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VITAMIN D AND COVID-19: MODULATION OF THE IMMUNE RESPONSE

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Abstract: Introduction: Due to the rapid spread of Sars-CoV-2 and COVID-19, at the beginning of 2020, the state of a pandemic by the coronavirus was installed and, since then, incessant research is being carried out in order to understand the pathophysiology of the disease and identify possible elements that predispose it. In this context, the association of vitamin D with the installation and progression of COVID-19 has been studied. The justification for the proposal of this work is due to the role of the vitamin in the modulation of the immune system, participating in the synthesis of catelecidin, a peptide that reduces viral replication; activation of defense cells; and the decrease of inflammatory cytokines. Objectives: To evaluate the plasma level of vitamin D, in the active form calcitriol, in individuals with COVID-19. Methods: Through a bibliographic survey in the "PubMed" database, with the keywords "COVID-19, SARS-CoV-2, VITAMIN D, PREVENTION, CONTROL, THERAPEUTIC USE", 146 complete articles were collected and eight were selected that showed the plasma concentration of calcitriol in individuals with COVID-19. Results: Analysis of the eight articles resulted in the identification of plasma levels of calcitriol in 1485 individuals with COVID-19. Of these, 82% had Vitamin D values below the minimum standard reference of 20 ng/mL. Conclusion: Through the descriptive literature review, it was concluded that the low plasma level of vitamin D can be a risk factor for infections by Sars-CoV-2 and an aggravating factor of the clinical picture of COVID-19.
Keywords: COVID-19; Sars-CoV-2; Vitamin D; immune response.

INTRODUCTION

Sars-CoV-2, S*evere Acute Respiratory Syndrome Coronavirus 2* (KARA *et al.*, 2020), identified in the city of Wuhan, China, at the end of 2019 and that causes the disease COVID-19 (FAGIONATO et al., 2021), is an enveloped virus with a single strand of RNA, of the Coronaviridae family, found in humans and other mammals (WIERSINGA et al., 2020).

With high transmissibility, contamination can occur through droplets of saliva and aerosols containing the virus, and can be spread in closed environments and health facilities (JAYAWEERA et al., 2020).

Although all individuals are subject to infection, elderly people over 60 years of age, obese, hypertensive, sedentary and diabetics seem to be more susceptible to the virus. Factors that lead to a decline in immunity, such as vitamin D deficiency and previous illnesses, also seem to facilitate the contamination and progression of COVID-19 (CARTER et al., 2020; KARA et al., 2020). Although numerous researches have been carried out, an effective drug against COVID-19 has not yet been discovered. Given this scenario, studies suggest that vitamin D could be a form of prevention and treatment of the disease.

PATHOPHYSIOLOGY OF SARS-COV-2

Sars-CoV-2 has a viral phospholipid envelope with glove-shaped proteins called S-proteins (spike). S-proteins have two subunits: the S1 subunit, which corresponds to the part of the protein projected outside the envelope, and the S2 subunit, a protein filament located in the envelope and which projects S1 to the external environment. The S-protein receptor in the human body is angiotensin-converting enzyme II (ACE2), with which it can bind via the receptor-binding domain (RBD) to allow fusion of the viral envelope. with the host cell (MISHRA & TRIPATHI, 2021).

ACE2 participates in the Renin Angiotensin Aldosterone System and its messenger RNA is expressed in the intestines, kidneys, heart, adipose tissue, lungs and blood vessels. The location of ACE2 is extremely relevant for the identification of Sars-CoV-2 target tissues, which may suffer direct damage from the infection (COOPER et al., 2021).

Sars-CoV-2 infection can initiate at ACE2 receptors in the lungs, inducing the release of pro-inflammatory cytokines by alveolar epithelial cells. These cytokines promote the recruitment of innate immunity phagocytes to fight the virus, such as macrophages and granulocytes. Dendritic cells, essential in the presentation of viral antigens and consequent recruitment of adaptive immunity cells, also release cytokines and chemokines that fuel the inflammatory reaction (CRUVINEL et al., 2010; KLOC et al., 2021).

If the virus cannot be eliminated by the body's controlled immune response, Acute Respiratory Distress Syndrome (ARDS) can settle in the lungs, as a result of the perpetuation and worsening of inflammation. Therefore, to prevent the spread of this response to other organs, with possible effects on the urinary, cardiovascular, reproductive and even nervous systems (DESHMUKH et al., 2021), some studies propose the use of anti-inflammatory drugs in order to avoid the production of cytokines and the recruitment of macrophages (KLOC et al., 2021).

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM AND COVID-19

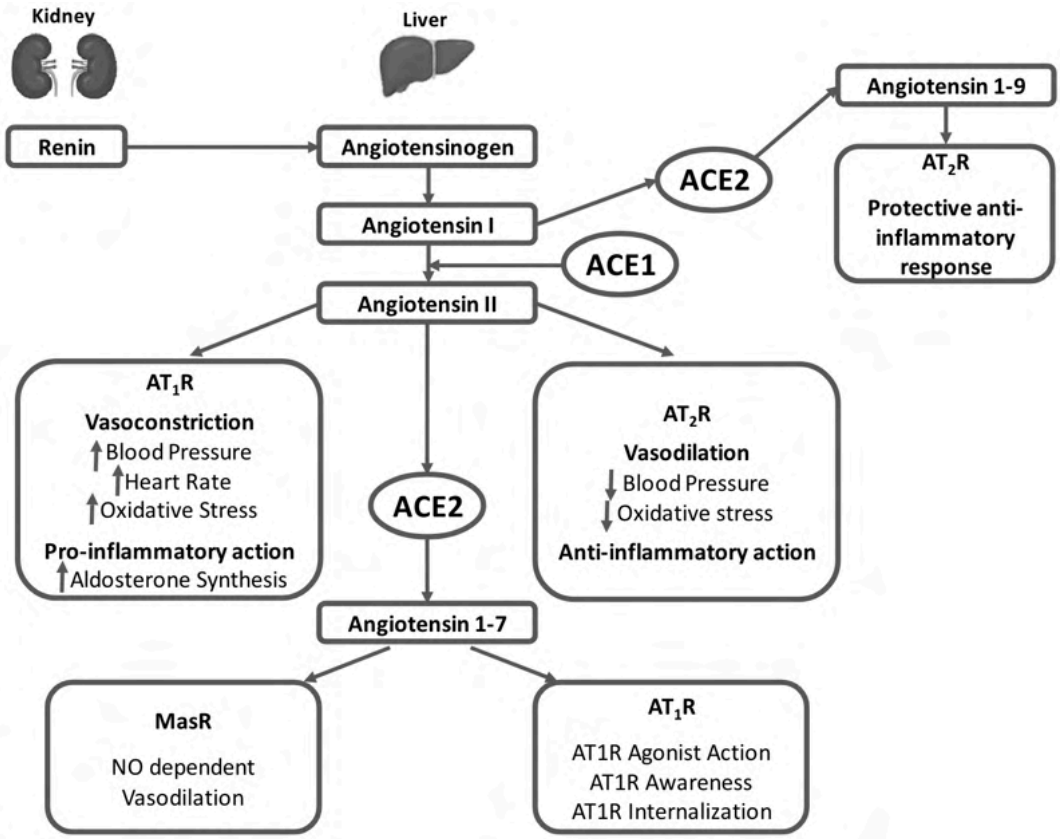
The Renin Angiotensin Aldosterone System (RAAS) comprises a reactional cascade of peptides, shown in figure 1, which ensure body homeostasis by regulating blood pressure and hydroelectrolytic balance (COOPER et al., 2021). Initially, the enzyme renin is secreted by renal cells, as a result of stimulation of the sympathetic autonomic nervous system, a decrease in renal perfusion or a decrease in sodium/chloride ion levels. Renin passes into the bloodstream and can reach various tissues, including the liver, which is responsible for the synthesis of angiotensinogen. This protein substrate undergoes the action of renin and is converted into angiotensin I, which, under the action of the angiotensin-converting enzyme I (ACE1), gives rise to angiotensin II (COOPER et al., 2021).

Angiotensin II can bind to two membrane receptors: the AT1R and the AT2R. By binding to AT1R, angiotensin II promotes vasoconstriction, elevation of blood pressure and heart rate, increased oxidative stress and pro-inflammatory action. Furthermore, this interaction is also involved in stimulating the synthesis of the mineralocorticoid aldosterone by the zona glomerulosa of the kidneys. Aldosterone is capable of increasing sodium retention by nephrons and, consequently, intravascular volume. Thus, imbalances in this link, such as increased levels of angiotensin II, seen in critically ill patients with COVID-19, and the expression of the AT1R receptor, identified in patients with cardiovascular changes, can cause arrhythmias, cardiac remodeling with hypertrophy, dysfunction endothelial and vascular inflammation, these last two alterations being more related to oxidative stress (COOPER et al., 2021).

On the other hand, the binding of angiotensin II with the AT2R receptor promotes effects opposite to those described above, such as vasodilation, decrease in blood pressure and oxidative stress, and anti-inflammatory effect. This way, this link acquires a cardioprotective role and can prevent the development of cardiovascular dysfunctions (COOPER et al., 2021).

In this reaction sequence, ACE2 acts by decreasing the amount of angiotensin II, by converting angiotensin I into angiotensin 1-9 and angiotensin II into angiotensin 1-7. Angiotensin 1-9 binds to the AT2R receptor and promotes a protective anti-inflammatory response. Angiotensin 1-7, on the other hand, interacts with the MasR receptor and induces nitric oxide (NO)-dependent vasodilation and prevents cardiac remodeling, in addition to acting as an agonist of AT1R receptors, generating its desensitization and internalizing it, in an attempt to attenuate cardiovascular changes mediated by angiotensin II (COOPER et al., 2021) (Figure 1).

Although more studies are needed, it is inferred that the regulation of the RAAS reaction cascade may be essential in controlling the homeostasis of patients with COVID-19. Sars-CoV-2 causes the loss of ACE2 function by using this enzyme to penetrate host cells. Thus, there is impairment of angiotensin II metabolism in angiotensin 1-7 and angiotensin 1-9 and inactivation of MarR receptors, in addition to increasing interaction with AT1R receptors. This imbalance in the RAAS results in a greater vasoconstriction and pro-inflammatory effect, facilitating the proliferation of the virus and the pathophysiological response of COVID-19 (COOPER et al., 2021). Even more severe cases of the disease were identified in previously hypertensive patients, which may be related to the deregulation of the RAAS caused by Sars-CoV-2 (KARA et al., 2020).



ECA = Angiotensin Converting Enzyme; ATR and MasR = Angiotensin Membrane Receptors; NO = nitric oxide.

Figure 1: Mechanism of action of the Renin Angiotensin Aldosterone System.

The participation of vitamin D in this mechanism has been widely studied due to its ability to inhibit the RAAS, and may exert therapeutic effects against COVID-19 by reducing the concentrations of pro-inflammatory cytokines and increasing anti-inflammatory ones (CARVALHO et al, 2021). This hypothesis would prevent more severe disease progression in patients with previous potentially inflammatory conditions, such as obesity, and with associated comorbidities, such as hypertension and diabetes (CARTER et al., 2020).

VITAMIN D

Vitamin D is a steroid hormone found in different structural chemical forms, as shown in figure 2. The form of ergocalciferol (Vitamin D2) is found in plants and fungi and that of cholecalciferol (Vitamin D3) is found in fish, as in tuna and salmon. In the human dermis, the pro-vitamin D 7-dehydrocholesterol is found, which, by thermal isomerization, originates cholecalciferol (GONÇALVES et al., 2020, CÂMARA et al., 2021).

Thus, Vitamin D2 and D3 are transported by vitamin D-binding protein (DBP) and undergo two hydroxylation reactions. The first occurs in the liver, under the action of cytochrome P450 enzymes, called hepatic 25-hydroxylases, and originates 25-hydroxyvitamin D or calcidiol, which has a half-life of 21 to 30 days. Calcidiol is the form measured in blood plasma, as it is predominant in the circulation and has a long half-life (CÂMARA et al., 2021). According to the Brazilian Society of Endocrinology and Metabology (SBEM, 2021), values between 20 to 60 ng/mL (50 to 150 nmol/L) of plasma vitamin D, dosed in the form of

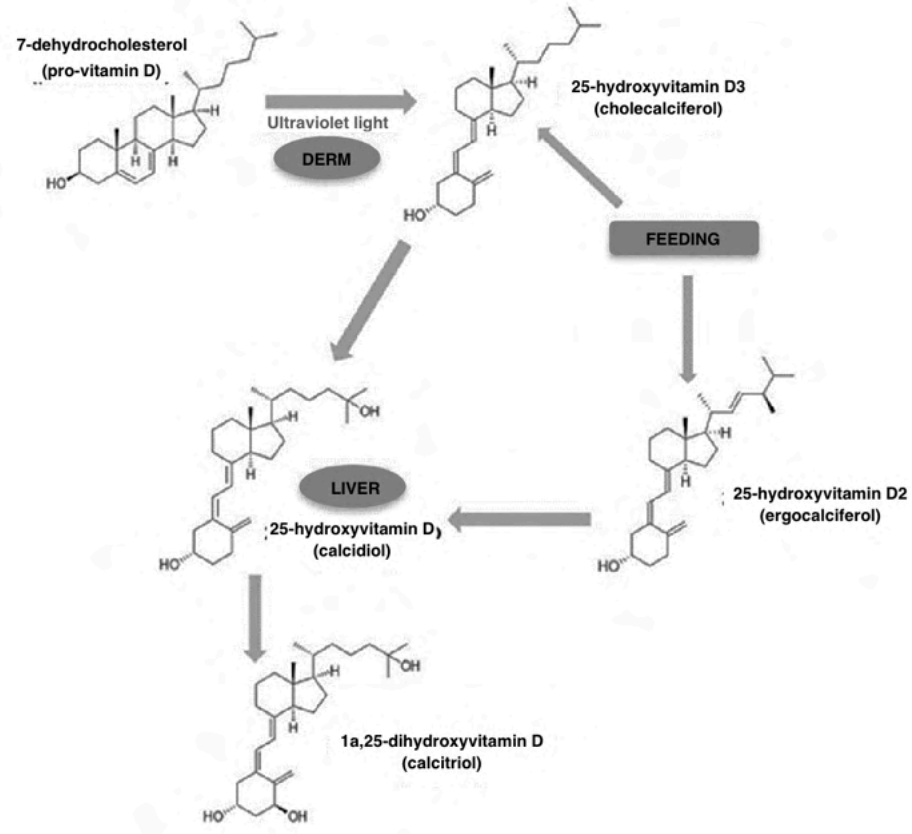


Figure 2: Main molecular structural forms of vitamin D (GONÇALVES et al., 2020).

calcidiol, are ideal for the functioning of a healthy organism.

The second hydroxylation, by the action of the enzyme 25(OH)1-α-hydroxylase, results in the formation of 1α, 25-dihydroxyvitamin D3 or calcitriol, considered the active form of vitamin D (GONÇALVES et al., 2020, CÂMARA et al., 2021).

The regulation of the active vitamin is essentially done by the levels of calcium and phosphorus in the blood, in a negative feedback mechanism. When these ions are reduced, there is stimulation of the synthesis of calcitriol and parathyroid hormone (PTH), produced by the parathyroid gland. This way, 1α, 25-dihydroxyvitamin D and PTH increase the absorption of calcium and phosphorus in the small intestine so that the serum levels of these ions are high, thus having an adequate bone mineralization (CÂMARA et al., 2021).

In addition to exerting an influence on the plasma levels of ions such as calcium, phosphorus and magnesium, this steroid hormone has other essential functions in the maintenance of body homeostasis, including the regulation of the immune response against infectious agents and modulation of inflammatory reactions, which are directly related to it. based on the mechanism of action of Sars-CoV-2 (KLOC et al., 2021).

Vitamin D and Immunology

Vitamin D has as one of its functions the modulation of the human innate and adaptive immune system. In the presence of an infectious process, calcitriol has the function of stimulating the synthesis of catelecidin and regulating the activation of defense cells, such as monocytes, macrophages, myeloid-derived suppressor cells (MDSCs) and natural killer cells. (NK); increase the oxygen-carrying capacity of the blood (SINGH et al., 2020; KLOC et al., 2021) and prevent the exacerbated expression of inflammatory cytokines (CHAROENNGAM & HOLICK, 2020). In an immune system response, there is the release of macrophages and monocytes that stimulate the conversion of calcidiol into calcitriol, responsible for regulating lymphocyte action, antibody and cytokine production (KARA et al., 2020).

Vitamin D also activates a chain reaction for the synthesis of catelecidin LL-37. This antimicrobial peptide is able to reduce viral replication, directly stopping the progression and spread of respiratory infections. Thus, calcitriol, through catelecidine, could have antiviral action and contain the progression of COVID-19 (KLOC et al., 2021).

1α, 25-dihydroxyvitamin D can act directly on human defense cells. The presence of vitamin D receptors (VDR) on T lymphocytes, dendritic cells and macrophages allows many genes that regulate the activity of these cells in the immune defense to be expressed by binding to calcitriol (KLOC et al., 2021). Furthermore, VDRs minimize the mitochondrial production of reactive oxygen species, important macrophage and pro-inflammatory factors signaling. Thus, the reaction against the infectious agent can be controlled and sufficient to combat the invasion (CHAROENNGAM & HOLICK, 2020; KLOC et al., 2021).

Vitamin D and COVID-19

The association between low serum vitamin D levels and the severity of viral respiratory infections has been advocated by several studies (CHAROENNGAM & HOLICK, 2020).

Infectious agents penetrate the respiratory epithelium through specific receptors and activate the body's immune response by causing tissue damage. This reaction consists of an inflammatory process of the airways that can progress to systemic inflammation, and calcitriol exerts an important immunological

function by stimulating the synthesis of catelecidine, regulating the activation of defense cells, increasing the ability to transport oxygen gas by the blood (SINGH et al., 2020; KLOC et al., 2021) and avoid the exacerbated expression of inflammatory cytokines (CHAROENNGAM & HOLICK, 2020). Furthermore, vitamin D is also believed to increase the speed of recovery from acute lung injuries (SINGH et al., 2020).

Specifically in relation to Sars-CoV-2, vitamin D may be involved in several stages of disease progression. Calcitriol acts on the inhibition of the RAAS and on the synthesis of related pro-inflammatory factors (CARVALHO et al., 2021); modulates the expression of defense cells in which it presents receptors, such as macrophages, the main responsible for the inflammatory response of COVID-19; and MDSC, on which it can inhibit the action by up to 70% (KLOC et al., 2021). Therefore, vitamin D prevents the spread and exacerbation of the immune reaction against the virus. Thus, supplementation of this steroid vitamin could reduce infections and progression of COVID-19 (CHAROENNGAM & HOLICK, 2020; CARTER et al., 2020; KLOC et al., 2021).

METHODS

In May 2021, a bibliographic survey was carried out in the "PubMed" database with the keywords "(COVID-19 OR SARS-CoV-2) AND VITAMIN D", with the "full text" filter, which resulted in 344 After adding the words "AND PREVENTION & CONTROL OR THERAPEUTIC USE", 146 articles were surveyed and selected for the current publication. After excluding bibliographic reviews, letters, editorials, essays of articles that did not meet the research objectives, as they did not present the plasma concentration of vitamin D, only eight articles were used for the preparation of this work. The article selection process is represented in figure 3.

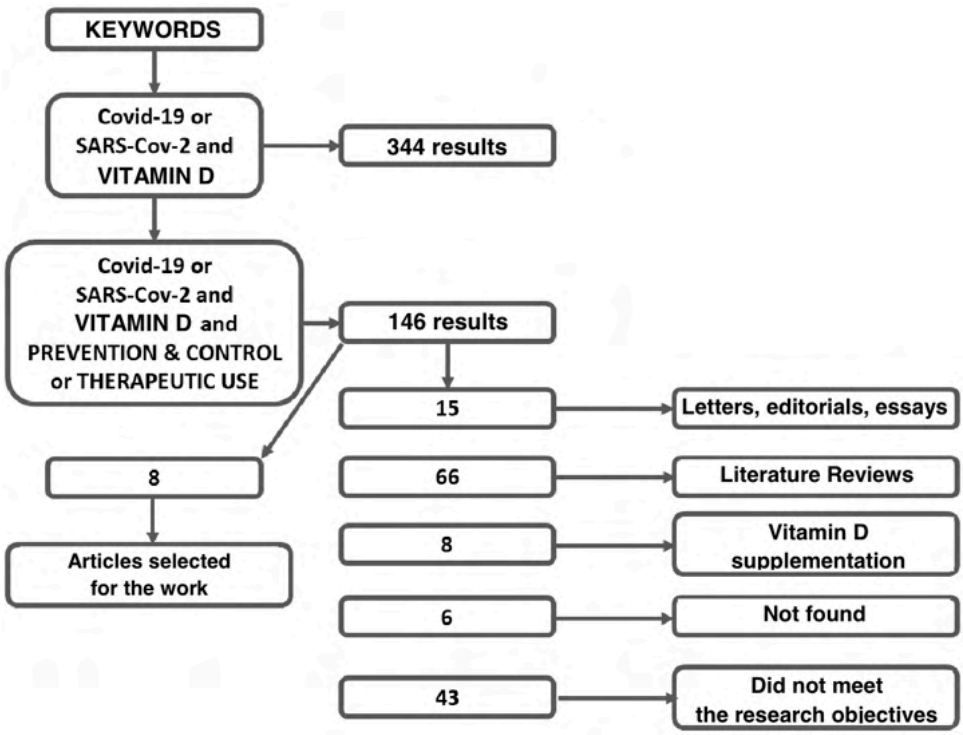


Figure 3: Data selection process flowchart.

RESULTS AND DISCUSSION

The analysis of the eight articles resulted in the identification of 1485 individuals proven to be diagnosed with COVID-19; in the mean age group of 66 years (± 9.8), with a mean body mass index of 27.8 kg/m2 (± 2.4) and, of these, 59% were male.

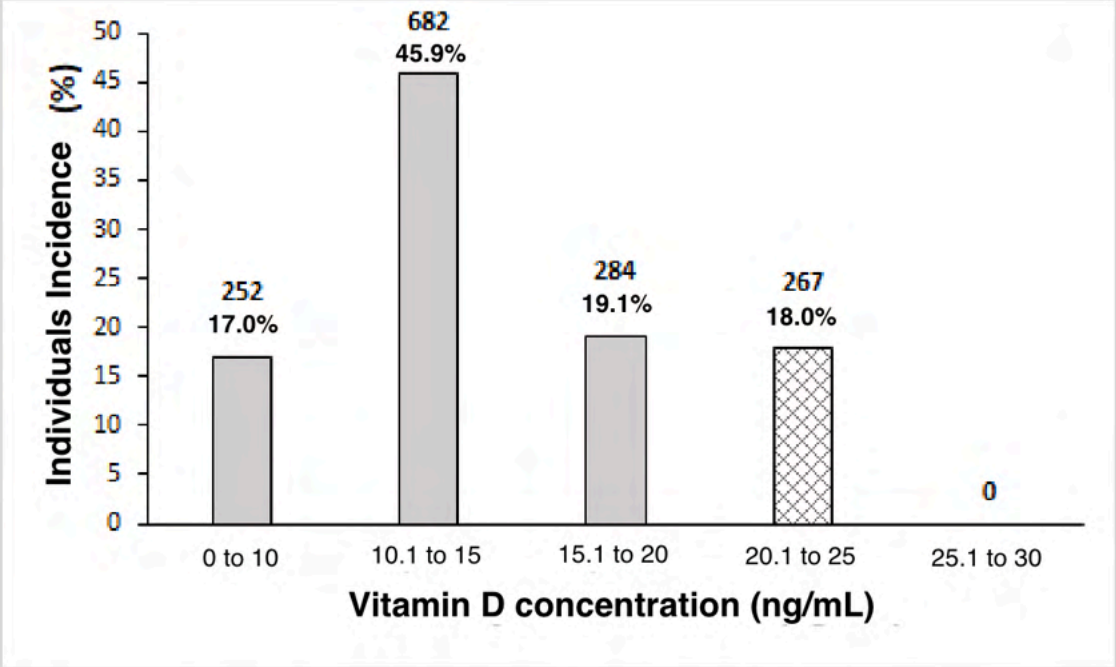
The mean plasma concentration of vitamin D, analyzed as calcidiol (25-hydroxy-vitamin D), was 13.7 ng/mL (± 6.1). Only 267 subjects (18%) had a calcidiol concentration above 20 ng/mL (= 50 nmol/L), which is considered the minimum recommended concentration (Moreira et al., 2020). Figure 4 represents the proportion of individuals who had a scaled calcidiol concentration considering the indices as the ideal rates (from 20 to 40 ng/mL = 50 to 100 nmol/L), insufficient (from 10 to 19.9 ng/mL = 25 at 49 nmol/L) and deficient (less than 10 ng/mL).

The analysis of the results indicates that the majority (82.0%) of the individuals with a proven diagnosis of COVID-19 had the plasma concentration of vitamin D below the value considered ideal. The highest rate of individuals affected with COVID-19 had a concentration of vitamin D from 10.1 to 15.0 mg/mL, that is, lower than recommended.

DISCUSSION

Through the data collected, it was found that most of the individuals surveyed, affected by COVID-19, had low plasma levels of vitamin D.

Considering the importance of vitamin D participation in (a) regulation of the innate and adaptive immune response (SINGH et al., 2020; KLOC et al., 2021; CRUVINEL et al., 2010) and (b) regulation of cell performance defense against microorganisms



Columns in full color correspond to individuals with a plasma concentration of Vitamin D below the ideal. The checkered column corresponds to individuals with vitamin D concentration in the ideal range.

Figure 4: Incidence of individuals in relation to the concentration of Vitamin D.

(CHAROENNGAM & HOLICK, 2020; KLOC et al., 2021), low plasma levels of calcitriol may be directly related to the severity of viral respiratory infections (CHAROENNGAM & HOLICK, 2020).

As demonstrated in the data presented, as more than 80% of the analyzed individuals with the disease had serum levels of vitamin D below the recommended minimum ideal value (MOREIRA et al., 2020; SBEM, 2021), of 20 ng/ml, inferred It was concluded that this group could present immunological impairment due to the inadequate concentration of this vitamin.

In view of the data collection carried out, it was concluded that the plasma concentration of vitamin D may be directly related to infections by Sars-CoV-2 and the progression of COVID-19. Thus, supplementation of this vitamin could reduce Sars-Cov-2 infections and the progression of COVID-19.

CONCLUSION

In view of the data collection carried out, it was concluded that the plasma concentration of vitamin D may be directly related to infections by Sars-CoV-2 and the progression of COVID-19. Thus, supplementation of this steroid vitamin could reduce infections and the progression of COVID-19.

CONSIDERAÇÕES FINAIS

Os resultados que constam nesse trabalho foram:

a) Apresentados e publicados nos anais dos congressos:

XXX Congresso Médico Acadêmico da UNICAMP – COMAU – 2021

XIX Pré-Congresso Médico Acadêmico Samuel Pessoa da Faculdade de Medicina da PUC-Campinas – Pré-COMASP, 2021

b) Publicado no site (link abaixo) da Sociedade de Medicina e Cirurgia de Campinas e ganhou o primeiro lugar do prêmio acadêmico – 2021.
https://smcc.org.br/wp-content/uploads/2022/06/FINAL-Artigo-revisao-SMCC-Premio-Academico.pdf

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