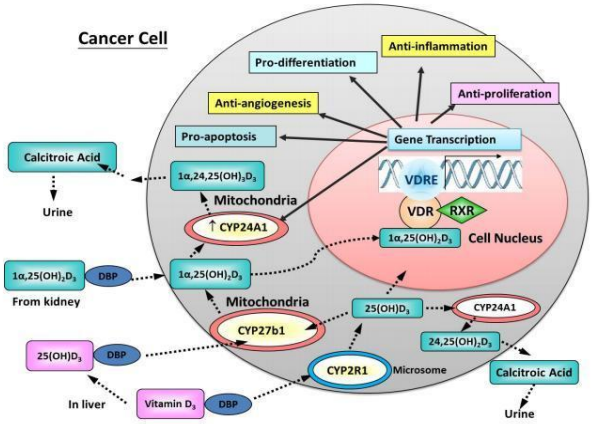

Fig. 6. Anticancer effects of vitamin D 3 [36]

D. Vitamin K

Vitamin K is a fat-soluble vitamin that comes in two natural forms: phylloquinone (K1) and menaquinone (K2), as well as a synthetic version called menadione (vitamin K3) [37].

Vitamin K levels have been linked to diseases such as inflammatory disorders and cancer in studies. However, there is little knowledge about how vitamin K affects immunological and inflammatory responses [37]. Vitamin K3 inhibited the nuclear translocation of NF-B p65 and the binding of NF-Bs to DNA in HEK293 cells after TNF stimulation. TNF-, an inflammatory cytokine, activates the NF-B signaling pathway by binding to the TNF-receptor (TNFR), triggering inflammatory responses that result in a variety of inflammatory illnesses [38]. The inhibition of pol gamma by VK3 is relatively selective, and this chemical appears to exert its anticancer effect in a concentration-dependent way through two putative mechanisms: At high doses, ROS-mediated cell death is induced; at lower concentrations, cell growth is inhibited, most likely due to the reduction of mitochondrial respiratory activity [39]. In cystic fibrosis, a hereditary condition affecting several organs, fat-soluble vitamin K malabsorption and shortage can occur. Vitamin K is believed to play a function in blood clotting as well as bone growth [40].

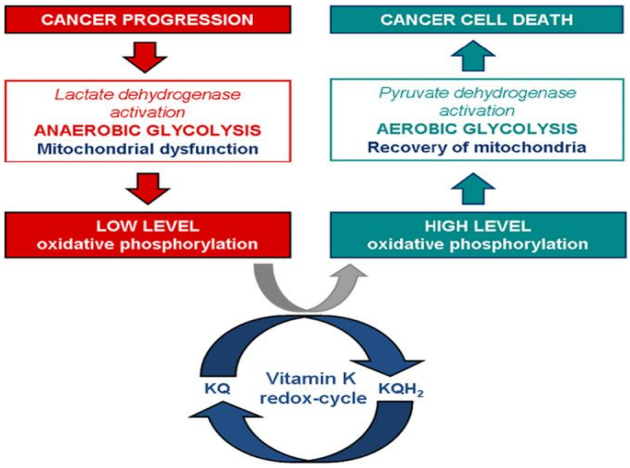

Fig. 7. Vitamin K has anti-cancer properties, as well as redox regulation and the avoidance of mitochondrial malfunction [41]

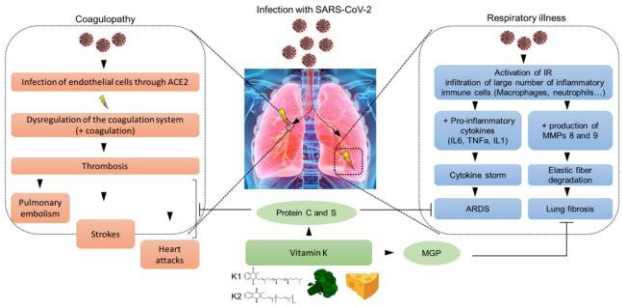

Fig. 8. The role of coagulopathy in the development of SARS-CoV-2 viral infection, as well as the possible benefits of vitamin K

Notably, the protein Gas6 has been demonstrated to play a role in neuron and glial cell survival, chemotaxis, mitogenesis, and cell proliferation [42]. The interaction of vitamins D3 and K2 is essential for bone metabolism. Vitamin D stimulates the creation of a protein that is dependent on vitamin K, while vitamin K activates proteins involved in bone metabolism. Vitamin K is required for the carboxylation of glutamic acid

(Glu) to GLA, which is the physiologically active form of OC that can bind and deposit calcium in the extracellular matrix [43], [44].

Following SARS-CoV-2 infection, the virus attaches to lung epithelial cells and endothelium cells that express high levels of the ACE2 receptor, causing respiratory (respiratory sickness) and vascular (coagulopathy) issues. Infiltrated macrophages secrete pro-inflammatory cytokines (Interleukin 6 (IL6), Tumor Necrosis Factor-alpha (TNFa), and Interleukin 1 (IL1)) and metalloproteinases (MMPs) in response to lung epithelial cell infection. A high viral load induces enormous tissue death in the lungs, leading to acute respiratory distress syndrome (ARDS) and lung fibrosis (right panel). Endothelial cell infection disrupts the normal coagulation process, resulting in venous and arterial thromboembolism, which can cause strokes, heart attacks, and pulmonary embolism (left panel). Vitamin K's numerous and different roles in blood clotting, elastin breakdown, immunomodulation, and vascular health management are summarized (lower panel) [45].

3. Conclusion

Inadequate vitamin and trace element intake and status can contribute to lowered immunity, which makes people more susceptible to illnesses and exacerbates malnutrition. Over the last decade, evidence has accumulated that these specific nutrients selectively influence the immune response in humans, induce dysregulation of the coordinated host response to infections in the case of deficiency and oversupply and that deficiency may impact the virulence of otherwise harmless pathogens. As a result, vitamins and trace elements must be consumed in adequate amounts for the immune system to function properly. vitamin K has a role in bone growth and blood clotting. Vitamin A, D, K has anti-cancer effects. Vitamin A and Vitamin K have significant effects against COVID-19 and related diseases. Vitamin d helps to strengthen the bone. All research evidence and data show that fat-soluble vitamins contribute to strengthening our immune system.

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