

# The Role of Vitamin D in Enhancing Immunity in the Face of the COVID-19 Pandemic and its Recommendations: A Literature Review

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**Abstract:** *Vitamin D is a fat soluble vitamin that has a very important role in regulating the body's calcium balance. It also plays an important role in cell growth, even optimizing the immune system. Ultra violet light obtained from sunlight, especially Ultraviolet B, can help the formation of vitamin D in human skin. Some experts encourage the public to optimize immunity by meeting vitamin D needs by sunbathing regularly. To protect the body from the risk of skin cancer due to UV rays, the American Academy of Dermatology recommends protecting skin from sunlight, such as activities in the shade, wearing long clothes and hats when the UV index is above (moderate to very high danger level. And if necessary use a broad spectrum Sunscreen, with an SPF of 30 or more. To meet daily vitamin D requirements, American Academy of Dermatology recommends the need for additional vitamin D orally.*

**Keywords:** Vitamin D, COVID-19, Imunity, Skin Cancer, Aging, Vitamin D Supplementation

## 1. Introduction

In the midst of the COVID-19 outbreak that struck almost all countries, including Indonesia, a variety of ways people did to reduce the risk of contracting the COVID-19 virus, one of which was to sunbathe. Ultra violet light obtained from sunlight, especially UVB, can help the formation of vitamin D in human skin.<sup>1</sup>

Vitamin D is a fat soluble vitamin that has a very important role in regulating the body's calcium balance. It also plays an important role in cell growth, even optimizing the immune system. So that sunbathing, can help the body produce vitamin D, which in turn can optimize the body's immunity against viral infections.<sup>1,2,3</sup>

Based on research, about 50% of the world's population is deficient in vitamin D. This problem of vitamin D insufficiency and deficiency is one of the public health problems faced by many countries. The population that experiences vitamin D deficiency is most represented by the group of people who are elderly, obese, and patients with long bed rest in hospital.<sup>3</sup>

The study described a country where most of its population had relatively low levels of vitamin D (Italy), which had a high infection and death rate due to COVID-19. In contrast to countries where populations have relatively sufficient vitamin D levels (Norway and Finland), they experience relatively low infection and death rates due to COVID-19.<sup>1</sup> Given these facts, some experts recommend that people optimize their immunity by meeting their vitamin D requirements by sunbathing regularly.<sup>2</sup>

## 2. Vitamin D Deficiency as Global Problem

Vitamin D status in the human body is classified based on 25-OH-D levels in serum<sup>4</sup>:

1. > 30 ng / ml = normal
2. 21-29 ng / ml = insufficiency

3. <20 ng / ml = deficiency

Based on research, on average about 50% of the world's population is deficient in vitamin D. This problem of vitamin D insufficiency and deficiency is one of the public health problems faced by many countries. The population that experiences vitamin D deficiency is most represented by the group of people who are elderly, obese, and long bed rest patients in the hospital.<sup>3,6,7</sup>

The large number of people who are deficient in vitamin D is thought to be caused mainly by the modern lifestyle that has a lot of activity indoors and several other environmental factors that cause less exposure to ultraviolet-B (UVB), and lack of vitamin D intake from food. The high prevalence of vitamin D deficiency and insufficiency is a serious public health problem because this is a risk factor for several deaths that occur in the wider community. Recent research has shown that vitamin D deficiency has been linked to cancer, cardiovascular disease, type 2 diabetes, autoimmune diseases, influenza, and depression.<sup>2,6,8</sup>

## 3. New Role of Vitamin D in Immunity

Classically, vitamin D has always been implicated in bone health by increasing calcium absorption in the intestine and regulating calcium and phosphate levels in the blood, but in the last 2 decades, a new role in vitamin D has been discovered.<sup>8</sup> Vitamin D also plays a role in cell proliferation and differentiation, regulation of the immune system, preventive effects on cardiovascular and neurodegenerative diseases, even anticancer and antiaging effects.<sup>2,8</sup>

Calcitriol has an important immunomodulatory role, including strengthening the innate immune system, inhibiting the response of the adaptive immune system, related to the synthesis of interleukin (IL) -4 by helper T-lymphocytes (Th) -2 cells, and upregulation of regulatory T lymphocytes (T-reg) cells.<sup>8,9</sup>

### 3.1 Regulation of innate immune responses to dendritic cells and macrophages

Calcitriol increases the defense capacity of macrophages by increasing cell differentiation, phagocyte capacity and antimicrobial activity (cathelicidin). Cathelicidin, a peptide formed from vitamin D stimulation, exhibits antimicrobial activity such as bacteria, fungi, and enveloped-viruses.<sup>9</sup> In fact, calcitriol inhibits monocyte proliferation and increases the differentiation of monocytes into macrophages. This effect is mediated by upregulation of Fc cell surface receptors and increased cell respiration. In addition, Calcitriol inhibits dendritic cell proliferation, maturation, and also the effect of stimulation of the immune system which ends with T-reg cell induction. It can be concluded, vitamin D deficiency can result in the body becoming less tolerant of foreign antigens.<sup>8</sup>

### 3.2 Inhibits the pro-inflammatory response of APC

Calcitriol inhibits cytokine expression from APC, including IL-1, IL-6, IL-12, and TNF- $\alpha$ . As well as reducing the expression of the cell surface protein Major Histocompatibility Complex (MHC) Class II in macrophages, the formation of Th1 and Th17 proinflammatory cells. By inducing T-reg and Th2 cells will automatically downregulate Th1 activity. Thus, Calcitriol inhibits IL-12 production and stimulates IL-10 production, while downregulating the expression of some molecules such as CD40, CD80, CD86 which are needed in the activation of APC and dendritic cells, thus leading to Th1 inhibition. Additionally, calcitriol works directly against T cells inhibiting the secretion of IL-2, which is an essential cytokine for the formation of additional lymphocytes and gamma IFN. Calcitriol also inhibits B cell differentiation and antibody production. In the case of psoriasis, calcitriol inhibits keratinocyte proliferation and also facilitates cell differentiation.<sup>8</sup>

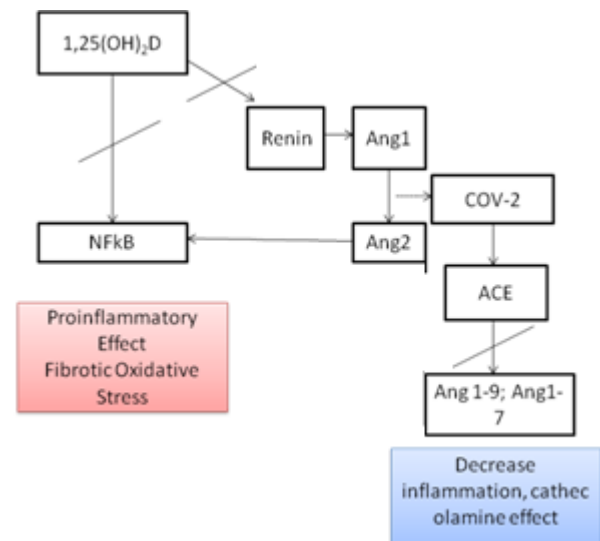
### 3.3 Covid-19 Association with Low Levels of Vitamin D

In a research model on inflammation induced by Lipopolysaccharides, vitamin D was able to reduce levels of pro-inflammatory cytokines IL-6.<sup>10,11</sup> It is IL-6 that plays an important role in COVID-19 induced acute respiratory distress syndrome (ARDS).<sup>10</sup>

In the classic Renin-angiotensin-system (RAS) system, renin produced will convert angiotensinogen to angiotensin I. Then angiotensin I is converted to angiotensin II by Angiotensin Converting Enzyme (ACE). If angiotensin II activates angiotensin 1 receptors (AT1R), there will be an increase in blood pressure and several other effects (vasoconstriction, inflammation, and catecholamine activity). To maintain homeostasis, the body has an Angiotensin 2 receptor (AT2R) activation system and a Mas receptor. Where Angiotensin I and II are converted by ACE2 to Angiotensin 1-9 and 1-7. Angiotensin 1-9 and 1-7 will activate AT2R, so that there will be a decrease in blood pressure, vasodilation, and inflammation. With the operation of these two systems, the body's homeostatic balance can be maintained as long as RAS activity can be controlled.<sup>9</sup>

Several studies have shown an increase in Renin, angiotensin II, and the activity of the Renin-angiotensin-system (RAS) due to low levels of vitamin D in the body. the same thing also applies that the low activity of Renin is related to high vitamin D levels.<sup>9</sup> Vitamin D decreases the expression of Renin by decreasing transcription activity in the Renin promoter gene. Low levels of vitamin D in the body result in increased secretion of Renin, which activates RAS, resulting in an increase in blood pressure. If there is an imbalance in this system (where there is an increase in the activity of Angiotensin II and Renin), it will result in an increase in the inflammatory response.<sup>9</sup>

SARS-CoV2 infection occurs by contacting spike proteins with ACE2 receptors on the cell surface. After that the virus can enter the cell with endocytosis. This also results in damage to the ACE2 receptor resulting in an imbalance in the RAS system. As a result, there is a change in vascular activity and the production of pro-inflammatory cytokines into the circulation.<sup>9</sup>



**Figure 1:** RAS regulatory system and the role of vitamin D in it (Reproduced from Biesalski, 2020).<sup>9</sup>

In one study explained that the administration of vitamin D can reduce the expression of renin, Angiotensin II, and AT1R. it is also able to increase ACE2 and angiotensin activities 1-7. Thus reducing the inflammatory process and reducing lung damage.<sup>11</sup>

Angiotensin II activates some pro-inflammatory stimulation in the immune system through AT1R activation. This activity results in the development of the inflammatory process that occurs, even aggravating the conditions of Hypertension and Diabetes. Vitamin D has the opposite effect on this condition through the Vitamin D receptor (VDR) receptors found in the immune system.<sup>1,9</sup>

A comparative study studying mortality index and the relationship of CRP (a cytokine storm marker) and vitamin D in COVID-19 patients in various countries says that high CRP tends to be found in groups of people who have low vitamin D levels.<sup>9,12</sup>

A study explained that people with low body vitamin D levels were associated with a risk of respiratory tract

infections and were more severe in people who had a history of lung disease. Other research also explains that vitamin D supplementation can reduce the risk of respiratory infections.<sup>1</sup> European studies describe a country where a large proportion of the population has relatively low vitamin D levels (Italy), experiencing high infection and death rates due to COVID-19. In contrast to countries where populations have relatively sufficient vitamin D levels (Norway and Finland), they experience relatively low infection and death rates due to COVID-19.<sup>1</sup>

### 3.4 About Ultraviolet

Ultraviolet light is part of the electromagnetic waves of solar radiation energy in the band 100-400 nm. Solar radiation that reaches the earth's surface itself is around a wavelength of 100 nm to 1 mm. Ultraviolet light which is in the wave band 100 - 400 nm is further divided into UVA, UVB and UVC with details, namely<sup>13</sup>:

1. UV A = 315 - 400 nm
2. UV B = 280 - 325 nm
3. UV C = 100 - 280 nm

Upon entering the atmosphere, almost all UV C will be retained in ozone layer and 90% UV B will be absorbed by ozone, water vapor and other gases in the atmosphere. The majority of UV A will be able to reach the earth's surface. Thus, of the total ultraviolet light contained in solar radiation when it reaches the earth's surface is UV A (90-99%) with a little UV B (<10%).<sup>13,14</sup>

Each scale has a UV Index equivalent to 0.025 Wm<sup>2</sup> of ultraviolet radiation. The scale was obtained based on spectral fluxes of UV radiation with functions that correspond to photobiological effects on human skin, integrated between 250 and 400 nm<sup>13</sup>:

### 3.5 Is It Enough to Maintain Vitamin D Levels With Sunbathing Only?

A portion of vitamin D is synthesized by the body in the skin with the help of ultraviolet-B rays. Therefore, some experts encourage the community to optimize immunity by fulfilling the needs of vitamin D by sunbathing regularly.<sup>2</sup> The World Meteorological Organization (WMO) writes that lack of sunlight will affect our mood and also increase the threat of vitamin D deficiency. excess has short-term and long-term effects that are bad for skin health, such as aging and skin cancer.<sup>15</sup> The data show that ultraviolet radiation is the cause of about 1.3 million cases of skin cancer per year in the United States.<sup>16</sup>

The process of carcinogenesis (formation of cancer cells) begins when a cell's DNA is damaged, which will be followed by a series of cellular processes of tumor formation. Ultraviolet (UV) radiation results in DNA damage, inflammation, erythema, immunosuppression, skin aging, gene mutase, and skin cancer. After DNA damage occurs, the p53 tumor suppressor protein will perform phosphorylation and translocation of the nucleus to repair damaged DNA, or make apoptosis. Excessive UV exposure will overwhelm cells with DNA damage resulting in mutations from p53. Keratinocytes with mutated p53 have a

very fast growth profile due to their resistance from apoptosis. It can be concluded that, cells that are resistant to apoptosis are an important requirement of carcinogenesis.<sup>17</sup>

The American Academy of Dermatology does not recommend getting vitamin D by sunbathing because it can increase the risk of skin cancer, especially Melanoma, the most deadly type of skin cancer.<sup>18</sup> Therefore, to protect the body from the risk of skin cancer due to light UV, some recent consensus and recommendations suggest protecting yourself from the sun, such as doing activities in the shade, using long clothes and hats when the UV index is  $\geq 3$  (moderate to very high danger level). And if necessary use a broad-spectrum Sunscreen, with SPF 30 or more.<sup>18,19</sup> To meet daily vitamin D needs, AAD recommends eating foods that are rich in vitamin D, or taking vitamin D supplements.<sup>18</sup>

Food sources that are rich in vitamin D include oily fish groups such as salmon, anchovies, and mackerel. A small portion of vitamin D is also found in the liver and eggs. The need for vitamin D is quite difficult to achieve through food sources alone.<sup>19</sup> Based on available scientific sources, to meet daily vitamin D requirements it is recommended to consume vitamin D supplements of<sup>18</sup>:

- 1) 400 International Units for infants / children 0-1 years
- 2) 600 IU for children, teenagers and adults 1-70 years
- 3) 800 IU for adults 71+ years

## 4. Conclusions

Vitamin D has immunomodulatory effect and in COVID-19 may serve as anti-inflammatory agent. More studies are needed to prove this action. Vitamin D supplementation are mandatory to fulfill the daily average needs. Sunbathing action to increase vitamin D is not practical because of no parameter of how long the duration must be taken. Again avoiding too long exposure of sun is needed to prevent the harm effect of the sun itself.

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