LITERATURE REVIEW

Vitamin D Supplementation and COVID-19

Gracia Dewitacita Tanaya[1*], Willa Mettacita Tanaya[2], Ayu Hutami Syarif[3]
[1] BaliMed Buleleng Hospital, Buleleng, Indonesia.
[2] Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3] Medical University Graz, Graz, Austria.

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) happened due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. It is the third coronavirus causing a pandemic. Cases of COVID-19 have increased rapidly. Epidemiological studies show droplets as a medium of transmission of this virus. The high rate of transmission and the death rate create urgency on the management of COVID-19. Unfortunately, until now there is no definitive therapy for the SARS-CoV-2 virus. Several potential therapies, including antivirals, immunomodulatory agents, convalescent plasma transfusions, and supportive therapies such as vitamin D supplementation, have been applied in the management of COVID-19. As a hormone, vitamin D has an immunomodulatory effect used in supportive therapy for various immune-related diseases and respiratory system infections. The immunomodulatory effects of vitamin D are strengthening the physical barrier (cell junction), the specific immune system (adaptive immunity), and the non-specific immune system (innate immunity). Vitamin D is known to suppress pro-inflammatory cytokines and increase the production of anti-inflammatory cytokines. In addition, vitamin D also performs as a substantial part in the induction of ACE2 receptors which gives a weighty influence on pathogenesis of COVID-19. Vitamin D deficiency can amplify the risk of infections including COVID-19. Presently, clinical trials of vitamin D supplementation and COVID-19 are limited. This literature review further examined the role of vitamin D supplementation in COVID-19.

INTRODUCTION

The first Coronavirus Disease 2019 (COVID-19) infection was found in December 2019, when the Wuhan Health Committee reported a pneumonia-like case of unknown etiology. World Health Organization (WHO) named the virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] It is the third coronavirus that causes a pandemic after SARS-CoV in 2002 and MERS-CoV in 2012.[2] Within a month, cases of COVID-19 increased rapidly. On 30 January 2020, 7,734 cases have been confirmed in China and another 90 cases have been reported by several countries in Asia to Europe with a case fatality rate (CFR) of 2.2% (170/7,824).[3] Until 16 February, 2021, WHO reported 108,246,992 confirmed cases worldwide with a death rate of 2,726,974 people, while in Indonesia there were 1,223,930 confirmed cases with a CFR of 2.7%.[4]

SARS-CoV-2 is transmitted to new host through the respiratory system. Epidemiological studies show that droplets expelled during speaking, coughing, or sneezing are the most common form in the transmission. COVID-19 can manifest in variegated degrees of disease severity, from asymptomatic to severe or critical. The worsening of the condition can occur suddenly, it is due to the presence of a cytokine storm which in turn triggers acute respiratory distress syndrome (ARDS) and multi-organ failure.[1] High transmission rate and mortality rate create urgency on the management of COVID-19. Unfortunately, until now there is no definitive therapy for the SARS-CoV-2 virus.

*Corresponding author: gracia.dtanaya@gmail.com

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Several potential therapies, including antiviral, immunomodulatory agents, convalescent plasma transfusions, and supportive therapies such as vitamin D supplementation, have been applied on COVID-19 management.[1] Vitamin D is a hormone that has an immunomodulatory effect and has been used in supportive therapy for various immune-related diseases and infections on the respiratory system. Clinical study about vitamin D supplementation and COVID-19 is still limited, thus their effectiveness has not been determined and their clinical use is controversial. This literature review discussed more about the correlation between vitamin D and COVID-19

Vitamin D Metabolism

There are two forms of vitamin D in the body, endogenous vitamin D (vitamin D3) and exogenous vitamin D (vitamin D2). Vitamin D3 obtained through sunlight exposure on the skin and vitamin D2 obtained from food and supplements require an activation process through enzymatic hydroxylation mechanisms in the liver and kidneys (Figure 1).[5]

Ultra Violet B (UVB) light (wavelength of 290-315 nm) which hits the skin will convert the sterol form of vitamin D precursors inside the subcutaneous tissue (7-dehydrocholesterol) to pro-vitamin D3.[5] In the liver, 25-hydroxycholecalciferol (25(OH)D) is synthesized, as a result of vitamin D hydroxylation by 25-hydroxylase and CYP2R1 and CYP27A1 (the cytochrome P450 enzymes family). Then, calcidiol will be converted into 1,25 dihydroxycholecalciferol by kidneys using CYP27B1 (1,25(OH)2D3)-the active form of vitamin D3 (a hormone).[6]

Although 1,25(OH)2D3 is the most biologically active metabolite of vitamin D, biomarker used to assess body deficiency status of vitamin D3 is calcidiol. This is due to the fact that it is circulated at a pg (picogram) concentration thousand times lesser than its previous metabolite and because it is regulated and stimulated by way of parathyroid hormone (PTH) and low calcium and phosphorus serum concentrations. However, it interferes with FGF-23(fibroblast growth factor) produced by osteocytes. It will be tough to assess the true concentration in patients with vitamin D deficiency.[6,7] According to Taha, *et al*., the normal levels are around 21–29 ng/mL (52.5–72.5 nmol/L).[6]

Immunomodulatory Effect of Vitamin D

Immunomodulatory effects of vitamin D are strengthening the physical barrier (cell junction), the specific immune system (adaptive immunity), and also the non-specific immune system (innate immunity). Physical barriers are strengthened by maintaining the integrity of tight, gap, and adherent junctions in body cells, hence it can be protected from infectious agents.[6]

Earliest defense system of the human body which is opposed to some infectious agents is called innate immune system. This immune system perceives microorganisms through the pathogen recognition receptor (PRR) which will activate a cascade ended with the destruction of infectious agent. When an infectious agent invades, Toll-like receptors (TLRs), part of the PRR, are activated and stimulate TLR-expressing cells releasing cytokines and antimicrobial peptides (AMPs). Stimulation of TLR 2/1 in macrophage or TLR 2 in keratinocytes will increase CYP27B1 and VDR activity which also increases 25(OH)D and 1,25(OH)2D. This adequate concentration of vitamin D will induce AMPs (cathelicidin, LL-37; 1,25-dihydroxyvitamin D14-15, and defensin16).[6,7] Antimicrobial peptides act by perforating cell membranes and neutralizing the biologic activity of pathogens endotoxins.[7] The TLR–CYP27B1–VDR–cathelicidin mechanism could explain how 1,25(OH)2D can inhibits *M. tuberculosis* bacteria in vitro and how atopic dermatitis patients with microbial infection show clinical improvement with vitamin D supplementation.[6] LL-37 has been proven to decrease influenza A virus replication in an experimental study on mice.[7]

Adaptive immune system is the second defense system of the body against infectious agents which mediate antigen-specific immune responses by using antigen presentation cells (APCs), such as dendritic cells (DCs) and T and B lymphocytes. T lymphocytes (T cells) are made up of several subgroups, such as: CD4 helper T-cells (Th cells), CD4 regulatory T-cells (Treg), CD8 cytotoxic T-cells, natural killer (NK) cells, and memory cells. Vitamin D is implicated directly on lymphocyte cells through VDR and indirectly on APC through paracrine signaling.[6] Vitamin D will inhibit the DCs

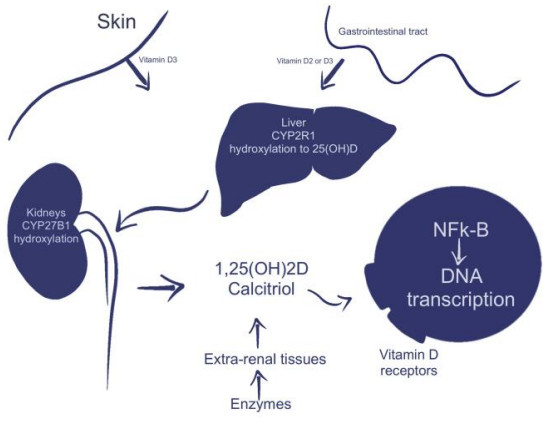

Figure 1. Vitamin D metabolism[3]

maturation process and reducing their ability as antigen-presenting cells and changing the profile of T helper cells (Th1, Th2 , Th9, Th17) and Treg cells. Vitamin D will inhibit Th1, hence it will suppress the releasing of pro-inflammatory cytokines, such as IL-2, granulocyte macrophage colony-stimulating factor (GMCSF), TNF-alpha, INF-beta, and INF-gamma. Alternately, vitamin D will increase production of anti-inflammatory cytokines (IL-4, IL-5, and IL-10) by Th2 and Tregs which will suppress the development of Th1, Th17, and Th9 cells and to prevent the inflammatory process.[6-9] Cells from active lupus patients show that vitamin D could inhibit the maturation of DCs cells stimulated by LPS or LTA (leipoteichoic acid). Meanwhile, in patients with autoimmune diabetes mellitus (T1DM), vitamin D via monocytes can suppress the production of proinflammatory cytokines (TNF-alpha, IL-1).[9]

Vitamin D could also inhibit the proliferation of memory cells and plasma cells and increasing B cell apoptosis which will suppress immunoglobulin production. This effect is very significant in autoimmune diseases.[6] For example, B cells derived from active lupus patients can be significantly reduced after pre incubation with vitamin D.[8] Immunomodulatory effect of vitamin D is shown in Figure 2.

Vitamin D and Renin-Angiotensin-System (RAS)

Renin-Angiotensin-System (RAS) performs a substantial part in regulating resistance of vascular and homeostasis of extravascular fluid. Synthesis and secretion of Renin by kidneys is triggered by the decrease of body fluid volume, salt concentration, and perfusion pressure. Renin produced by kidneys will convert angiotensinogen secreted by the liver into Angiotensin I. Furthermore, by Angiotensin-Converting-Enzyme (ACE), Angiotensin I will be converted into Angiotensin II (an active form). Angiotensin II will bind to Angiotensin Receptor 1 or 2 (AT1R or AT2R). Angiotensin II which binds to AT1R causes a pro-inflammatory, pro-oxidative effects, release of catecholamines, and constriction of vascular. Renin will be inhibited by the high concentrations of this active form of Angiotensin. In contrast, renin secretion is triggered by low concentrations of Angiotensin II, ACE Inhibitor or Angiotensin Receptor Blocker (ARB).[6,10] As an ACE homolog enzyme, ACE2 raises the possibility of other alternative pathways of RAS (Figure 3). ACE1 does not inhibit ACE2 activity, although ACE1 and ARB can increase ACE2 secretion.[11] Expression of ACE2 gene is found in macrophages of endothelial cells, smooth muscle cells, in the lungs, in cardiovascular system including blood vessels, cardiomyocytes and cardiac fibroblasts, renal cortex and medulla, and some tissues in the digestive tract and testes.[6,11]

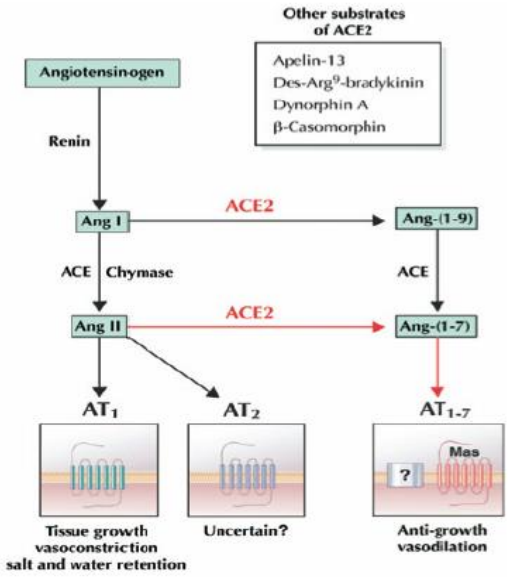

Figure 3. ACE2 and RAS[12]

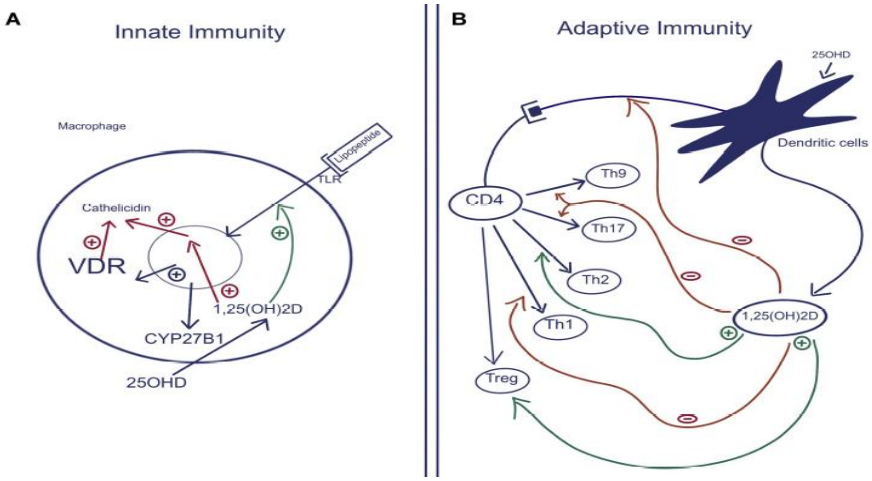

Figure 2. Role of vitamin D in the regulation of the innate and adaptive immune pathways[6]

Angiotensin I will be converted to Angiotensin 1–9 through AT2R by ACE2 which will create a cardioprotective effect. On the other hand, by ACE2, Angiotensin II will converted to Angiotensin 1–7 through Mas Oncogene.[6,10,11] This transformation will decrease the availability of Angiotensin I and II for other axis (ACE-Angiotensin II-AT1 axis). This will balance the pathological effects of RAS overstimulation such as inflammation, vasoconstriction, hypertrophy, and fibrosis. ACE2 will reduce the activation of proinflammatory by RAS through strengthening the ACE2-Angiotensin 1-7-Mas Oncogen axis.[6]

As shown on Figure 4, the concentration of vitamin D plasma is related to the activity of RAS. A low concentration of vitamin D-induced increases RAS activity and Angiotensin II concentration. Studies proved that through an independent pathway, adequate plasma vitamin D concentrations can suppress the gene promoter of renin which has an impact on decreasing RAS activity.[13,14] It means that adequate vitamin D level induces the decrease of renin secretion. This process is not depending on Angiostensin II like the classic pathway.[6] Other studies suggested that vitamin D can increase ACE2 expression and can inhibit the activation of NFκB, a transcription factor that performs a substantial part in regulating immune response in infection.[15]

Immunopathogenesis of COVID-19

Eijk, *et al*. summarized the pathophysiology of COVID-19 in 5 mechanisms, such as: (1) SARS-CoV-2 directs cytopathic effect; (2) down-regulation of ACE2 results in RAAS imbalance and the decreasing of des-Arg9-bradykinin inactivation; (3) cytokine storm caused by immune system dysregulation; (4) coagulopathy; and (5) autoimmunity (Figure 5).[16] SARS-CoV-2 which enters the host cells throughout receptor-mediated endocytosis is facilitated by interactions between proteins Spike (S) with ACE2 receptor and serine protease-TMPRSS2 (Transmembrane Protease Serine 2). TMPRSS2 helps the priming process of S which will produce 2 main subunits namely S1 and S2. It is known that Furin and Neuropilin-1 (NRP1) can also help S priming process. S1 and S2 are involved in viral attachment and entry.[12] Release of viruses from endosomes into host cells is dependent on cathepsin L (CTSL). TMPRSS2 is also able to facilitate direct fusion of SARS-CoV-2 with host cells. The binding between SARS-CoV-2 and ACE2 receptor triggers both innate and adaptive immune system activation.[16]

Myeloid cells (monocytes, macrophages, dendritic cells, and granulocytes), innate lymphoid, and IFNβ perform a substantial part in innate immune response.[17] Alveolar macrophages are placed as the first line against SARS-CoV-2 in the lungs. Macrophages detect pathogen-associated molecular patterns (PAMPs) via PRRs, it will then activate intracellular signaling cascade which involves the transcription factors activation like NF-B and interferon regulatory factors (IRFs). It will trigger the release of pro-inflammatory cytokines and IFNs (type I interferon).[16]

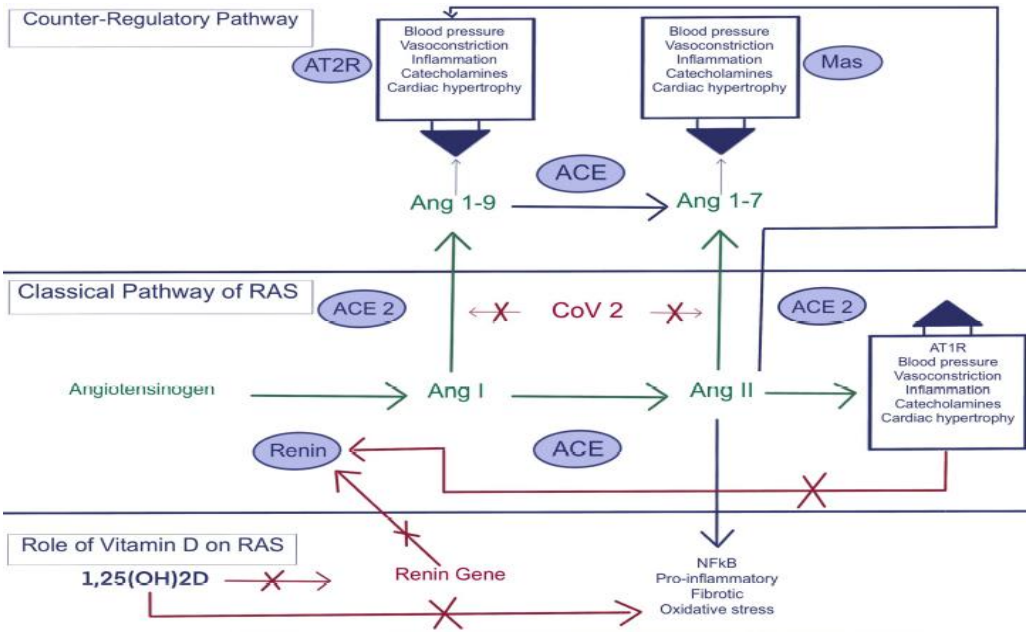

Figure 4. Vitamin D and RAS[3]

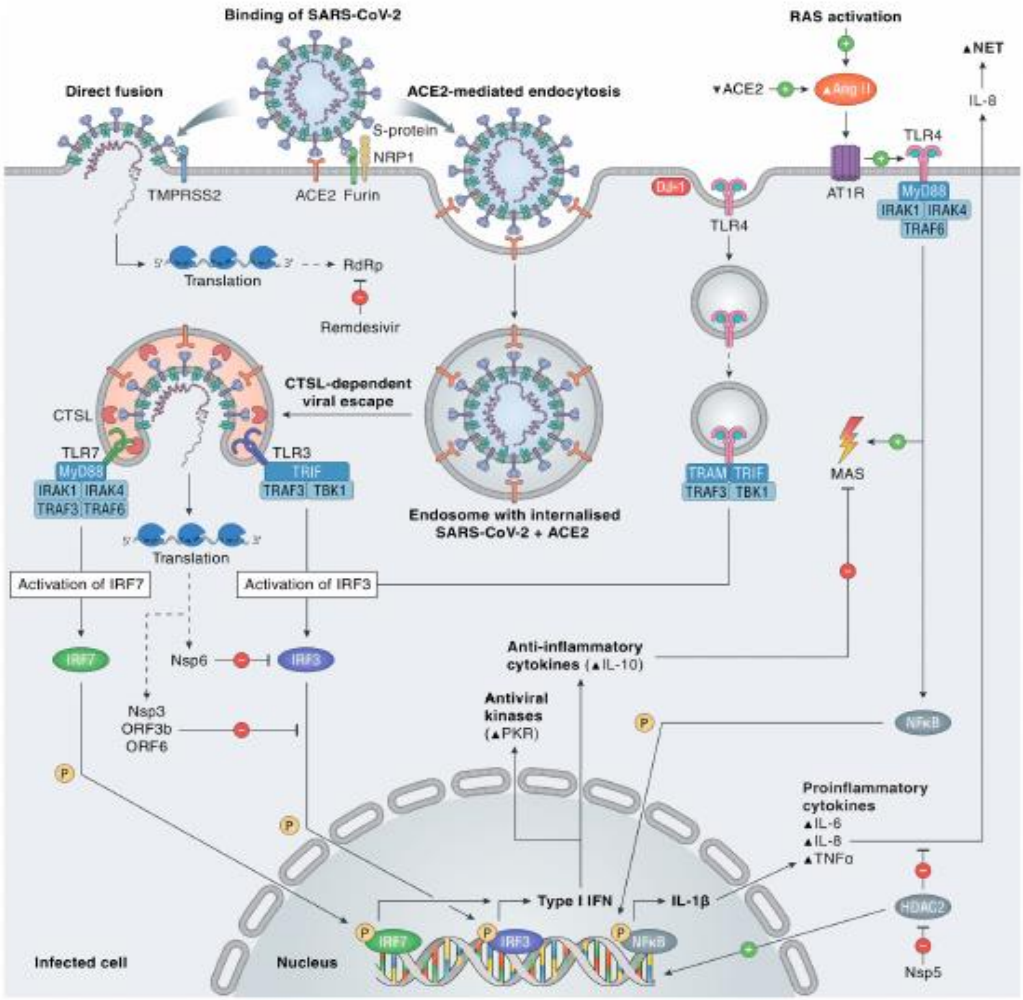

Figure 5. SARS-CoV-2 entry and immune activation

A good IFN response will induce an adequate immune system, hence it can limit viral replication and induce apoptosis. Nevertheless, several SARS-CoV-2 proteins (6 (ORF6) and ORF3b) were proven to suppress IFN-I.[18] Delayed IFN-I response at the onset of infection followed by uncontrolled viral replication promotes increased production of IFN-I which will worsen hyperinflammatory process.[16] Another study showed that ACE2 receptor is also expressed on macrophages, thus SARS-CoV-2 can attack macrophages directly, inhibit IFN I production, cause hyperinflammation, and inhibit virus eradication.[19] In COVID-19, there is excessive activation of the complement system which results in hyperinflammation, dysfunction of endothelial cell, and immunothrombosis (coagulation happened in intravascular). Immunothrombosis causes systemic coagulopathy. Activation of the extrinsic coagulation pathway caused by recognition of PAMPs and damage-associated molecular patterns (DAMPs) through PRR also plays a role in immunothrombosis. In addition, the dysregulation of neutrophil extracellular traps (NETs) formed by activated neutrophils responsible for killing pathogens also exhibits a strong procoagulation effect.[16]

When the virus enters the cell, the adaptive immune system will present the SARS-CoV- antigen via antigen presenting cells (APC) to the lymphoid system, such as epithelial cells, macrophages, and/or dendritic cells. After the recognition of viral antigens, CD4+ and CD8+ T cells will be formed as a result of differentiation of T lymphocytes which are responsible on the production of cytokines, activation of B lymphocytes to produce antigen-specific antibodies, namely IgA and IgG, and the process of lysis of cells which have been infected with viruses.[16,20] IgA antibodies on the mucosal surface are the first line of defense, while IgG provide systemic protection against specific pathogens.[21] The presentation of the SARS-CoV-2 antigen will trigger the differentiation of CD4+ cells into Th I which secretes granulocyte macrophage colony stimulating factor (GM-CSF), then induces CD14+ monocytes, CD16+ with high concentrations of IL-6, and increases the inflammatory

process.[22] Aside from Th1, activation of Th17 also releases IL-17 and other pro inflammatory cytokines such as IL-1β and IL-6 by triggering monocytes, macrophages, and neutrophils to the site of infection.[23] Other pro inflammatory cytokines which contribute to cytokine storms including TNF-, IP-10, MCP- and CSF. Meanwhile, IL-15, IFN-α, IL-12, IL-21, and IFN-γ are cytokines which play a role in viral clearance.[16] T regulatory (Treg) performs a major role in maintaining the equilibrium of the immune system. The study by Qin, *et al*. showed reduced levels of Tregs in peripheral blood test of patients with severe COVID-19.[24] T helper cells and the stimulation on cytokine will trigger B cell activation and differentiation to produce antibodies which contribute to innate immunity. Severe cases of COVID-19 are characterized by certain immune cell dysfunction, elevated monocytes and neutrophils, and de-escalated of the effector T lymphocytes levels. Other pathophysiological processes include increased thrombogenic state (microangiopathy, NETs formation), hemophagocytosis, decreased hematopoiesis, and increased apoptosis/pyroptosis.[16] Immune response to SARS-CoV-2 infection is briefly described in Figure 6.

Clinical Study about the Effect of Vitamin D on COVID-19

Many studies have described the immunomodulatory role of vitamin D, but studies on the effect of vitamin D on SARS-CoV-2 infection and the factors that influenced it are still very limited. A cross-sectional study conducted by Marzon, *et al*. using 7,807 samples, who had been tested for plasma 25(OH)D levels and COVID-19 infection, showed that 10.02% were confirmed as COVID-19 and 89.98% were not. COVID-19 population was reported to have a significant lower serum vitamin D levels of 19.00 ng/mL with 95% CI (18.41-19.59). Meanwhile, the serum vitamin D level in the non COVID-19 population was 20.55 ng/mL with 95% CI (20.32-20.78). They also found a correlation between low calcidiol levels and an increased risk of COVID-19 infection and hospitalization for COVID-19 through univariate analysis (COVID-19 infection: rough OR 1.58 (95% CI: 1.24-2.01, $p < 0.001$; hospitalization: crude OR 2.09 (95% CI: 1.01-4.30, $p < 0.05$)). This study also found positive association between male (aged over 50 years old) with low to middle socio-economic status

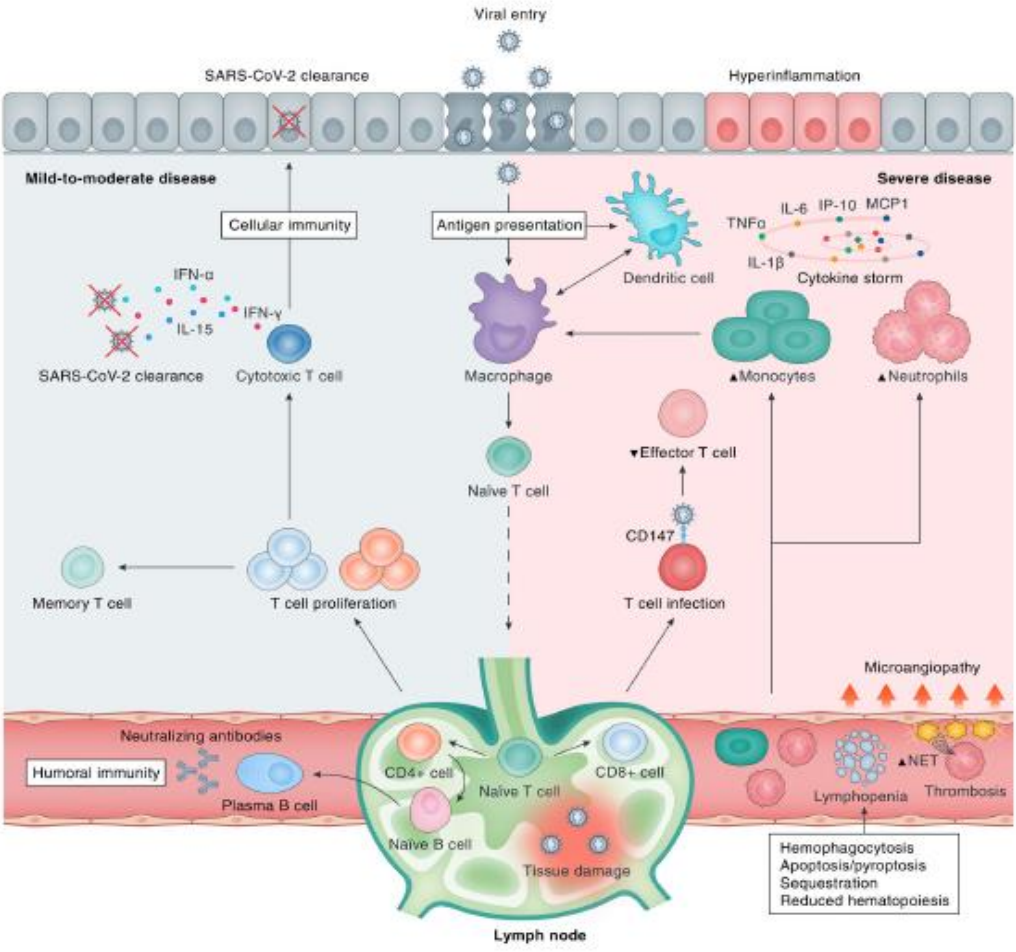

Figure 6. Immunological response to SARS-CoV-2 infection

with the risk of COVID-19 infection and hospitalization caused by COVID-19. They concluded low calcidiol plasma level as an independent risk factor for COVID-19 infection and hospitalization.[25]

Correspondent results were obtained in the study conducted by Rastogi, *et al*. with a randomized, placebo controlled study designed to determine the relationship between high dose oral vitamin D supplementation in asymptomatic or mild COVID-19 samples with vitamin D deficiency to the proportion of patients who became SARS-CoV-2 negative before day 21 and inflammatory markers. Randomly, 60,000 IU of cholecalciferol were given for a week for 2 groups of patients, the intervention group with total samples of 16 persons and control group with total samples of 24 persons with 25(OH)D plasma level target > 50 ng/ ml. The level of 25(OH)D was checked again after the 7th day. Supplementation would be continued if the 25(OH)D level of the participant was less than the target which had been set. Variables measured periodically on this study was SARS-CoV-2 RNA and some inflammatory markers. The results showed that on day 7th, serum 25(OH)D level on 10 participants of intervention group was elevated and followed by 2 more participants on day 14th ($p < 0.001$). After the supplementation, 62.5% samples observed on intervention group and 20.8% samples observed on control group tested negative for COVID-19 ($p < 0.018$). They also found that 1 out of 4 inflammatory markers observed, fibrinogen, was significantly decreased with high dose supplementation of cholecalciferol ($p = 0.007$).[26]

A study about the effects of vitamin D dietary supplementation by Castillo, *et al*. with a randomized parallel pilot, open label design, double masked clinical trial using 50 participants with COVID-19 positive patients who were radiologically confirmed had an acute respiratory infection, was conducted to assess the effect of calcifediol which observed through death rate or ICU admission rate. The patients were randomly grouped in admission day, according to the ratio of 2 persons take calcifediol supplementation (0.532 mg) and 1 person without the supplementation. On day 3rd and 7th, samples on intervention group continued taking calcifediolon orally but only half dose from the initial dose, then followed by weekly supplementation until the participants went home or moved to intensive care unit (ICU). They found that constant calcifediolon dietary supplemmentation could decrease ICU demand on COVID-19 patients ($p < 0.001$). There were no patients who died in the intervention group.[27]

Another study with a multicentre-double blind-parallel group-randomized-placebo controlled trial by Murai, *et al*. aimed at investigating the implication of single high dose vitamin D3 dietary supplementation (200,000 IU) on 240 moderate-severe COVID-19 patients observed through the length of stay (LOS) in hospital. This study randomly gave oral single high dose of vitamin D3 to the intervention group or placebo group ($n = 120$ on each group). Secondary outcomes were also observed, including mortality rate, ICU admission rate, usage of mechanical ventilation including its duration, and the concentration of calcidiol, C-reactive protein, total calcium, and creatinine. Contrast to the previous study, this study concluded that there was no significant relationship between the two variables studied except for serum 25-hydroxyvitamin D levels with $p < 0.001$.[28]

The same conclusion was obtained in a retrospective cohort study by Ali, *et al*., using sample of 1,000,000 populations in European countries, which found a negative denotative correlation for vitamin D concentration and COVID-19 cases ($p = 0.033$). On the other hand, they found insignificant correlation ($p = 0.123$) of vitamin D and mortality rate on COVID-19. This study concluded that the inconclusive results were due to the varying results of retrospective studies observed. Some studies observed on this study shown no correlation between two variable observed when confounding variables were adjusted, but some other studies showed a denotative positive correlation. This study also concluded that vitamin D supplementation was safe and effective against acute respiratory infections.[29]

Meanwhile, Raisi-Estabragh, *et al*. conducted a prospective cohort-multivariate logistic regression study of 1,326 COVID-19 positive samples observing some factors which influence ill severity on COVID-19 patients. The study looked at the correlation of age, sex, ethnicity and (1) cardiometabolic factors, (2) 25(OH)-vitamin D, (3) dietary patterns, (4) Townsend deprivation scores, (5) living conditions, and (6) behavioral factors (social abilities) in COVID-19 patients. This study concluded that there was no conclusive conclusion between the two groups of variables studied. More comprehensive research is needed, considering that ethnicity, socio-economic conditions, and behavior are very complex.[30]

SUMMARY

Literature data about the effect of vitamin D supplementation in COVID-19 are still inconclusive. Immunopathogenesis of COVID-19 involves a complicated interaction between the virus (SARS-CoV-2) and the immune system. It is known that vitamin D has several beneficial immunomodulatory effects, such as: (1) strengthening innate immune response through TLR–CYP27B1–VDR–cathelicidin (AMPs) axis, (2) strengthening the adaptive immune response by implicating directly on lymphocyte cells through VDR

and indirectly on APC through paracrine signaling which will suppressed some pro-inflammatory cytokines and increasing the secretion of some anti-inflammatory cytokines, which may reduce the severity of the cytokine storm happened in patients, and (3) it can also counter the effects of COVID-19 infection resulting in down regulation of ACE2 (RAAS imbalances) which leads to inflammation, vasoconstriction, hypertrophy, and fibrosis. Further clinical studies are needed to adjudge the best dose for vitamin D supplementation

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Conflict of Interest
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Authors's Contribution
Conceived the study: GDT, WMT. Wrote the manuscript: GDT. Revised and proofread: GDT, WMT, AHS. All authors have approved the final version.

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