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Vitamin D Deficiency and Risk of COVID-19 Infection

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ABSTRACT: There is an urgent need for new supportive treatment options against infectious viral diseases, given the rapid spread and huge number of individuals affected worldwide by these diseases, so cost-effective, globally available and safe options with minimal side effects and simple application are highly assured. This study will therefore discuss the potential of vitamin D supplementation as a preventive and therapeutic agent in combination with other strategies, as this vitamin meets all the criteria described above. A variety of data are available on the association of vitamin D with respiratory infections and viral infections, as well as on the immune response by supplementation with this vitamin.Vitamin D deficiency adds to the variables that make people more susceptible to infection and the damaging development of COVID-19, as there is a correlation between its levels in the body and the severity of COVID-19 infections. Due to its direct antiviral and anti-inflammatory properties, it can be assumed that maintaining it within normal levels in the body is necessary to maintain the health of the body, and when its level in the body is below the optimal level, this can be compensated for with vitamin D supplements.

KEYWORDS: infectious diseases, COVID-19, anti-inflammatory, vitamin D.

1. INTRODUCTION

The ongoing COVID-19 pandemic is one of the deadliest epidemics in human history. It has been declared a global health emergency, with millions of infections and many deaths [1-3]. The first person recorded to be infected in Wuhan; China in December 2019 [4], and the World Health Organization (WHO) described it as a pandemic in late February 2020 [5]. This disease is caused by the seventh coronavirus that infects humans and can result in multiple organ failure [6,7]. The first reported case of this infection in Iraq was an Iranian student in the city of Najaf, and then reporting of cases escalated to include almost all Iraqi governorates [8,9]. The severity of COVID-19 disease can be influenced by various factors such as age, gender, race, and underlying comorbidities [10,11]. The most important clinical symptoms are fever, fatigue, loss of smell and taste, cough, sore throat, and others [12,13]. Although many treatments have been proposed, there is no approved antiviral treatment specific for this infection [14]. Recently, the European Society for Clinical Nutrition and Metabolism proposed practical recommendations for the management of COVID-19 patients [15].

Recommendations included preventing malnutrition by providing adequate amounts of nutrients to maintain energy, protein, fat, and carbohydrate requirements [16]. Moreover, adequate supply of vitamins and minerals is important to prevent viral infections [17,18]. A nutritional status study conducted on COVID-19 patients showed significant vitamin D and selenium deficiencies in patients with pneumonia. Vitamin D deficiency has also been linked to a number of different viral diseases, including influenza and hepatitis [19]. The aim of this study is to clarify the role of vitamin D in immunity, and its beneficial effects in reducing the risks of infectious diseases, especially COVID-19 infection.

VITAMIN D

It is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, phosphate, and many other biological effects. This vitamin is traditionally known as an essential component required in the diet [20]. In humans, the most important compounds in this group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). The main natural source of the vitamin is the synthesis of cholecalciferol in the lower layers of the epidermis through a chemical reaction based on exposure to sunlight (Figure 1). Cholecalciferol and ergocalciferol can be ingested from the diet and from nutritional supplements [21]. Only a few foods, such as the flesh of fatty fish, naturally contain significant amounts of it. In many countries, cow's milk and plant-derived milk alternatives are fortified with vitamin D [22]. Dietary recommendations usually assume that a person's vitamin D intake is

taken orally, as sun exposure in the population is variable and recommendations about the amount of safe sun exposure are uncertain given the risk of skin cancer [23].

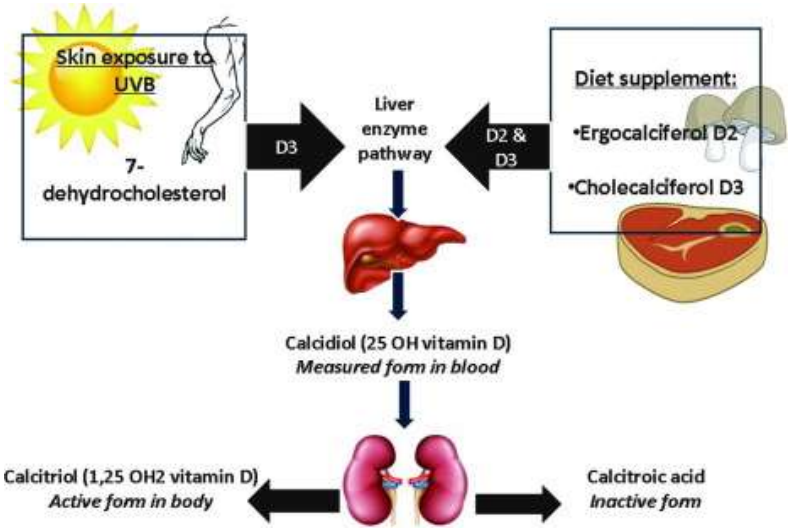

Figure 1: different sources and forms of vitamin D [24].

Vitamin D deficiency, or hypo-vitaminosis D, is defined as a vitamin D level below normal. This most commonly occurs in people with insufficient exposure to sunlight (especially sunlight with sufficient UVB). Vitamin D deficiency can also be caused by insufficient dietary intake, disorders that limit absorption, conditions that impair the conversion of vitamin D into active metabolites - including some liver and kidney disorders, and genetics [25]. Deficiency impairs bone mineralization, leading to bone softening diseases such as rickets in children. It can also worsen osteomalacia and osteoporosis in adults, leading to an increased risk of bone fractures. Muscle weakness is also a common symptom of vitamin D deficiency, which increases risk of falls and bone fractures in adults [26]. Its deficiency is also linked to the development of schizophrenia [27].

RISKS FACTORS OF VIT D DEFICIENCY

The individuals most at risk of vitamin D deficiency are the least exposed to sunlight. Certain climates, clothing habits, avoiding sun exposure, and using too much sun protection products can reduce vitamin D production.

- Older adults are more likely to develop vitamin D deficiency due to a combination of multiple risk factors, including: decreased exposure to sunlight, decreased intake of vitamin D in diet, and decreased skin thickness leading to further decreased absorption of vitamin D from sunlight [28].
- Because vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are fat-soluble, humans need to store some fat. Without fat, it becomes difficult to absorb vitamin D2 and vitamin D3. The lower the percentage of fat, the greater the risk of vitamin deficiency, and this is what happens with some athletes who strive to get as fatter as possible[29].
- Lack of exposure to sunlight does not result in rickets unless the diet deviates from the Western carnivorous pattern characterized by a high intake of meat, fish, and eggs and a low intake of highly extracted grains. In sunny countries where rickets occurs among older children and children, vitamin D deficiency is attributed to low dietary calcium intake. This is a feature of grain-based diets with limited access to dairy products [30].
- There is an increased risk of vitamin D deficiency in people who are overweight or obese based on their body mass index (BMI). There are various factors that can contribute to this relationship, especially diet and sun exposure. Because vitamin D is fat-soluble, excess amounts can be stored in adipose tissue and used during the winter, when exposure to sunlight is limited [31].
- Using a sunscreen with an SPF can theoretically inhibit more than 95% of vitamin D production in the skin. However, in practice, sunscreen is applied so that it has little effect on the status of this vitamin. Wearing clothing is also more effective in reducing the amount of skin exposed to UV rays and reducing natural vitamin D synthesis. Clothing that covers a significant portion of the skin, when worn on a consistent and regular basis, such as the burqa, is associated with lower vitamin D levels and an increased prevalence of vitamin D deficiency. In addition, its deficiency has been linked to urbanization in terms of air pollution, which blocks ultraviolet rays, and an increase in the number of people working indoors. Older adults are generally exposed to less UV light due to hospitalization, immobilization, institutionalization, and being homebound, which results in lower vitamin D levels [32,33].

Vitamin D Deficiency and Risk of COVID-19 Infection

- Low pigmentation in people with fair skin may have higher levels of vitamin D, due to melanin acting as a sunscreen, and individuals with darker skin may have higher levels of this vitamin deficiency. Three to five times more sun exposure is necessary for people with naturally dark skin to produce the same amount of vitamin D as those with fair skin [34].
- Rates of vitamin D deficiency are higher among people with untreated celiac disease, inflammatory bowel disease, and exocrine pancreatic insufficiency resulting from cystic fibrosis, all of which can lead to malabsorption problems. Its deficiency is also more common after surgical procedures that reduce absorption from the intestine, including weight-loss procedures [35].
- Vitamin D deficiency is associated with increased mortality in serious illnesses. People who take vitamin D supplements before entering intensive care are less likely to die than those who do not. In addition, vitamin D levels decrease during a stay in intensive care. Taking vitamin D3 (cholecalciferol) or calcitriol by mouth may reduce mortality without significant adverse effects [36].

ROLE OF VIT D IN IMMUNITY

Adequate levels of vitamin D in the body can be achieved by consuming adequate amounts of vitamin D and exposure to sunlight. Adequate concentrations of 25-hydroxyvitamin D have been associated with a reduced risk of acute respiratory infections in adults. In addition, adequate levels of 25-hydroxyvitamin D in serum were inversely associated with the risk of viral respiratory infections in children [37].

Vitamin D reduces risk of viral infections; it improves the body's physical barrier by regulating the production of proteins for tight junctions, adhesion junctions, and gap junctions, which can be affected by infection by microorganisms, including viruses [38]. In addition, lung epithelial cells express 1-hydroxylase which converts 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3, the active form of vitamin D. Active vitamin D increases the expression of vitamin D-regulating genes, such as cathelicidin and CD14-like receptors in bronchial epithelial cells. Double-stranded RNA produced by most viruses can increase 1-hydroxylase expression, leading to increased production of active vitamin D and expression of cathelicidins in bronchial epithelial cells [39].

Therefore, vitamin D may prevent the invasion of coronaviruses by enhancing physical barriers and increasing the production of antimicrobial peptides in the lung epithelium.Vitamin D stimulates the production of antimicrobial peptides which have antimicrobial activities against various microorganisms, including bacteria, viruses, and fungi. Human beta-defensin-2 exhibits antiviral activity by destabilizing the viral envelope in respiratory enveloped virus, preventing infection in human lung epithelial cells. Thus, it is important to maintain adequate levels of vitamin D for the production of antimicrobial peptides [40,41].

VIT D IN REDUCING RISK OF COVID -19 AND VIRAL INFECTIONS

Recent studies have shown some pathways through which vitamin D reduces the risk of microbial infections, following different mechanisms in reducing the risk of viral infections and mortality. To reduce the risk of infections, vitamin D uses three pathways: physical barrier, natural cellular immunity, and adaptive immunity [42]. It also has a potential role in reducing the risk of COVID-19 infection and mortality, by maintaining cellular junctions, gap junctions, increasing cell-mediated immunity by reducing the cytokine storm that has an effect on interferon and tumor necrosis factor, and regulating adaptive immunity through suppressing type I helper T cell responses and stimulating T cell induction [43].

One of the main manifestations of severe COVID-19 infection is lymphopenia; many studies have shown that vitamin D plays an important role in respiratory homeostasis either by stimulating the production of antimicrobial peptides or by directly interfering with the replication of respiratory viruses. Thus, vitamin D deficiency could be involved in acute respiratory distress syndrome and heart failure and these are manifestations in people with severe diseases such as COVID-19. Therefore, vitamin D deficiency enhances the renin-angiotensin system (RAS), which may lead to chronic cardiovascular disease and decreased lung function, patients with such comorbidities account for a higher proportion of severe cases of COVID-19[44,45].

Some clinical and epidemiological studies support the identification of the hypothesis regarding COVID-19 and its relationship to vitamin D status. Recent studies have indicated that COVID-19 is associated with increased production of pro-inflammatory cytokines and C-reactive protein, acute respiratory distress syndrome, pneumonia, and heart failure [46,47]. Clinical studies reported that respiratory infections were significantly lower in the vitamin D supplement individuals than in control ones. Another studies indicated the beneficial effects of vitamin D supplements in reducing the risk of acute respiratory infection [48,49].

BENEFICIAL EFFECTS OF VIT D SUPPLEMENTS

Currently, there is no clear evidence that vitamin D supplements prevent severe COVID-19 infection and death. Vitamin D supplements have been proven to be safe and effective in preventing acute respiratory infections [50]. They also added that people with severe vitamin D deficiency saw the maximum benefit from supplementation. The protective role of vitamin D was higher in people with normal baseline serum levels compared to those with less than normal levels, daily or weekly vitamin D intake showed protective effects against acute respiratory infections, especially in people with vitamin D deficiency. Vit D supplements have also been found to increase antioxidant-related gene expression [51].Increased glutathione production avoids the use of vitamin C, which

has potential antimicrobial activities and has been suggested to prevent and treat COVID-19 infection [52]. The body's response to a given dose of supplements varies widely between individuals due to differences in demographic and biological variables, such as race, age, duration of exposure, seasonal changes, body mass index, intake of certain medications, basal concentration of vitamin D, genetics, and type of vitamin D supplement. Moreover, population heterogeneity as well as vitamin D dose must be considered while determining the protective role of vitamin D in COVID-19. A recent study has also suggested that magnesium supplementation with vitamin D supplements as magnesium helps regulate phosphate and calcium homeostasis. It appears that the enzymes involved in vitamin D metabolism need magnesium, which plays an important role as a cofactor in enzymatic reactions, especially in the kidneys and liver[53].

CONCLUSIONS

Vitamin D supplements have protective effects against respiratory infections. Therefore, people at risk of developing vitamin D deficiency should consider taking vitamin D supplements to maintain optimal levels and prevent exposure to respiratory infections, as there is a hypothesis that there is a relationship between cases of COVID-19 infection and its outcomes with vitamin D .Because vitamin D supplements are not expensive and can be considered safe, individuals at risk of deficiency of this vitamin are highly recommended to supplement. More attention should be given to monitoring nutritional status, because minerals and trace elements are inevitably linked to an effective immune response.

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