



Review Article

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Vitamin D and its Effects on COVID-19

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Abstract

Vitamin D plays an important role in supporting the immune system. Its expression on vital immune cells like B, T, and antigen-presenting cells has become an important topic of research in response to the current COVID-19 pandemic. The purpose of vitamin D is vital not only to supporting the role of bones and muscle development, but also in its involvement in the regulation of mood and the immune system. This “sunshine vitamin”, due to its role in developing immunity within both adaptive and innate forms, is important to investigate with regards to disease prevention. There has been a recent push by many researchers to increase the recommended dosage of vitamin D because research shows that vitamin D deficiency can increase susceptibility to communicable diseases such as SARS-CoV-2. In this paper, we plan to highlight the immediate need to increase the national recommended dosage for Vitamin D due to the current population statistics indicating a significant overall deficiency, especially in areas with a high population density and within many minority groups. The purpose of this paper is also to highlight how the public’s vitamin D deficiency may also be contributing to the COVID-19 pandemic crisis as well.

Keywords

Vitamin D, COVID -19, Angiotensin-Converting Enzyme-2(ACE-2), Innate and Adaptive Immune Systems, Magnesium, Vitamin K, Acute Respiratory Infection (ARI), Middle East Respiratory Syndrome (MERS), Antigen Presenting Receptors

The Novel Coronavirus and the Immune System

The immune system can be classified into two parts: the innate and the adaptive system. Generally, the innate system prevents viral infections by providing defensive physical barriers like the skin, mucus membranes within oral and nasal cavities, and the cilia escalator lining the lower respiratory tract. Additionally, some innate chemical barriers, like sebum found on the skin, sweat, saliva, and gastric acid, also assist in preventive measures against viruses. Though the extent of virulence of a pathogen depends on its mechanism of action as well as its mode of entry, the innate immune system plays an important role to fight against infection.

Even with the notable protection of the innate immune system, viruses like the COVID-19 are quite capable of overriding them to enter the body. The novel coronavirus attaches to the Angiotensin Converting Enzyme-2 (ACE-2) receptor found on epithelial and respiratory cells and then invades its host. The antigens on the host are recognized and targeted by the T-cells of the adaptive immune system in response. Since the adaptive immune response is a vital secondary defense for combating viruses, it is important to have and maintain a strong immune response. Studies have shown that patients are most susceptible to respiratory and pneumonia infections when they are vitamin D deficient [1,2] (Table 1).

According to an international study involving over 10,000 participants in 14 different countries, it was determined that vitamin D was demonstrated to be very safe, and individuals who are very deficient had benefited well from extra vitamin D supplementation and reduced the risk of an ARI significantly from 42% to 39% [3]. Regarding individuals who are significantly deficient in vitamin D, the effects of vitamin D have been demonstrated to reduce the risk of an ARI from 60% to 32% [3]. This statistic is significant because acute respiratory distress is a primary adverse effect of COVID-19 and is also a primary medical concern in terms of hospitalization [4].

Vitamin D Absorption and Mechanism within the Body

About 80% of the vitamin D uptake occurs directly from

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Table 1: Classification of vitamin D level (serum 25(OH)D levels).

Classification	Nanograms	Nanomoles	Recommended D
Danger of toxicity	> 100 ng/ml/l*	> 250 nmol/l	
Normal or optimal	> 30 ng/ml	> 75 nmol/l	400-4000 IU/day
Insufficient	21-29 ng/ml	51-74 nmol/l	4000-6000 IU/day
Deficient	11-20 ng/ml	26-50 nmol/l	7000 IU/day
Severely deficient (often not distinguished from deficient)	< 10 ng/ml	25 nmol/l	10000 IU/day × 1 month or 500,000 IU × 1

*Some sources found that 150 ng/ml was not harmful. 1 µg Vitamin D = 40 International Units (IU).

Adapted from: Benskin, 2020.

the sun and is synthesized through the skin [5]. During the summer season, when the days are longer, we tend to obtain a sufficient amount of Vitamin D from the sun, and it is synthesized within the body as Vitamin D3. Since the body produces D3, it is often considered to be the most natural form of Vitamin D [6]. The body contains numerous amounts of vitamin D receptors on epithelial cells. As sunlight radiates ultraviolet B onto the skin, the cholesterol in the skin cells undergoes a series of chain reactions to convert the vitamin into a hormone that is used to activate necessary immune cells in response to a pathogen. Vitamin D is also obtained from diet is metabolized by the liver, and kidneys [6]. Vitamin D available through diet is found in foods like salmon, sardines, red meats, and mushrooms as Vitamin D2 [5]. Obtaining vitamin D2 through a diet can be difficult for populations that do not consume meat or mushrooms, which provides another explanation as to why vitamin D deficiency is common in some ethnic and cultural groups and not in others. It is also important to note that since many regions of the world do not experience consistent amounts of sunlight, vitamin D is often difficult to come across. However, regardless of how it is obtained either through sunlight or food, both forms aid in the absorption of calcium and phosphorus along with supporting immune benefits. Typically, a 4000 IU (100 mcg) dose is generally regarded as a safe amount for supplementation [1].

In the summer of 2020, during the worldwide coronavirus pandemic, many bars, restaurants, gyms, and other recreational centers limited their hours or closed in order to minimize exposure to Covid-19. Thus, many people turned to outdoor recreational activities instead. With this increase in outdoor activity, the public is better exposed to sunlight and thus vitamin D. However, a few hours of additional sunlight are not often enough to restore someone who is severely deficient back to regular levels without supplementation. According to a meta-analysis conducted based on 25 randomized controlled trials by 23 participating institutions in 2017, prolonged supplementation of vitamin D was the most protective measure for those who were vitamin D deficient, and that a lack of vitamin D within specific areas of a population may potentially induce other pandemics in the future as well [1].

Wuhan, China, where the novel Coronavirus originated from, experiences much rainfall due to its location near the coast. Typhoons are also common seasonally along with cold and dark winters. Although the city does have some sunny

days, the general weather and climate are gray. In general, vitamin D inadequacy tends to be more common within the Asian and African populations. In a study published in January 2017, over 6000 healthy members of the Chinese population were evaluated using a cross-sectional analysis to correlate a link between vitamin D deficiency, immune system regulation and their environment. It was found that vitamin D deficiency was most prevalent among individuals who were underweight, received low levels of UVB from sunlight, and lived in large cities [7]. The current available research has indicated that vitamin D does play a supporting role in the immune system by also playing a role in regulating the uptake of calcium. Calcium has been demonstrated to activate key cells within the immune system like neutrophils, basophils, lymphocytes, and T-cells that are necessary to combat viral infections [8].

Vitamin D Deficiency and its Correlation to the COVID Death Rates

In a study conducted at Medical University Hospital in Heidelberg, 185 patients were admitted into the hospital for treatment after being diagnosed with COVID-19 [9]. Out of those 185 patients, it was determined that 118 (64%) of them were vitamin D deficient. Out of all those patients who were diagnosed with COVID, all 16 of the patients who died were vitamin D deficient as well. It is important to note that in this study vitamin D deficiency is identified as serum total 25(OH)D level < 12 ng/mL [9]. The conclusion of this study has implications for the public health relevance of risk since 87% of COVID-19 deaths were related to a vitamin D deficiency. In fact, research indicates that a patient’s vitamin D level could predict the severity of illness and treatment needed with regards to COVID-19 [10]. Thus, it is only logical and ethical to at least place some weight for recommending vitamin D supplementation for those at high risk for COVID-19 at the very least, because supplementation has been demonstrated to be beneficial with minimal risk and adverse effects [3].

Vitamin D and Combination Therapy

Vitamin K allows for proper blood clotting and is composed of two primary compounds: Vitamin K1 and vitamin K2. Vitamin K2 is often used for the treatment of osteoporosis when supplemented with Vitamin D and calcium [11]. The white blood cells that fight against infections are developed within the bone marrow. It is important to maintain proper

bone health to prevent fractures as well as pathogens. There have been recent studies demonstrating the importance of combination therapy in individuals who have been diagnosed with comorbidity along with COVID, such as hypertension, kidney disease, or obesity. This is because individuals, who may have comorbidities, may also be vitamin K deficient [12]. Vitamin D and vitamin K combination therapy may also be beneficial because an increase of vitamin D through supplemental intake may increase calcium permeability of elastic fibers and stimulate degradation of these fibers. Vitamin K activates the Matrix Gla Protein (MGP) which serves as an inhibitor against the calcification of soft tissue and fiber degradation [13]. It is also important to note that soft tissues and fibrous tissues, especially those located in the upper respiratory tract, may serve as targets for SARS-CoV-2 due to the potential abundance of ACE-2 receptors although limited studies support this claim [12]. Vitamin C is best known for its amazing benefits for supporting immune health. The regular intake of vitamin C has been demonstrated to reduce the number of colds over the long term and shorten the duration of a cold during the short term. About 20% of coronaviruses are the cause of the common cold. However, certain strains of coronaviruses have been noted to cause more severe respiratory infections such as severe acute respiratory syndrome (SARS) or Middle Eastern Respiratory Syndrome (MERS) [14].

Quercetin has also been noted to have antiviral preventative properties, and the flavonoid has been demonstrated to have strong antioxidant properties too [15]. Quercetin is beneficial against combating COVID-19 because it can bind to the spiked proteins of the virus and thus prevent the virus from attaching to the appropriate receptor cells and gaining entry [15]. The cell receptor refers to angiotensin-converting enzyme-2 (ACE2) receptor and mainly affects the lower respiratory tract. SARS-CoV-2 also binds to ACE2 on the alveolar epithelial cells after infecting the human body [16].

There are other vitamins, minerals, and medications that are beneficial for use with regards to combination therapy as well. This includes melatonin, which helps the patient sleep and conserves energy, and zinc which aids in the development of immune cells [17]. According to a recent study, melatonin can behave as a potential preventative measure against COVID-19 due to its ability to work as an indirect inhibitor of the ACE2 receptor in which the SARS-CoV-2 binds. By melatonin's ability to bind and inhibit calmodulin (CaM), which in turn regulates the ACE2 expression, the signs, and symptoms of COVID can be essentially minimized [18]. The use of melatonin has also been demonstrated to decrease immunosuppression with aging, which is important in preventing infection as well. It is also interesting to note that since melatonin is released from the pineal gland in response to darkness, and vitamin D is often synthesized in sunlight, the effects of vitamin D and melatonin may work contrary to each other. Although melatonin activates the innate immune system, it is also known to lower body temperature which may inhibit or reset the circadian rhythm [19]. Overall, many ongoing clinical trials with medications, supplements alone or in combination are being conducted in response to the push for an increase in vitamin D supplementation.

Vitamin D Deficiency and Those Most Susceptible

The American Academy of Pediatrics (AAP) recommends that exclusively and partially breastfed infants should supply 400 IU/day of vitamin D after birth and continue to receive vitamin D supplements until they are weaned and consume more than 1000 mL/day of vitamin D-fortified formula milk [20].

For the elderly above 70, the recommended dose is about 800 IU (20 mcg) per day. Vitamin D deficiency is defined as 11-20 nanograms/ml and insufficiency is defined as less than 30 nanograms/ml. However, since vitamin D is critical for modulating many aspects of our immune system and is thus necessary for fighting off infection, there has been a push to increase the recommended dose of vitamin D to be 4000 IU (100 mcg) [21]. This is because scientific evidence shows the correlation between high amounts of vitamin D with a significantly reduced risk of infection [21]. Since there are minimal side effects associated with taking vitamin D, and the body can synthesize more amounts of vitamin D from sunlight. Vitamin D deficiency poses such a significant risk of getting infected with SARS-CoV-2. However, vitamin D may significantly deplete magnesium levels and thus, it may be recommended to increase intake of magnesium as well along with vitamin D [22]. It is also important to understand that the vitamin D supplementation mentioned in this paper refers to the oral supplementation only.

There is a myth that those with darker skin, like those who identify as South Asian or African American, get enough sun due to the warm climate within their locations of origin so they do not need to worry about vitamin D. However, within the darker skinned population, they tend to have an increased risk of being or becoming vitamin D deficient due to the presence of melanin in the skin. African Americans are the most at risk for having a vitamin D deficiency regardless of age and health status. Among African Americans, the median level of vitamin D tends to be lower than any other group regardless of the time of year, outdoor activity level, or supplemental intake [23]. Overall, African Americans are the most vulnerable among the population from being infected with COVID-19. According to a study conducted by Johns Hopkins University, those from predominantly black neighborhoods are 3x more likely to become infected with the virus and die from it [24]. Although other factors are contributing to this cause such as lower socioeconomic status, an increase in stress and reduced access to proper healthcare, genetic and predisposed deficiencies would play a significant role as well [24]. Although different communities have different health concerns, during a pandemic, it is important to address the concerns that are the most beneficial to the overall public health and to these groups specifically.

Conclusion

Due to Vitamin D's supporting role in multiple aspects of the body, supplements can be and should be used for those who may be more at risk for being Vitamin D deficient. However, providers often prescribe Vitamin D to treat specific

conditions related to the bone like osteomalacia, rather than for combating viral infections like COVID. Although vitamin D does play a supporting and preventative role within the immune system by activating key immune cells, other methods of treatment and combating viral respiratory infections would also increase the effectiveness in preventing COVID-19 infections, such as vaccination, certain antiviral medications and supplements either alone or in combination. Also, it is often emphasized how important it is to go outside and engage in physical activities as well as eating a well-balanced diet. One of the reasons behind this is to maintain a balanced immune system and health as well as maximizing the adsorption of natural vitamins that support our immune system and overall health. Since most of the population is vitamin D deficient, clinicians and scientists have begun advocating for the increased supplementation and dosing of vitamin D. The overall costs for supplementation are significantly low compared to the direct and indirect costs associated with infections, hospitalization, and death. Although it is a preventative measure much like that of wearing a mask in public, the consensus calls for a significant increase in the recommended dose to 4000 IU (200 mcg). This approximates to an increase of 6x the currently listed dose by NIH in the foreseeable future, especially in the presence of a worldwide pandemic.

Authors Contribution

AS conceived the idea, SI and AS did the literature search; AS and SI contributed towards the design and writing of the manuscript; AS, SI and MI critically reviewed and approved the manuscript.

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