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The role of vitamin D and cardiovascular risk in COVID-19 patients

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REVIEW

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The role of vitamin D and cardiovascular risk in COVID-19 patients

El papel de la vitamina D y el riesgo cardiovascular en pacientes con COVID-19

Ivana Purnama Dewi,*‡§ Louisa Fadjri Kusuma Wardhani,*§ Kristin Purnama Dewi,*¶ Iswanto,‖ Andrianto*§

Keywords:
Vitamin D deficiency, vitamin D and COVID-19, cardiovascular disease.

Palabras clave:
Deficiencia de vitamina D, vitamina D y COVID-19, enfermedad cardiovascular.

ABSTRACT

Vitamin D deficiency has long been associated with the incidence of cardiovascular disease. It also thought to play a role in the severity of COVID-19 patients. A serum concentration of 25(OH) D < 50 nmol/L (vitamin D deficiency) is found in patient with severe COVID-19 manifestation requiring intensive care. These patients are thought to stem from an uncontrolled complex immune response. The role of vitamin D in the COVID-19 infection reaction is by supporting antimicrobial peptides response in the respiratory epithelium and reducing inflammatory reactions to SARS-CoV-2 infection. Therefore, it can reduce the severity of COVID-19 infection. Vitamin D has also involved in several cardiovascular diseases that could increase the severity of COVID-19 infection; i.e., hypertension, lipid metabolism, atherosclerosis, and heart failure. Vitamin D affects endothelial cell function, thus regulating vasodilatation of dependent endothelial cells. It can prevent atherosclerosis and vascular calcification, which COVID-19 patients are at an increased risk. It also reduces pro-inflammatory cytokines, which has an anti-remodelling effect to reducing the fatality risk of obesity and heart failure among COVID-19 patients. Understanding the importance of avoiding vitamin D deficiency, the fulfilment of daily intake should be taken into account. The recommended daily dose of vitamin D is 200 IU per day for those aged < 50 years, 400 IU per day for those aged 50-70 years and 600 IU for individuals aged > 70 years. It is estimated that for every 100 IU of vitamin D, the 25(OH)D level increases by 2.5 nmol/L.

RESUMEN

La deficiencia de vitamina D se ha asociado durante mucho tiempo con la incidencia de enfermedades cardiovasculares. También se cree que juega un papel en la gravedad de los pacientes con COVID-19. Se encuentra una concentración sérica de 25(OH)D < 50 nmol/L (deficiencia de vitamina D) en pacientes con manifestaciones graves de COVID-19 que requieren cuidados intensivos. Se cree que estos pacientes provienen de una respuesta inmune compleja no controlada. El papel de la vitamina D en la reacción de infección por COVID-19 es el apoyo a la respuesta de los péptidos antimicrobianos en el epitelio respiratorio y la reducción de las reacciones inflamatorias a la infección por SARS-CoV-2. Por lo tanto, puede reducir la gravedad de la infección por COVID-19. La vitamina D también se ha involucrado en varias enfermedades cardiovasculares que podrían aumentar la gravedad de la infección por COVID-19; es decir, hipertensión, metabolismo de lípidos, aterosclerosis e insuficiencia cardíaca. La vitamina D afecta la función de las células endoteliales, regulando así la vasodilatación de las células endoteliales dependientes. Puede prevenir la aterosclerosis y la calcificación vascular, a lo que los pacientes con COVID-19 tienen un mayor riesgo. También reduce las citocinas proinflamatorias, que tiene un efecto anti-remodelador para reducir el riesgo de muerte por obesidad e insuficiencia cardíaca entre los pacientes con COVID-19. Entendiendo la importancia de evitar la deficiencia de vitamina D, se debe tener en cuenta el cumplimiento de la ingesta diaria. La dosis diaria recomendada de vitamina D es de 200 UI al día para los menores de 50 años, 400 UI al día para los de 50 a 70 años y 600 UI para los mayores de 70 años. Se estima que por cada 100 UI de vitamina D, el nivel de 25(OH)D aumenta en 2.5 nmol/L.

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INTRODUCTION

Cardiovascular disease is the most common cause of death and morbidity in many countries. Evidence suggests a possible link between vitamin D deficiency and cardiovascular disease (CVD), including hypertension, coronary heart disease (CAD), heart failure (HF), peripheral vascular disease (PAD), diabetes mellitus (DM), and

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metabolic syndrome.[1,2] Vitamin D deficiency is associated with the prevalence and incidence of cardiovascular disease.[3] Vitamin D acts as a bone bioregulator and mineral metabolism in the cardiovascular system. Vitamin D supplementation is beneficial for calcium-phosphorus metabolism and affects myocardial contractility.

Vitamin D deficiency causes secondary hyperparathyroidism. Both primary and secondary hyperparathyroidism is associated with cardiovascular disorders. Secondary hyperparathyroidism further leads to increased insulin resistance and pancreatic β cell dysfunction, a predisposing factor for metabolic syndrome and DM. Secondary hyperparathyroidism also activates the renin-angiotensin-aldosterone system (RAAS), increases blood pressure (BP), and causes left ventricular (LV) hypertrophy, which in turn causes apoptosis and fibrosis of the heart cells. Systemic and vascular inflammation, as well as an increased risk of atherogenesis, may also occur.[4,5]

Coronavirus disease 2019 (COVID-19) is an infectious disease of the respiratory system caused by the coronavirus SARS-CoV-2. Although the primary clinical symptoms are respiratory-related, many studies show a high prevalence of cardiovascular comorbidities in COVID-19 patients.[6] Vitamin D is thought to play a role in the severity of COVID-19 patients. Studies show that vitamin D deficiency (serum concentration 25(OH) D.[7] In this literature review, the discussion focuses on recent evidence, potential mechanisms, and the possible role of cardiovascular vitamin D supplementation, especially in COVID-19 patients.

VITAMIN D METABOLISM

Vitamin D is one of the four fat-soluble vitamins required by the body. Vitamin D is a potent steroid vitamin made in the body from cholesterol through a process triggered by ultraviolet light (UVB) or sunlight. Whether made in the body or obtained from food, Vitamin D is the result of hydroxylation in the liver to the dominant form in the circulation, calcidiol or 25(OH)D. Calcidiol is then converted by rehydroxylation in the kidneys and tissues to calcitriol or 1,25-dihydroxyvitamin D ($12.5(OH)_2D$). Calcitriol, with a half-life of 15 hours, is the main active form of vitamin D.

Vitamin D deficiency (serum 25(OH)D 2D), binds to the vitamin D receptor (VDR). VDR is particularly prevalent in endothelium, vascular smooth muscle, enterocytes, and osteoblasts.[8,9] In the cardiovascular system, VDR is found in the myocardium and endothelial cells.[10] *In vitro*, vitamin D inhibits the proliferation and hypertrophy of cardiomyocytes.[11]

VITAMIN D PATHOPHYSIOLOGY AND CARDIOVASCULAR DISEASE IN COVID-19

The pathophysiology underlying the clinical manifestations of COVID-19 infection is thought to stem from an uncontrolled complex immune response. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE 2) receptor, which is expressed in the lungs, intestinal system, kidneys, and blood vessels. When SARS-CoV-2 binds to the ACE 2 receptor, there is a downregulation of ACE 2 activity and expression resulting in a disruption of the balance between ACE/ACE 2, which causes increased activity of angiotensin II (Ang II) and increased production of pro-inflammatory cytokines.[12]

Cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL) 1β, IL-8, and IL-12 play important roles in the disease pathogenic cascade. The most important mediator of this cytokine storm is IL-6. IL-6 can be produced by immune system cells (B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells), stromal cells, and many non-lymphocyte cells, including fibroblasts and endothelial cells. IL-1β and TNF-α are key activators for IL-6 secretion.[7]

The role of vitamin D in the COVID-19 infection reaction is to support the production of antimicrobial peptides in the respiratory epithelium so that viral infections and the development of signs and symptoms of COVID-19 are lighter. In addition, vitamin D can also help reduce inflammatory reactions to SARS-CoV-2 infection. Changes in the regulation of the response to these inflammatory reactions, particularly RAAS, are characteristic of COVID-19, and excessive activation levels

are associated with a poor prognosis. Previous research identified an association between higher ACE 2 levels and increased COVID-19 morbidity outcomes.[13]

Several studies have demonstrated increased plasma renin activity, Ang II concentrations, and higher RAAS activity due to low vitamin D status. The same is true for renin activity which decreases with increasing vitamin D levels. There is an inverse relationship between circulating 25(OH)D and renin. Vitamin D is a negative regulator of renin expression and reduces renin expression by repressing the renin gene promoter's transcription activity. $1,25(OH)_2D$ induced repression of renin gene expression is independent of Ang II feedback regulation. A permanent increase in renin levels with an increase in angiotensin I (Ang I) formation, indicating that in vitamin D deficiency, renin expression and secretion are increased in the early stages. This will increase fluid and salt intake and cause an increasing in BP. *Figure 1* provides a brief overview of vitamin D's impact on RAAS in COVID-19.[14]

Patients with chronic disease have a higher risk of death from respiratory infections. On the other hand, vitamin D deficiency is associated with an increased risk of various diseases, including CVD. Since preliminary studies on the relationship between hypovitaminosis D and COVID-19, vitamin D has been recognized as a potentially useful therapy for SARS-CoV-2 infection based on its anti-inflammatory and antithrombotic properties.[15] Vitamin D, as an anti-inflammatory, can modulate nitric oxide (NO) production and inhibit endothelial protein expression for leukocyte adhesion. Meanwhile, as an antithrombotic, vitamin D plays a role in the downregulation of pro-thrombotic plasminogen activator inhibitor-1 (PAI-1) and thrombospondin-1 mRNA expression, as well as plays a role in the upregulation of thrombomodulin.[15]

Vitamin D and hypertension in COVID-19

The renin-angiotensin-aldosterone system plays a crucial role in the pathogenesis of

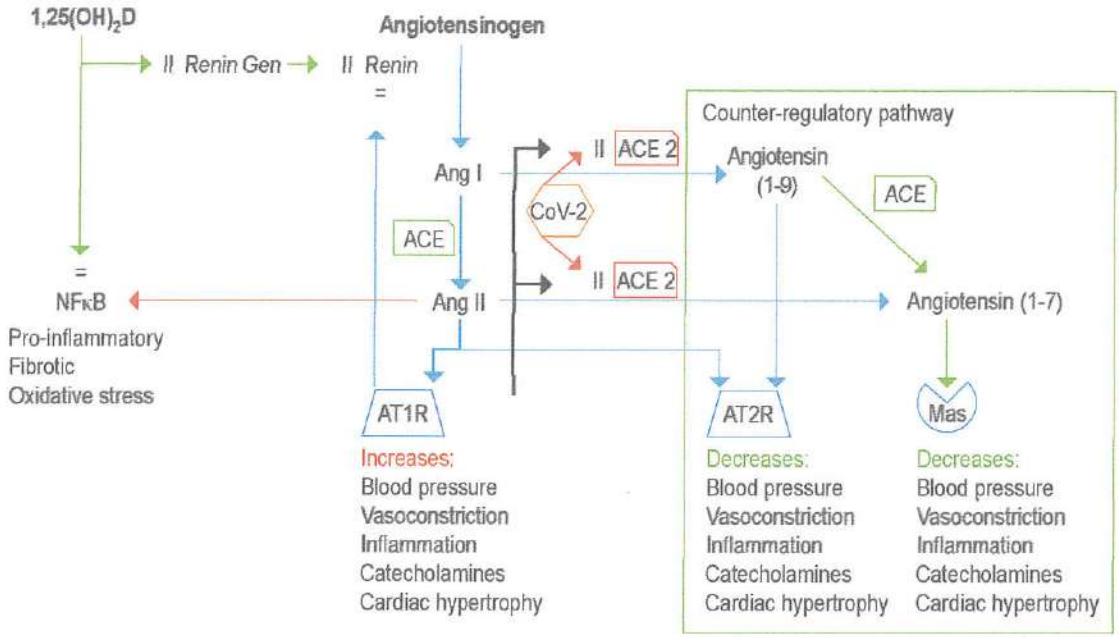

Figure 1: An imbalance system of RAAS regulation will increase Ang II formation, renin synthesis, and inflammatory response. This is important in low vitamin D levels because vitamin D ($1,25(OH)_2D$) can combat this imbalance through a negative expression of the renin gene resulting in lower renin synthesis, independent of Ang II. If this counter-regulation is disrupted by ACE 2 dysfunction due to SARS-CoV-2 infection, the classic pathway becomes uncontrolled and increases the pro-inflammatory reaction and BP contributing to cardiovascular problems and acute respiratory distress syndrome (ARDS).[14]

the cardiovascular disease. Vitamin D plays RAAS regulation, and vitamin D deficiency predisposes to RAAS upregulation and smooth muscle cell hypertrophy and LV. Left ventricular hypertrophy is a known risk factor or marker for CVD. $1,25(OH)_2D$ inhibits RAAS and can reduce BP. One study showed that UVB radiation from sunbathing three times a week for three months caused an almost 200% increase in 25(OH)D levels and a 6 mmHg decrease in BP in both systolic and diastolic BP. Vitamin D also affects endothelial cell function, regulating vasodilation of dependent endothelial cells.[9,16,17] The risk factors for clinical severity of COVID-19 patients predicted based on C-reactive protein (CRP) levels with low vitamin D levels (75 nmol).[14]

Vitamin D and lipid/obesity metabolism in COVID-19

The enzyme, 3-hydro-3-methylglutaryl coenzyme A (HMG-CoA) reductase, plays a key role in regulating cholesterol synthesis. Defay et al. found that the hydroxylation of vitamin D inhibited HMG-CoA reductase activity in lymphocyte stimulation with phytohemagglutinin. Experimental studies on multiple cells have shown that therapy with cholecalciferol (vitamin D3) and its metabolites, 25(OH)D, $1,25(OH)_2D$, and 24,25-dihydroxycholecalciferol inhibits cholesterol synthesis due to inhibition of HMG-CoA reductase activity. Vitamin D deficiency can result in an abnormal lipid profile with increased peripheral insulin resistance and contributes to metabolic syndrome. Serum levels of $1,25(OH)_2D$ were inversely correlated with very-low-density lipoprotein (VLDL) and triglycerides. Studies show that statin therapy can increase vitamin D levels, which is a nonlipid pleiotropic effect of statins.

Obesity is a risk factor for the clinical severity of COVID-19 infection. In a cohort study of 383 COVID-19 patients, patients with a BMI > 28 kg/m² had a 142% risk of developing clinically severe pneumonia than patients with a normal BMI.[14] In the adipose tissue biopsy of obese patients, there is an increase in the number of macrophages contributing to the increase in cytokines such as IL-6, TNF-α, and IL-1β. This increase in inflammation is associated with increased mortality.[18] Vitamin D is active in adipocyte cells and interacts with membrane phosphatase receptors and coregulatory nuclear proteins, participating in gene expression and cell signaling. Based on *in vivo* studies, vitamin D reduced levels of pro-inflammatory cytokines and chemokines in lipopolysaccharide-injected mice and obesity model mice. Vitamin D's anti-inflammatory effect is mediated by inhibition of the NFκB and MAPK signaling pathways and decreased expression of the toll-like receptor (TLR).[19]

Vitamin D and coronary artery disease in COVID-19

Vitamin D can be linked to CAD through its effects on BP, glycemic and parathyroid (PTH) control. In COVID-19 infection, elevated PTH levels increase intensive care risk compared to patients with normal PTH levels. Disruption of the PTH-vitamin D axis during the healing phase was also associated with a longer length of stay.[20] Low 25(OH)D and elevated PTH levels increase the risk of inflammation, indicated by elevated levels of CRP and IL-10. Administration of $1,25(OH)_2D$ in vitamin D deficiency has been shown to reduce inflammatory biomarkers such as CRP and IL-10 in COVID-19 patients.[17,21] Vitamin D also has an effect on endothelial function and decreases vascular calcification. Vitamin D can prevent atherosclerosis and vascular calcification, directly affecting vascular smooth muscle cells (VSMCs). A multicentre study evaluating hospitalized patients with acute coronary syndrome (ACS) found that about 96% of patients had abnormal 25(OH)D levels.

The lowest level of 25(OH)D was around 17.8 ng/mL in the general population. This epidemiological study indicated that poor vitamin D status was associated with poor cardiovascular outcome.[1,22] CAD is a prevalent condition in COVID-19 patients, ranging from 2.5-10% of cases with a mortality probability up to three times that of COVID-19 patients without clinical CAD.[23] In another study, COVID-19 patients experiencing mortality had clinical CAD (82% vs 55%, $p = 0.02$) as well as low levels of 25(OH)D (15.2 vs 18.9 ng/mL, $p = 0.02$).[24]

Vitamin D and heart failure

Much evidence supports that calcitriol deficiency contributes to the severity of chronic heart failure (CHF).[25,26] Some of the potential mechanisms that explain vitamin D's direct protective effect on heart failure include effects on myocardial contractile function, regulation of natriuretic hormone secretion, effects on extracellular matrix remodelling, reduction of LV hypertrophy, and regulation of inflammatory cytokines. Indirectly, vitamin D can also affect heart function by altering PTH and serum calcium levels.[26] In uremic cardiomyopathy patients undergoing dialysis, treatment with 1-α hydroxyl cholecalciferol 1 μg/day for six weeks resulted in decreased plasma parathyroid concentrations and increased shortening of fractional fibers on M-mode echocardiography.[1]

The causes of heart failure are not fully understood. In recent years, CHF's pathophysiological concept has changed from an isolated hemodynamic view to a more complex one; involving neurohormonal overactivation and increased concentrations of pro-inflammatory cytokines, such as TNF-α and IL-6. In particular, TNF- α may contribute to the pathogenesis and progression of CHF. Therefore, measures to mitigate the adverse effects of TNF-α on CHF progression may be a promising therapeutic approach.[27]

Regarding COVID-19 infection, a study of 452 COVID-19 patients in Wuhan showed that patients with clinical severity had elevated levels of TNF-α.[28] Increased cytokine TNF-α can cause septic shock and multi-organ failure, lead to myocardial damage and circulatory failure.[29]

SOURCES OF VITAMIN D AND NORMAL SERUM LEVELS

The synthesis of vitamin D3 in the skin from sun exposure is the primary source (80-90%) of human vitamin D under natural conditions. Total-body sun exposure to at least 1 erythemal dose when wearing a swimsuit is equivalent to 250-500 g (10,000-20,000 IU) of vitamin D per day. Serum 25(OH)D is the major metabolite of circulating vitamin D and reflects vitamin D input from the synthesis in the skin and dietary intake. Serum levels of $1,25(OH)_2D$ may be normal or even elevated in patients with vitamin D deficiency.

Vitamin D derived from the daily diet is small compared to the build-up in the skin but can be an essential vitamin D source in supplement form. Fish oil derived from salmon, mackerel, herring, and sardines is a rich source of vitamin D. Fortified milk and juices contain 100 IU of vitamin D per 8-oz. Daily dietary sources typically provide 2.5 g (100 IU) of vitamin D per day, and fortified foods can provide up to 5-10 g (200 to 400 IU) of vitamin D daily.[30]

Hernandez et al. showed that vitamin D deficiency was found in 82.2% of COVID-19 cases and 47.2% in the control population ($p < 0.0001$). The serum 25(OH)D levels in COVID-19 patients were significantly lower than in the control population (13.8 ± 7.2 ng/mL vs 20.9 ± 7.4 ng/mL, $p < 0.0001$).[22] The most useful serum 25(OH)D level is at 30 ng/mL or 75 nmol/L. In COVID-19 patients, the goal of vitamin D therapy is to normalize vitamin D levels. Patients with vitamin D levels below 50 nmol/L should be treated until they reach a vitamin D level of at least 75 nmol/L.[14] Vitamin D intoxication is indicated when the level of 25(OH)D > 375 nmol/L.[31]

Serum vitamin D levels may also be involved in determining the prognosis of COVID-19. Vitamin D deficiency has been shown to contribute to acute respiratory distress syndrome and the increased case mortality rates with age and populations with comorbid conditions such as hypertension and CVD, which have also been reported as low prognostic factors for COVID-19.[12,22]

DAILY INTAKE RECOMMENDATIONS, TOXICITY, AND VITAMIN D TESTING IN COVID-19

In the United States, the recommended daily dose of vitamin D is 200 IU per day for those aged 70 years. It is estimated that for every 100 IU of vitamin D, the 25(OH)D level increases by 2.5 nmol/L.[32]

Research by Ohaegbulam et al. on COVID-19 patients with vitamin D deficiency showed that patients with high doses of vitamin D supplementation (50,000 IU) showed shorter treatment times and duration of oxygen use

than patients with standard-dose vitamin D supplementation (1,000 IU).[33] This clinical evidence is also supported by decreased levels of CRP and lactate dehydrogenase (LDH). The protective effect of vitamin D supplementation was more significant in patients with serum 25(OH)D 25 nmol/L.[34] Another study showed high doses of vitamin D (250,000-500,000 IU) were safe for use in critically ill patients on ventilator support and was associated with a reduced duration of treatment.[35] The study by Liu et al., provided vitamin D supplementation at a higher dose of 300,000 IU single dose by the oral or intramuscular route, taking into account the safety level of vitamin D supplementation and the rare toxicity.[36] Whereas in the ongoing COVIT Trial study, COVID-19 patients were divided into two study groups, a group that took vitamin D at a single dose of 50,000 IU orally and the next group was given vitamin D with the highest dose of 400,000 IU orally a single dose.[37]

Vitamin D intoxication is very rare but can be caused by excessive consumption or too high a dose. Doses > 50,000 IU per day raise 25(OH)D levels to more than 375 nmol/L and are associated with hypercalcemia and hyperphosphatemia. A dose of 10,000 IU of vitamin D3 per day for up to five months usually does not cause toxicity. A case report showed that vitamin D 150,000 IU per day for 28 years and serum concentrations up to 1.126 nmol/L did not result in significant hypercalcemia side effects.[1,38] Vitamin D hypervitaminosis has been reported when supplementing with vitamin D at a dose of 500,000 IU with the effect of increasing the risk of falls and fractures in older women.[39] There are no studies related to hypervitaminosis of vitamin D in COVID-19 patients.

VITAMIN D AND MORTALITY IN COVID-19

Numerous studies and meta-analysis studies suggest that vitamin D deficiency negatively affects survival, whereas supplementation decreases overall mortality. Regular intake of vitamin D supplements has been associated with reduced mortality. The relationship between baseline vitamin D status, vitamin D supplement dose and total mortality remains to be investigated. Apart from CVD, vitamin D deficiency is associated with an increased risk of total mortality. Most studies on this topic have noted increased mortality in patients with low 25(OH)D concentrations. A meta-analysis in 6,853 patients showed increased PTH secretion, activation of RAAS, and decreased death risk. These findings are in line with the results of the RCT meta-analysis, in this Autier and Gandini report that vitamin D supplementation was associated with a significant reduction of 7% in total mortality.[40]

Another meta-analysis study showed that vitamin D deficiency has a significant correlation with the outcome and prognosis of COVID-19 patients.[41] A study in India by Sasikala et al., showed a positive correlation between vitamin D deficiency and mortality in COVID-19 patients.[13] Whereas in another study that measured the fatality rate of COVID-19 patients with and without vitamin D deficiency, it was found that patients with vitamin D deficiency had a fatality rate of 21% compared to patients without vitamin D deficiency of 3.1%.[7]

Studies related to the outcome of vitamin D supplementation in COVID-19 patients with vitamin D deficiency have not been widely studied. Studies related to respiratory tract infections showed a 64% reduction in the risk of developing respiratory tract infections after vitamin D supplementation (95% CI 0.49-0.84; p = 0.0014).[12] One study on COVID-19 patients with a small sample size showed that giving high doses of vitamin D (50,000 IU) for five days had an effect on reducing the duration of treatment and oxygen supplementation; compared to patients receiving vitamin D therapy in standard doses (1,000 IU), where patients with high doses of vitamin D were able to achieve concentrations of ≥ 75 nmol/L while patients with standard doses were unable to achieve minimum levels of vitamin D concentrations.[33]

SUMMARY

Vitamin D has various essential functions among RAAS regulation, as anti-inflammatory by reducing the production I of pro-inflammatory cytokines including L^{-6} and TNF-α, as

antithrombotic, plays a role in lipid metabolism through inhibition of the enzyme HMG-CoA reductase, plays a role in heart function through PTH regulation, and calcium. Vitamin D deficiency is associated with cardiovascular events as well as an increased fatality rate in COVID-19 patients. Giving high doses of vitamin D is relatively safe, with case reports of hypervitaminosis are infrequent.

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